Original Article

Revisiting Pentacam Parameters in the Diagnosis of Subclinical and Mild Keratoconus Based on Different Grading System Definitions

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Abstract

Objectives: To retest the performance of Pentacam parameters in the detection of eyes with subclinical keratoconus (KC) and mild KC based on different definitions from the Amsler-Krumeich (AK), Collaborative Longitudinal Evaluation of Keratoconus (CLEK), and ABCD systems.

Materials and Methods: This cross-sectional university-based study comprised 24 eyes with subclinical KC, 144 eyes with mild KC (based on AK in 101 eyes, CLEK in 28 eyes, and ABCD in 15 eyes), and 70 controls. Diagnostic ability of the thinnest point (TP) pachymetry, KISA% index, inferior-superior asymmetry, corneal aberrations, Pentacam indices, front/back elevations, pachymetric progression index, Ambrósio-Relational Thickness (ARTmax), and Belin/Ambrósio Enhanced Ectasia Display scores (Df, Db, Dp, Dt, Da, and D-final) were evaluated.

Results: ARTmax (83.3% sensitivity/74.3% specificity) had the highest ability in distinguishing subclinical KC from normal, followed by TP pachymetry, Dt, and Da. D-final showed excellent sensitivity/specificity in mild KC diagnosis based on AK (98%/100%) and CLEK (97.4%/100%) descriptions. In the mild KC-ABCD group, index of vertical asymmetry accurately detected all eyes with mild KC and 97.1% of the controls.

Conclusion: This study points out the gray zone in the detection of eyes with subclinical and mild KC due to overlapping terminology and grading criteria. Pentacam parameters seem to have modest capability in subclinical KC detection, indicating the necessity for additional diagnostic modalities. However, eyes with mild KC can be diagnosed with high accuracy using Pentacam parameters, although the strongest parameters may vary according to the definition of "mild KC." Nevertheless, uniform and definitive criteria for subclinical and clinical KC classification are required for a diagnostic and therapeutic consensus in KC.

Keywords: Diagnosis, Pentacam, Scheimpflug, subclinical keratoconus

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Introduction

Keratoconus (KC) is an asymmetrically bilateral progressive corneal ectasia characterized by visual deterioration and stromal thinning. In moderate and advanced stages, the diagnosis of KC can easily be made based on apparent clinical and topographical findings, whereas detecting eyes with KC in its earliest form remains a challenge.[1]

There is growing interest in developing a powerful parameter or formula for distinguishing subclinical cases of KC to avoid iatrogenic post-laser ectasia.[2,3,4,5,6,7] However, there is no consensus in the literature on the nomenclature for early stages of KC.[2,3,4,5,6,7]

A recent systematic review reported that the most commonly used definition of subclinical KC is an eye with topographic signs of KC and/or suspicious topographic findings with normal slit-lamp examination and KC in the fellow eye.[8,9,10,11,12,13] Regarding clinical KC, various classification systems such as the Amsler-Krumeich (AK), KC severity score, Collaborative Longitudinal Evaluation of Keratoconus (CLEK), ABCD, and RETICS (*Red Temática de Investigación Cooperativa en Salud)* were introduced to grade disease severity.[14,15,16,17,18] The RETICS was developed by Alió et al.[16] as a visual limitation-based KC classification.

Recently, Belin and Duncan[18] proposed the ABCD system, which incorporates anterior/posterior corneal curvature data, thinnest point (TP) on pachymetry, and corrected distance visual acuity (CDVA) for progression follow-up in eyes with KC. The

ABCD system has been also integrated into the Pentacam HR software (Oculus Optikgerate GmBH, Wetzlar, Germany).[18]

Pentacam technology has an important place in the diagnosis of KC because it provides a variety of quantitative parameters, and the utility of these parameters in early KC detection is still being tested. However, previous studies reported diverse sensitivity and specificity values for Pentacam parameters in the diagnosis of subclinical and mild KC due to overlaps among these definitions and a lack of globally accepted uniform criteria.[1,7,10,11,12,13,14,17,18]

This study aimed to re-evaluate the performance of Pentacam parameters in the discrimination of eyes with subclinical KC and mild KC using different definitions of "mild KC" from the AK, CLEK, and Belin ABCD systems against the backdrop of previously published similar studies.

Materials and Methods

The Pamukkale University Non-Interventional Clinical Research Ethics Committee approved the study protocol (decision no: 23, date: 08.12.2020) and the tenets of Declaration of Helsinki on the use of human subjects in research were followed. This retrospective university-based, single-center, cross-sectional study included 24 eyes with subclinical KC (24 patients), 144 eyes with mild KC (144 patients), and 70 control eyes with normal tomography (70 subjects).

All included subjects had reliable records for ophthalmological examinations including CDVA (Snellen) measurement, slit-lamp biomicroscopic examination, dilated fundus examination, and Pentacam imaging. Contact lens wearers were requested to remove their contact lenses prior to the measurements (at least 2 weeks for soft contact lenses and 3 weeks for hard contact lenses).

Each patient was only included in one group to ensure independence of the groups. One eye per patient was used for the statistical analysis. The randomization function of SPSS Statistics for Windows version 24.0 (IBM Corp., Armonk, NY, USA) was used for eye selection in bilateral cases.

Study Groups and Selection Criteria

Subclinical KC

An eye with suspicious topographical alterations but normal biomicroscopy and manifest KC in the contralateral eye was classified as subclinical KC.[7,8] Eyes included in this group also met all of the following criteria (Figure 1):

- CDVA (spectacle correction) ≤0 logarithm of the minimal angle of resolution (logMAR),
- Presence of any suspicious patterns on axial curvature map such as superior steep, inferior steep, irregular, inferior-steep asymmetric bowtie, superior-steep asymmetric bowtie, symmetric or asymmetric bowtie with SRAX >21 degrees and/or localized front (5-7 µm) and/or back (10-17 µm) elevation at the TP,
- Corneal thickness at the TP >470 µm,
- 3-mm inferior-superior keratometric asymmetry (I-S) <1.4 diopters (D),
- Central keratometry (K) <47.2 D.

Manifest KC in the contralateral eye was defined using the following criteria in combination: presence (if any) of biomicroscopic signs of KC (Vogt's striae, Fleischer's ring, Munson's sign or Rizzuti's phenomenon) and/or topographical map patterns typical for KC (round, oval, superior steep, inferior steep, irregular, inferior-steep asymmetric bowtie, superior-steep asymmetric bowtie, and symmetric or asymmetric bowtie with SRAX >21 degrees) accompanied by focal steepening (front elevation >7 µm and/or back elevation >17 µm at the TP) and corresponding corneal thinning, 3-mm I-S keratometric difference >1.4 D, central K >47.2 D, and TP pachymetry <470 µm.

Mild KC Group

In eyes with confirmed diagnosis of KC (based on the above-mentioned topographic criteria for manifest KC), three independent mild KC groups were extracted using definitions of "mild KC" from the AK (mild KC-AK; corresponds to stage 1, induced myopia and/or astigmatism <5 D, corneal radii ≤48 D, and no corneal scarring), CLEK (mild KC-CLEK; steep K <45 D and TP pachymetry >450 µm), and ABCD (mild KC-ABCD; corresponds to stage 0, anterior average radii of curvature in the 3-mm zone >7.25 mm, posterior average radii of curvature in the 3-mm zone >5.90 mm, TP pachymetry >490 µm, CDVA ≤0 logMAR, and no corneal scarring) classification systems.[14,17,18]

Control Group

Eyes included in the control group met the following criteria:

- Bilateral normal corneal tomography and ophthalmological examination,
- None of the above-mentioned pathological findings,
- Normal front and back corneal surface (front elevation <5 µm and back elevation <10 µm at the TP),
- CDVA (spectacle) ≤0 logMAR,
- No history of persistent eye rubbing, atopy or vernal keratoconjunctivitis and no family history of KC.

Exclusion Criteria

Poor Pentacam scan quality (defined as the presence of any quality specification score other than "OK" displayed on the screen; e.g., "data gaps," "model," "fix," "align") and history of corneal pathology (e.g., infection, trauma, scarring, surgery, and other corneal thinning disorders) were defined as the exclusion criteria.

Pentacam Imaging and Main Outcome Measures

Pentacam (Pentacam HR, Oculus Optikgeräte GmbH, Wetzlar, Germany) measurements were performed by the same single experienced technician (F.K.) under scotopic conditions without pharmacological pupil dilation. Scans were obtained in the same way for all individuals in automatic release mode, and the best-quality scan with an "OK" score was utilized for statistical analysis. Throughout the study, the same Pentacam software version (1.25r15) was used, and all patient data was stored in an SPSS (IBM Corp., Armonk, NY, USA) database.

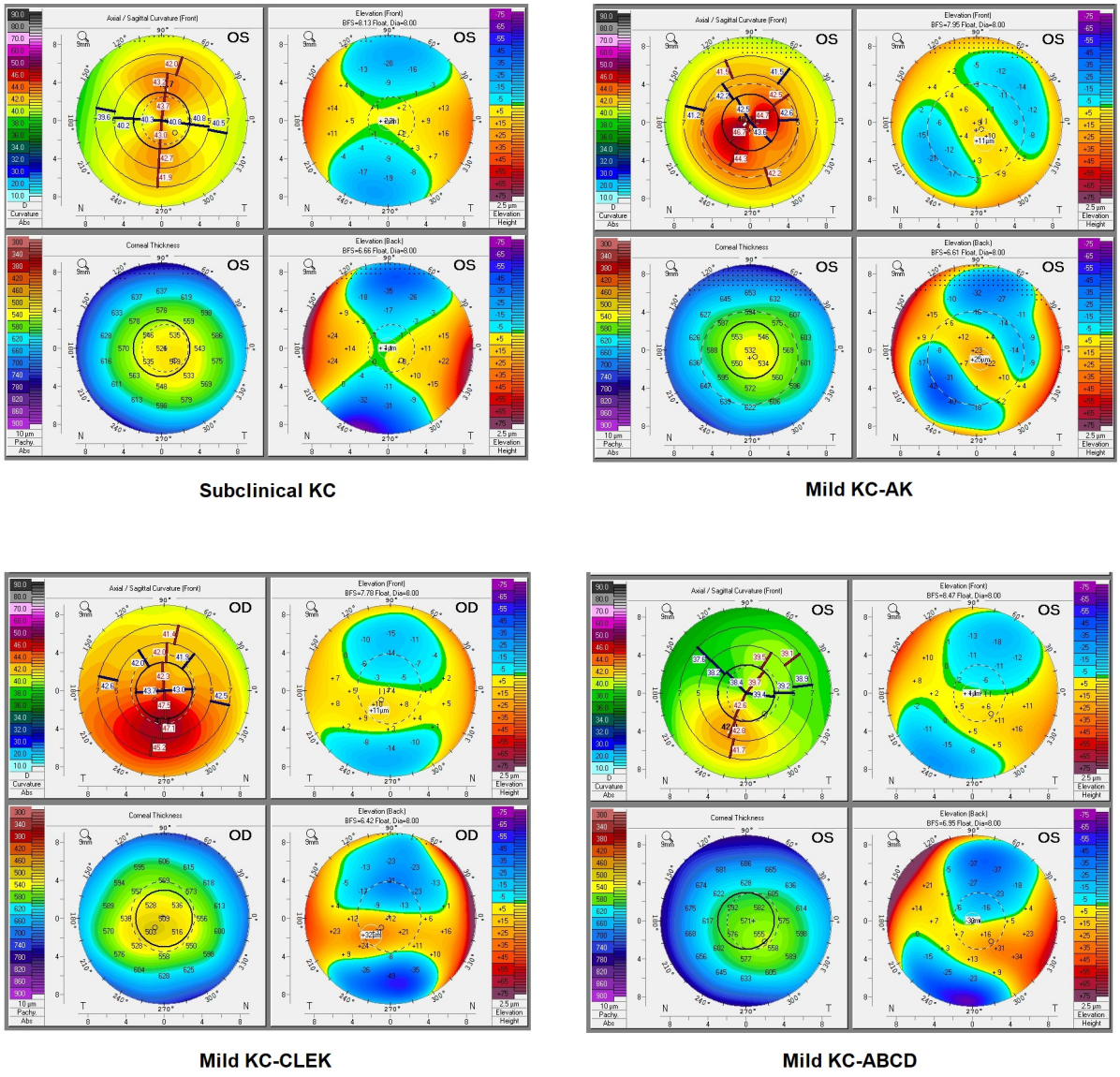

Figure 1. Representative Pentacam images (axial/sagittal curvature, corneal thickness and anterior/posterior elevation maps) of eyes with subclinical KC and mild KC based on the AK, CLEK, and ABCD classification systems

The Pentacam HR utilizes a 360° rotating Scheimpflug camera that captures high-resolution cross-sectional images of the anterior segment. These images are transformed into a three-dimensional (3-D) form to obtain qualitative data for anterior/posterior corneal topography, elevation, pachymetry, corneal power distribution, Zernike corneal wavefront analysis, anterior chamber anatomy, and KC detection/staging.

Mean and maximum keratometry (Kmean and Kmax), the TP pachymetry, KC percentage index (KISA, automatically calculated by the Pentacam system), I-S (automatically calculated by the Pentacam system), root-mean-square (RMS) values for higher order (HOA), spherical, vertical coma, and total aberrations, index of surface variance (ISV), index of vertical asymmetry (IVA), keratoconus index (KI), center keratoconus index (CKI), index of height asymmetry (IHA), index of height decentration (IHD), minimum radius of curvature (Rmin), front elevation at the TP (F.Ele.Th), back elevation at the TP (B.Ele.Th), pachymetric progression index (PPI-min, max and avg), maximum Ambrósio Relational Thickness (ARTmax), and Belin/Ambrósio Enhanced Ectasia Display (BAD-D) scores were noted. ARTmax was calculated by the Pentacam system according to the following formula: ARTmax = TP pachymetry/PPI-max.

Regarding BAD-D scores, Pentacam software generates an "enhanced reference image (best fit sphere)" for the anterior and posterior corneal surfaces by excluding a 3.0-mm area centered on

the TP. The difference between standard and enhanced surfaces are mapped on the screen and highlighted by color code to facilitate visualization of the suspected areas. BAD-D values representing the standard deviation (SD) of front elevation difference (Df), back elevation difference (Db), average pachymetric progression (Dp), TP thickness (Dt), and ARTmax (Da), as well as a final D score (D final) are provided by the system. A D value <1.6 SD is accepted as "normal" (white), ≥1.6 SD (up to 2.6 SD) is indicated as "suspicious" (yellow) and a D value ≥2.6 SD (for D final, ≥3.0 SD) indicates "abnormality" (red).

The ABCD KC grading system, which uses the anterior (A) and posterior (back) (B) radius of curvature taken from the 3.0-mm exclusion zone (centered on the TP), corneal thickness at the TP (C), CDVA (D), and presence or degree of corneal scarring is available in the Pentacam software.[18]

All of the above-mentioned Pentacam parameters were compared among the control, subclinical KC, mild KC-AK, mild KC-CLEK, and mild KC-ABCD groups. Furthermore, we tested the ability of the Pentacam parameters to discriminate subclinical KC and mild KC from normal. For "mild KC" classification, the AK, CLEK, and ABCD systems were used separately to assess the effect of different definitions of "mild KC" on the diagnostic performance of Pentacam parameters.

Sample Size Calculation

Assuming an effect size (d) of 0.4, at least 162 total cases were required to achieve 95% power at 95% confidence level (G*Power version 3.1.9.4 computer software, Universität Düsseldorf, Germany).

Statistical Analysis

Statistical analysis was performed using SPSS statistics version 24.0 (IBM Corp., Armonk, NY, USA). Age and quantitative Pentacam parameters were given as mean ± SD. The Kolmogorov-Smirnov test was used to assess normal distribution of the variables. Bonferroni-corrected Kruskal-Wallis test was used to compare age and Pentacam parameters among the control, subclinical KC, mild KC-AK, mild KC-CLEK, and mild KC-ABCD groups, as none of the variables were normally distributed and met the parametric test conditions. Receiver operating characteristic (ROC) curve analysis was performed and area under the ROC curve (AUC) was calculated to test the ability of the Pentacam parameters to discriminate eyes with subclinical KC, mild KC-AK, mild KC-CLEK, and mild KC-ABCD from normal controls. AUC values were interpreted as excellent (0.90-1.00), good (0.80-0.89), fair (0.70-0.79), poor (0.60-0.69), and worthless (0.50-0.59). The ROC curve plots the true positives (sensitivity) against false positives (1-specificity) for different threshold values. The value with the best sensitivity/specificity pair on the ROC curve was accepted as the cut-off value based on the Youden index. Sensitivity/specificity values for a variable with an AUC value <0.80 were not presented in the article due to its low clinical importance. The DeLong test was conducted (MedCalc® Statistical Software version 20.009, MedCalc Software Ltd, Ostend, Belgium) to assess the statistical significance between the ROC curves for the relevant Pentacam parameters in distinguishing subclinical KC from normal. A p value <0.05 indicated statistically significance at 95% confidence interval for the Kruskal-Wallis test, whereas a p value <0.005 was accepted as statistically significant for pairwise comparisons among the five groups (Bonferroni correction), as the Mann-Whitney U test was performed 10 times.

Results

There was no statistically significant difference in age among the control (n=70 eyes; 27.1±9.9 years), subclinical KC (n=24 eyes; 26.2±6.1 years), mild KC-AK (n=101 eyes; 30.2±9.5 years), mild KC-CLEK (n=28 eyes; 29.4±14.4 years), and mild KC-ABCD (n=15 eyes; 29.3±7.5 years) groups (p=0.060, Kruskal-Wallis test). However, Kmean, TP pachymetry, Kmax, ISV, IVA, KI, CKI, IHA, IHD, Rmin, I-S, KISA, RMS values (total, HOA, spherical, and vertical coma aberrations), F.Ele.Th, B.Ele.Th, PPI (min, avg, and max), ARTmax, and BAD-D scores (all) showed significant differences among the five groups (p<0.05, Kruskal-Wallis test, Tables 1, 2).

Pairwise Comparisons of Pentacam Parameters Between the Groups

Control vs. Subclinical KC Group

Eyes with subclinical KC had lower TP pachymetry, spherical aberration (more negative), and ARTmax but higher IVA, KISA, PPI (min, avg, and max), Df, Dp, Dt, Da, and D final values when compared to the control group (Bonferroni correction, p<0.005 for all).

Control vs. Mild KC-AK Group

Compared to the control group, the mild KC-AK group had significantly higher Kmean, Kmax, ISV, IVA, KI, CKI, IHA, IHD, I-S, KISA, total RMS, RMS-HOA, F.Ele.Th, B.Ele.Th, PPI (min, avg, and max), and BAD-D scores (all) and lower TP pachymetry, Rmin, ARTmax, spherical and vertical coma aberration RMS values (Bonferroni correction, p<0.005 for all).

Control vs. Mild KC-CLEK Group

Eyes with mild KC-CLEK had higher Kmax, ISV, IVA, KI, IHA, IHD, I-S, KISA, total RMS, RMS-HOA, F.Ele.Th, B.Ele.Th, PPI (min, avg, and max), and BAD-D scores (all) when compared to those of the control group (Bonferroni correction, p<0.005 for all). In contrast, TP pachymetry, Rmin, ARTmax, and vertical coma RMS values were lower in the mild KC-CLEK group (Bonferroni correction, p<0.005 for all).

Control vs. Mild KC-ABCD Group

ISV, IVA, IHA, IHD, KISA, RMS-HOA, F.Ele.Th, B.Ele.Th, PPI (min, avg, and max) and BAD-D scores (all) were higher, whereas TP pachymetry and ARTmax were lower in the mild KC-ABCD group than in the control group (Bonferroni correction, p<0.005 for all).

Subclinical KC vs. Mild KC-AK Group

Eyes with subclinical KC had lower Kmean, Kmax, ISV, IVA, KI, CKI, IHA, IHD, I-S, KISA, total RMS, RMS-HOA, F.Ele.Th, B.Ele.Th, PPI (min, avg, and max) and BAD-D scores

Table 1. Comparison of keratometry, pachymetry, topographic indices, inferior-superior asymmetry, KISA, and front/back elevation among the study groups

	Control (A)	Subclinical KC (B)	Mild KC-AK (C)	Mild KC-CLEK (D)	Mild KC-ABCD (E)	p*(KW)	Statistically significant pairwise comparisons (p<0.005) (KW with Bonferroni correction)**
Kmean (D)	43.0±1.3	42.7±1.4	45.8±1.2	42.9±.9	43.4±1.4	<0.0001	C vs. all groups (p<0.0001)
TP (µm)	553.7±30.1	515.8±27.5	464.9±30.9	483.5±33.3	517.7±25.2	<0.0001	A vs. all groups (p<0.0001); B vs. C (p<0.0001) and D (0.002); C vs. E (p<0.0001)
Kmax (D)	44.6±1.9	44.2±1.7	50.9±2.6	46.6±1.7	45.7±1.8	<0.0001	A vs. D (p=0.001); C vs. all groups (p<0.0001); B vs. D (0.001)
ISV	22.2±9.5	20.4±6.9	56.0±22.8	43.0±16.8	33.2±10.2	<0.0001	A vs. C, D (p<0.0001 for both) and E (p=0.001); B vs. C, D and E (p<0.0001 or all); C vs. E (p<0.0001)
IVA	0.10±0.04	0.15±0.07	0.59±0.34	0.51±0.26	0.32±0.09	<0.0001	A vs. B (p=0.004), C, D and E (p<0.0001 for all); B vs. C, D and E (p<0.0001 for all); C vs. E (p=0.001)
KI	1.02±0.02	1.03±0.02	1.14±0.08	1.09±0.06	1.04±0.04	<0.0001	A vs. C and D (p<0.0001 for both); B vs. C (p<0.0001) and D (p=0.003); C vs. D (p=0.002) and E (p<0.0001)
Center KI	1.01±0.01	1.01±0.01	1.03±0.02	1.01±0.01	1.01±0.01	<0.0001	A vs. C (p<0.0001); C vs. all groups (p<0.0001)
IHA	4.71±3.78	5.49±4.33	25.37±18.69	22.14±20.39	14.65±9.50	<0.0001	A vs. C, D (p<0.0001 for both) and E (p=0.001); B vs. C, D and E (p<0.0001 for all)
IHD	0.01±0.01	0.01±0.01	0.07±0.05	0.05±0.03	0.03±0.01	<0.0001	A vs. C, D (p<0.0001 for both) and E (p=0.001); B vs. C, D and E (p<0.0001 for all); C vs. E (p<0.0001)
Rmin (mm)	7.49±0.85	7.65±0.29	6.64±0.34	7.24±0.27	7.39±0.29	<0.0001	A vs. D (p<0.0001); B vs. D (p<0.0001); C vs. all groups (p<0.0001)
I-S (D)	0.06±0.51	0.26±0.54	3.78±2.76	2.79±1.83	0.84±1.60	<0.0001	A vs. C and D (p<0.0001 for both); B vs. C and D (p<0.0001 for both); C vs. E (p<0.0001)
KISA (%)	3.24±2.0	10.70±11.4	228.25±307.19	136.27±164.93	35.77±22.13	<0.0001	A vs. all groups (p<0.0001); B vs. C, D and E (p<0.0001 for all); C vs. E (p=0.004)
F.Ele.Th (µm)	2.84±1.66	3.29±1.46	13.93±6.57	10.61±6.21	5.87±2.95	<0.0001	A vs. C, D and E (p<0.0001 for all); B vs. C, D (p<0.0001 for both) and E (p=0.001); C vs. E (p<0.0001)
B.Ele.Th (µm)	6.31±2.78	8.04±3.00	34.69±12.93	32.61±17.60	13.87±7.10	<0.0001	A vs. C, D and E (p<0.0001); B vs. C and D (p<0.0001); C vs. E (p<0.0001); D vs. E (p<0.0001)

All values given as mean ± standard deviation. *KW: Kruskal-Wallis test (used to compare Pentacam parameters among the 5 groups; p<0.05 was accepted as statistically significant); **p<0.005 was accepted as statistically significant for pairwise comparisons after Bonferroni correction (Mann-Whitney U test)

(all) but higher TP pachymetry, Rmin, ARTmax, and vertical coma aberration RMS values compared to eyes with mild KC-AK (Bonferroni correction, p<0.005 for all).

Subclinical KC vs. Mild KC-CLEK Group

In the subclinical KC group, Kmax, ISV, IVA, KI, IHA, IHD, I-S, KISA, total RMS, RMS-HOA, F.Ele.Th, B.Ele.Th, PPI (min, avg, and max), Db, Dp, Dt, Da and D final scores were lower while TP pachymetry, Rmin, ARTmax, and vertical coma aberration RMS values were higher than in the mild KC-CLEK group (Bonferroni correction, p<0.005 for all).

Subclinical KC vs. Mild KC-ABCD Group

The subclinical KC group had lower ISV, IVA, IHA, IHD, KISA, total RMS, RMS-HOA, F.Ele.Th, Db, and D final values when compared to the mild KC-ABCD group (Bonferroni correction, p<0.005 for all).

Mild KC-AK vs. Mild KC-CLEK Group

Kmean, Kmax, KI, CKI, total RMS, Df, Db, and D final scores were significantly higher in the mild KC-AK group than in the mild KC-CLEK group (p<0.005), whereas Rmin and spherical aberration RMS values were lower in the mild KC-AK group (Bonferroni correction, p<0.005 for all).

Mild KC-AK vs. Mild KC-ABCD Group

Eyes with mild KC-AK had higher Kmean, Kmax, ISV, IVA, KI, CKI, IHD, I-S, KISA, total RMS, RMS-HOA, F.Ele. Th, B.Ele.Th, PPI (min, avg, and max) and BAD-D scores (all) but lower TP pachymetry, Rmin, ARTmax, and vertical coma aberration RMS values when compared to eyes with mild KC-ABCD (Bonferroni correction, p<0.005 for all).

Table 2. Comparison of corneal aberrometry, progression index, Ambrósio Relational Thickness and Belin/Ambrósio Enhanced Ectasia Display scores among the study groups

	Control (A)	Subclinical KC (B)	Mild KC-AK (C)	Mild KC-CLEK (D)	Mild KC-ABCD (E)	p* (KW)	Statistically significant pairwise comparisons (p<0.005) (KW with Bonferroni correction)**
RMS-total (µm)	1.97±1.11	1.26±0.60	4.94±2.44	3.37±1.90	2.41±1.34	<0.0001	A vs. C (p<0.0001) and D (p=0.001); B vs. C (p<0.0001), D (p=0.001) and E (p<0.0001); C vs. D (p=0.001) and E (p<0.0001)
RMS-HOA (µm)	0.26±0.13	0.28±0.11	1.29±0.77	0.90±0.52	0.63±0.22	<0.0001	A vs. C, D and E (p<0.0001 for all); B vs. C, D and E (p<0.0001 for all); C vs. E (p<0.0001)
Spherical aberration (µm)	0.14±0.07	0.09±0.07	-0.03±0.23	0.13±0.15	0.12±0.11	<0.0001	A vs. B and C (p<0.0001 for both); C vs. D (p=0.001)
Vertical coma (µm)	-0.01±0.12	-0.06±0.13	-1.01±0.76	-0.69±0.52	-0.17±0.43	<0.0001	A vs. C and D (p<0.0001 for both); B vs. C and D (p<0.0001); C vs. E (p<0.0001)
PPI-min	0.68±0.10	0.77±0.13	1.28±0.36	1.25±0.36	0.78±0.11	<0.0001	A vs. B (p=0.002), C, D (p<0.0001 for both) and E (p=0.004); B vs. C and D (p<0.0001); C vs. E (p<0.0001); D vs. E (p<0.0001)
PPI-avg	0.96±0.10	1.09±0.19	1.74±0.35	1.66±0.34	1.13±0.13	<0.0001	A vs. B (p=0.002), C, D and E (p<0.0001 for all); B vs. C and D (p<0.0001); C vs. E (p<0.0001); D vs. E (p<0.0001)
PPI-max	1.20±0.15	1.49±0.32	2.56±0.62	2.43±0.51	1.57±0.25	<0.0001	A vs. B, C, D and E (p<0.0001 for all); B vs. C and D (p<0.0001); C vs. E (p<0.0001); D vs. E (p<0.0001)
ARTmax	465.2±70.7	362.8±88.0	190.7±53.7	209.3±52.0	338.0±56.8	<0.0001	A vs. all (p<0.0001); B vs. C and D (p<0.0001); C vs. E (p<0.0001); D vs. E (p<0.0001)
BAD-Df	0.09±0.79	0.77±0.68	5.24±3.00	2.85±1.76	2.04±1.48	<0.0001	A vs. B, C, D and E (p<0.0001 for all); C vs. all groups (p<0.0001)
BAD-Db	-0.26±0.58	0.06±0.81	4.53±2.54	2.88±1.45	1.10±0.87	<0.0001	A vs. C, D and E (p<0.0001 for all); C vs. all groups (p<0.0001); B vs. D (p=0.001) and E (p=0.001)
BAD-Dp	0.35±0.65	1.28±1.25	5.68±2.39	5.08±2.32	1.51±0.90	<0.0001	A vs. B (p=0.001), C, D and E (p<0.0001 for all); B vs. C and D (p<0.0001); C vs. E (p<0.0001); D vs. E (p<0.0001)
BAD-Dt	-0.36±0.86	0.71±0.89	2.51±1.18	1.81±1.20	0.63±0.75	<0.0001	A vs. B, C, D and E (p<0.0001 for all); B vs. C (p<0.0001) and D (p=0.002); C vs. E (p<0.0001)
BAD-Da	0.21±0.65	1.15±0.80	2.70±0.46	2.55±0.48	1.37±0.52	<0.0001	A vs. B, C, D and E (p<0.0001 for all); B vs. C and D (p<0.0001 for both); C vs. E (p<0.0001); D vs. E (p<0.0001)
BAD-D final	0.81±0.52	1.60±0.78	5.83±1.81	4.54±1.25	2.36±0.51	<0.0001	A vs. B, C, D and E (p<0.0001 for all); C vs. all groups (p<0.0001); B vs. D (p=0.001) and E (p=0.002); D vs. E (p<0.0001)

All values given as mean ± standard deviation. *Kruskal-Wallis test (used to compare Pentacam parameters among the 5 groups; p<0.05 was accepted as statistically significant); **p<0.005 was accepted as statistically significant for pairwise comparisons after Bonferroni correction (Mann-Whitney U test)

Mild KC-CLEK vs. Mild KC-ABCD Group

B.Ele.Th, PPI (min, avg, and max), Dp, Da, and D final values were higher and ARTmax was lower in the mild KC-CLEK group than in the mild KC-ABCD group (Bonferroni correction, p<0.005 for all).

The full range of data for pairwise comparisons is provided in Tables 1 and 2.

Diagnostic Ability of Pentacam Parameters

Discrimination of Subclinical KC from Normal

ARTmax, TP pachymetry, Dt, Da, D final, PPI-max, spherical aberration, KISA, Df, KI, IVA, and Dp had good to fair diagnostic ability in distinguishing subclinical KC from normal (listed from highest to lowest AUC, ranging from 0.831 to 0.702, p<0.05) (Table 3 and Figure 2). The DeLong test revealed no statistically significant differences in diagnostic power of AUC values for subclinical KC among the best-performing (AUC >0.800) Pentacam parameters (ARTmax, TP pachymetry, Dt, and Da) (p=0.970).

Discrimination of Mild KC-AK from Normal

D final, ARTmax, Da, Db, PPI-max, IVA, Dp, PPI-avg, B.Ele.Th, HOA, PPI-min, KISA, Df, F.Ele.Th, TP pachymetry, Dt, IHD, KI, vertical coma, I-S, ISV, Kmax, Rmin, IHA, Rmin, total RMS, Km, CKI, and spherical aberration RMS value had AUC values ranging from 0.999 to 0.724 (listed from highest to lowest, p<0.05) in the diagnosis of mild KC-AK.

Table 3. Diagnostic ability of Pentacam parameters in distinguishing subclinical KC and mild KC (based on AK classification) from normal based on the receiver operating characteristic analysis

	Subclinical KC vs. control				Mild KC-AK vs. control			
	AUC	Sensitivity and specificity (%)	Cut-off value	p*	AUC	Sensitivity/ specificity (%)	Cut-off value	p*
Kmean (D)	<0.700	NA	NA	p>0.05	0.819	74.8/70	≥43.8	<0.0001
TP pachymetry (µm)	0.828	87.0/71.4	≤544	<0.0001	0.956	87.8/90	≤506.5	<0.0001
Kmax (D)	<0.700	NA	NA	p>0.05	0.909	84.4/88.6	≥46.2	<0.0001
ISV	<0.700	NA	NA	p>0.05	0.915	80.3/81.4	≥31.5	<0.0001
IVA	0.714	NA	NA	0.003	0.988	98/95.7	≥0.165	<0.0001
KI	0.727	NA	NA	0.001	0.943	87.8/92.9	≥1.045	<0.0001
Center KI	<0.700	NA	NA	p>0.05	0.781	NA	NA	<0.0001
IHA	<0.700	NA	NA	p>0.05	0.884	81/84.3	≥8.15	<0.0001
IHD	<0.700	NA	NA	p>0.05	0.949	91.8/94.3	≥0.019	<0.0001
Rmin (mm)	<0.700	NA	NA	p>0.05	0.906	83.7/90	≤7.245	<0.0001
I-S asymmetry (D)	<0.700	NA	NA	p>0.05	0.935	90.5/82.9	≥0.605	<0.0001
KISA (%)	0.757	NA	NA	<0.0001	0.966	89.8/100	≥8.83	<0.0001
RMS-total (µm)	<0.700	NA	NA	p>0.05	0.839	74.8/70	≥2.585	<0.0001
RMS-HOA (µm)	<0.700	NA	NA	p>0.05	0.969	93.2/94.3	≥0.365	<0.0001
Spherical aberration (µm)	0.762	NA	NA	<0.0001	0.724	NA	NA	<0.0001
Vertical coma (µm)	<0.700	NA	NA	p>0.05	0.934	85.7/95.7	≤ -0.226	<0.0001
F.Ele.Th (µm)	<0.700	NA	NA	p>0.05	0.962	87.8/95.7	≥5.50	<0.0001
B.Ele.Th (µm)	<0.700	NA	NA	p>0.05	0.983	93.2/100	≥13.50	<0.0001
PPI-min	<0.700	NA	NA	p>0.05	0.966	91.2/97.1	≥0.835	<0.0001
PPI-avg	<0.700	NA	NA	p>0.05	0.986	93.2/100	≥1.155	<0.0001
PPI-max	0.777	NA	NA	<0.0001	0.988	93.2/100	≥1.525	<0.0001
ARTmax	0.831	83.3/74.3	≤424	<0.0001	0.990	93.2/100	≤329.50	<0.0001
BAD-Df	0.756	NA	NA	<0.0001	0.963	91.2/88.6	≥0.960	<0.0001
BAD-Db	<0.700	NA	NA	p>0.05	0.990	91.8/100	≥0.985	<0.0001
BAD-Dp	0.702	NA	NA	0.004	0.987	93.2/100	≥1.680	<0.0001
BAD-Dt	0.820	87/70	≥-0.165	<0.0001	0.952	86.4/90	≥1.00	<0.0001
BAD-Da	0.817	82.6/74.3	≥0.585	<0.0001	0.990	92.5/100	≥1.475	<0.0001
BAD-D final	0.788	NA	NA	<0.0001	0.999	98/100	≥1.985	<0.0001

*p<0.05 indicates statistical significance. NA: Not analyzed (sensitivity and specificity values not presented for variables with a p value >0.05 and AUC <0.800)

Discrimination of Mild KC-CLEK from Normal

D final, KISA, Db, ARTmax, Da, PPI-max, IVA, Dp, PPI-avg, B.Ele.Th, Df, HOA, IHD, F.Ele.Th, PPI-min, TP pachymetry, Dt, I-S, KI, vertical coma, ISV, IHA, Kmax and Rmin had excellent to fair ability to discriminate mild KC-CLEK from normal (listed from highest to lowest AUC, ranging from 0.997 to 0.715, p<0.05) (Table 4 and Figure 3).

Discrimination of Mild KC-ABCD from Normal

IVA, KISA, D final, HOA, IHD, Da, ARTmax, Db, PPI-max, Df, Dp, IHA, PPI-avg, B.Ele.Th, F.Ele.Th, TP pachymetry, Dt, ISV, PPI-min, and KI had AUC values ranging from 0.998 to 0.722 (listed from highest to lowest, p<0.05) in distinguishing mild KC-ABCD from normal.

Discussion

The current study provides a comprehensive re-evaluation of Pentacam parameters in the diagnosis of mild and subclinical KC, also comparing with the earlier publications that utilized a variety of patient selection criteria and definitions. This study demonstrated that the efficacy of Pentacam parameters in diagnosing mild KC was influenced by differences in the "mild KC" criteria between the AK and CLEK classification systems. The present study also demonstrated the performance of Pentacam metrics in identifying eyes with KC that were classified as stage 0 by the Belin ABCD progression display.[14,17,18]

This study showed that among the Pentacam parameters, ARTmax had the highest individual performance in

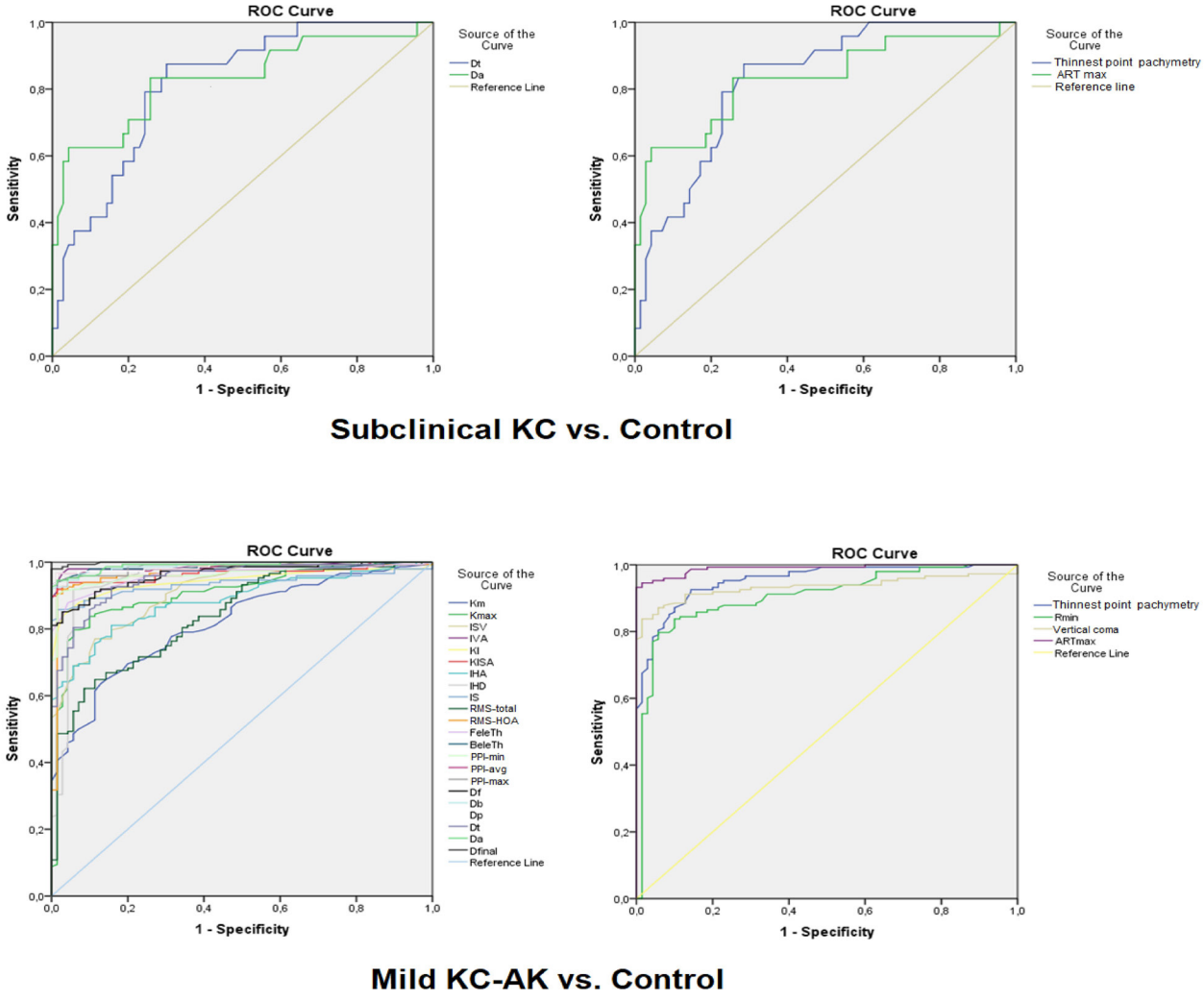

Figure 2. AUC presenting sensitivity and 1-specificity values for Pentacam parameters that had an AUC value over 0.800 in the diagnosis of subclinical KC (top), and mild KC based on the AK classification system (bottom)

distinguishing eyes with subclinical KC from normal (83.3% sensitivity and 74.3% specificity), followed by TP pachymetry, Dt, and Da. However, D final, KISA, I-S, topometric indices, corneal aberrations, and elevation values had no or poor utility in the detection of subclinical KC. In contrast, most of the Pentacam parameters showed highly satisfying performance in the diagnosis of mild KC, although the most powerful Pentacam parameters and their sensitivity/specificity differed depending on the definition of "mild KC" used. For instance, final D score showed excellent performance in the detection of mild KC based on both the AK (98% sensitivity and 100% specificity) and CLEK (97.4% sensitivity and 100% specificity) definitions when the threshold value was ≥1.985. However, when the ABCD stage 0 descriptors were used, IVA accurately detected all eyes (100%) with KC and 97.1% of the normal eyes, for which D final had 93.3% sensitivity and 95.7% specificity. It should also be noted that ARTmax, KISA, IVA, IHD, RMS-HOA, Da, Db, and PPI-max were the common (for all mild KC-AK, -CLEK and -ABCD groups) powerful Pentacam parameters that showed very high performance (AUC>0.900) in the diagnosis of mild KC.

In agreement with the most common definitions of subclinical KC, all eyes in our subclinical KC group had 20/20 corrected vision and normal biomicroscopy, keratometry, and pachymetry but subtle tomographical alterations not reaching the threshold for KC diagnosis.[7,8,9] Therefore, the subclinical KC group in the current study was able to represent real-world risky cases for laser refractive surgery.

In the present study, ARTmax, TP pachymetry, Dt, and Da had the best sensitivity and specificity values (range: 82.6%-87% and 70%-74.3%, respectively) in subclinical KC detection. Interestingly, these parameters were all associated with corneal thickness and its distribution, suggesting that corneal thickness-related Pentacam data might be particularly useful in the diagnosis of subclinical KC. The sensitivity and specificity values for the Pentacam parameters found in this study were

Table 4. Diagnostic value of Pentacam parameters in diagnosis of mild keratoconus based on the CLEK and Belin ABCD classification systems based on the receiver operating characteristic analysis

	Mild KC-CLEK vs. control				Mild KC-ABCD vs. control			
	AUC	Sensitivity and specificity (%)	Cut-off value	p*	AUC	Sensitivity and specificity (%)	Cut-off value	p*
Kmean (D)	<0.700	NA	NA	p>0.05	<0.700	NA	NA	p>0.05
TP pachymetry (µm)	0.904	87.2/85.7	≤518	<0.0001	0.815	80/78.6	≤530.5	<0.0001
Kmax (D)	0.721	NA	NA	<0.0001	<0.700	NA	NA	p>0.05
ISV	0.854	87.2/70	≥27.50	<0.0001	0.786	NA	NA	0.001
IVA	0.978	92.3/100	≥0.220	<0.0001	0.998	100/97.1	≥0.175	<0.0001
KI	0.875	82.1/82.9	≥1.035	<0.0001	0.722	NA	NA	0.007
Center KI	<0.700	NA	NA	p>0.05	<0.700	NA	NA	p>0.05
IHA	0.833	82.1/73.9	≥6.65	<0.0001	0.868	86.7/72.9	≥6.75	<0.0001
IHD	0.930	89.7/94.3	≥0.019	<0.0001	0.931	86.7/92.9	≥0.017	<0.0001
Rmin (mm)	0.715	NA	NA	<0.0001	<0.700	NA	NA	p>0.05
I-S asymmetry (D)	0.886	74.4/100	≥1.025	<0.0001	<0.700	NA	NA	p>0.05
KISA (%)	0.993	94.9/100	≥8.83	<0.0001	0.997	100/95.7	≥6.95	<0.0001
RMS-Total (µm)	<0.700	NA	NA	p>0.05	<0.700	NA	NA	p>0.05
RMS-HOA (µm)	<0.700	NA	NA	p>0.05	<0.700	NA	NA	p>0.05
Spherical aberration (µm)	0.940	87.2/98.6	≥0.474	<0.0001	0.974	93.3/94.3	≥0.365	<0.0001
Vertical coma (µm)	<0.700	NA	NA	p>0.05	<0.700	NA	NA	p>0.05
F.Ele.Th (µm)	0.862	79.5/95.7	≤ -0.226	<0.0001	<0.700	NA	NA	p>0.05
B.Ele.Th (µm)	0.929	76.9/95.7	≥5.50	<0.0001	0.827	86.7/70	≥3.50	<0.0001
PPI-min	0.963	84.6/100	≥14.00	<0.0001	0.829	73.3/90	≥9.50	<0.0001
PPI-avg	0.906	76.9/97.1	≥0.835	<0.0001	0.735	NA	NA	0.004
PPI-max	0.968	92.3/90	≥1.075	<0.0001	0.860	73.3/90	≥1.075	<0.0001
ARTmax	0.980	89.7/95.7	≥1.455	<0.0001	0.907	86.7/80	≥1.330	<0.0001
BAD-Df	0.983	87.2/98.6	≤344.5	<0.0001	0.921	93.3/81.4	≤396	<0.0001
BAD-Db	0.944	84.6/87.1	≥0.925	<0.0001	0.892	86.7/82.9	≥0.775	<0.0001
BAD-Dp	0.988	94.9/92.9	≥0.700	<0.0001	0.909	86.7/81.4	≥0.280	<0.0001
BAD-Dt	0.970	92.3/92.9	≥1.195	<0.0001	0.869	73.3/92.9	≥1.195	<0.0001
BAD-Da	0.897	87.2/84.3	≥0.585	<0.0001	0.801	80/77.1	≥0.210	<0.0001
BAD-D final	0.983	89.7/95.7	≥1.185	<0.0001	0.921	86.7/85.7	≥0.935	<0.0001

*p<0.05 indicates statistical significance. NA: Not analyzed (sensitivity and specificity values not presented for variables with a p value >0.05 and AUC <0.800)

similar to those reported in published studies on subclinical KC diagnosis, which were summarized as follows: 82%-90.5% and 70%-86.5% for ARTmax, 89.2% and 90.3% for Da, and 52.6%-95.5% and 32.4%-94.1% for D final (Supplementary Table S1).[3,10,11,12,13,19,20,21,22,23,24,25] On the other hand, it can be seen in Supplementary Table S1 that there were overlaps among the criteria for "subclinical KC" and "mild KC". For instance, Heidari et al.[3] included clinically normal eyes with anterior elevation >12 µm, posterior elevation >17 µm, SRAX <20, Kmax >47.2 D (but <48.7 D) and I-S value >1.4 D (but <1.9 D) at the 3-mm radii as subclinical KC, whereas these criteria practically describe mild KC without biomicroscopic findings.

However, it should be pointed out that the present study and related literature review mainly focused on the individual performance of Pentacam parameters in the diagnosis of subclinical and mild KC. Therefore, we do not discuss the topography-based multifactorial regression formulas introduced in previous studies or parameters from other imaging modalities. Nevertheless, it is obvious from the published literature that corneal epithelial imaging, corneal biomechanical measurements (i.e., CorVis ST, Oculus Inc.® and Ocular Response Analyzer, ORA, Reicherts®) and 3-D morphovolumetric analysis have significant value in diagnosing subclinical KC in addition to corneal topography/tomography.[4,5,6,23,26,27,28,29,30]

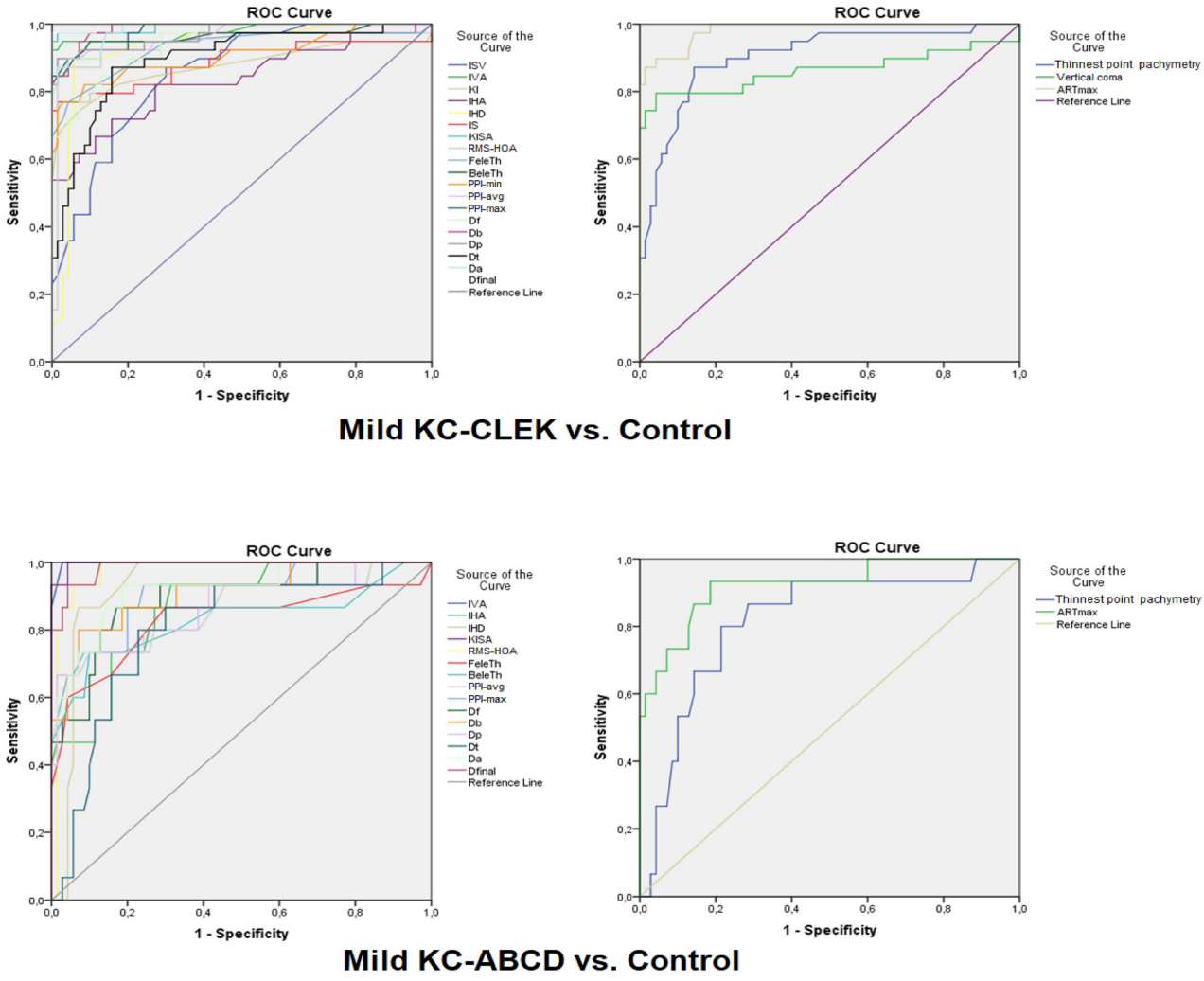

Figure 3. Sensitivity and 1-specificity values for Pentacam parameters that had an AUC value over 0.800 in distinguishing mild KC based on the CLEK (top) and Belin ABCD (bottom) classification system criteria

In terms of mild KC diagnosis, the majority of studies in the current literature used the AK stage 1 KC criteria, and excellent to good sensitivity/specificity was observed for F.Ele.Th (sensitivity/specificity: 97.8%/94.8%), B.Ele.Th (100%/99.4%), D final (98%-100%/95.9%-100%), IVA (97.8%/95.8%), KI (93.3%/97.9%), and PPI values (Supplementary Table S2).[14,22,27,29,31] These values were very similar to those found in the present study in the diagnosis of mild KC based on the AK, CLEK, and ABCD criteria (sensitivity/specificity ranged from 87.2% to 97.4%/92.9% to 100%). These results might indicate that Pentacam parameters are able to detect an eye with mild KC with high sensitivity regardless of the presence of biomicroscopic signs.

Regarding the "mild" KC-ABCD group in the current study, the ABCD system was actually developed by Belin and Duncan[18] to track KC progression, and stage 0 theoretically describes "normal" eyes. However, we detected 15 eyes with mild KC (all had typical topographical map patterns for KC and the contralateral eye had manifest KC) that were labelled as "stage 0" by the Pentacam ABCD system in our database. These eyes were also included in the present study as the "mildest" KC stage for the ABCD grading system instead of using cases with ABCD stage 1 KC, since Belin and Duncan[18] already reported that ABCD stages 1-4 were closely matched with the AK stages 1-4 in terms of anterior curvature. However, assuming "stage 0" as the mildest grade in the ABCD system may have led to the selection of milder KC cases compared to the mild KC-AK and -CLEK groups. Therefore, the diagnostic performance of the Pentacam parameters might have been underestimated in the mild KC-ABCD group. On the other hand, although the size of the mild KC-ABCD group was relatively small due to its rarity, to our knowledge there is no other study testing the diagnostic performance of Pentacam parameters in the detection of keratoconic eyes categorized as "ABCD stage 0." One exception is a study by Zhang et al.,[28] who used the ABCD stage 0 criteria as "topographic normality" for their forme fruste

KC group, which could have led to the inaccurate classification of keratoconic eyes as normal.

Study Limitations

The relatively small number of cases in the subclinical KC group might be considered a limitation of the current study. This study also did not include eyes with "forme fruste KC," which in the majority of the existing literature describes "a clinically and topographically normal eye with manifest KC in the contralateral eye." The term "forme fruste" was first proposed by Amsler[9] to define unilateral cases as an incomplete, abortive, or atypical form of KC. This conclusion was made mostly due to the fact that unilateral KC is genetically described as a form of autosomal dominant transmission with complete penetrance but partial expression, and if individuals are followed for long enough, the opposite eye may eventually show evidence of KC. In 2015, the Global Consensus on Keratoconus and Ectatic Diseases agreed that environmental, biomechanical, genetic, and biochemical anomalies all contribute to the pathogenesis of KC and true unilateral KC does not exist. However, a recent report by Saad et al.[32] presented a case of stable "unilateral KC" with the longest follow-up period of 14 years.

Conclusion

As a result of the non-uniform definitions and selection criteria employed in the literature, sensitivity and specificity values show substantial variation in the diagnosis of "subclinical KC." The current study revealed that corneal thickness-related Pentacam parameters might have value for detecting subclinical KC. However, even with this sophistication, Pentacam has modest capability in the diagnosis of subclinical KC, and further approaches such as corneal biomechanical assessment, epithelial mapping, and 3-D morphovolumetric analysis, which provide robust data on subclinical alterations in the cornea, appear to be necessary.[4,5,6,23,26,27,28,29,30]

On the other hand, this study also confirmed that Pentacam is able to detect eyes with mild KC with high accuracy, despite the fact that the most powerful parameters have varying specificities and sensitivities depending on the "mild KC" criteria used. Nevertheless, definitive and objective criteria for grading subclinical and clinical KC are essential to attain a global consensus regarding the early diagnosis and management of KC, and clinicians should follow a multi-diagnostic strategy rather than relying solely on Pentacam data prior to corneal refractive surgery.

Abbreviations

ABCD: Belin ABCD classification system, AK: Amsler-Krumeich classification, ARC: Anterior average radii of curvature, ART: Ambrósio Relational Thickness, AUC: Area under the receiver operating characteristic curve, BAD-D: Belin/Ambrósio Enhanced Ectasia Display scores (Df, Db, Dp, Dt, Da, and D final), B.Ele.Diff: Back elevation difference, B.Ele.Th: Back elevation at the thinnest point, CDVA: Corrected distance visual acuity, CLEK: Collaborative Longitudinal Evaluation of Keratoconus study, D: Diopters, F.Ele.Diff: Front elevation difference, F.Ele.Th: Front elevation at the thinnest point, HOA: Higher-order aberrations, IHA: Index of height asymmetry, IHD: Index of height decentration, I-S: Inferior-superior keratometric difference at 3-mm radii, ISV: Index of surface variance, IVA: Index of vertical asymmetry, K: Keratometry, KC: Keratoconus, KI: Keratoconus index, KISA: KC percentage index, LogMAR: Logarithm of the minimal angle of resolution, PPI: pachymetric progression index, PRC: Posterior average radii of curvature, Rmin: Minimum radius of curvature, RMS: Root mean square, SRAX: Skewed radial axes, ST-IN: Superotemporal-inferonasal asymmetry, TKC: Topographical Keratoconus Classification, TP: Thinnest point, Kmax: Maximum keratometry, SD: Standard deviation

Ethics

Ethics Committee Approval: The Pamukkale University Non-Interventional Clinical Research Ethics Committee approved the study protocol (decision no: 23, date: 08.12.2020).

Informed Consent: Retrospective study. Consent for all procedures was obtained in advance.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: İ.T., J.A., C.E.G., Design: İ.T., J.A., Data Collection or Processing: İ.T., C.M., C.E.G., Analysis or Interpretation: İ.T., J.A., Literature Search:. İ.T., C.M., C.E.G., Writing: İ.T.

Conflict of Interest: The authors declare no financial or proprietary interest in any product or company associated with any device, instrument or drug mentioned in this article.

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