Combined biomechanical and tomographic keratoconus staging: Adding a biomechanical parameter to the ABCD keratoconus staging system

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ABSTRACT.

Purpose: **This retrospective cross-sectional study evaluated the potential of an additional biomechanical parameter 'E' as an addition to the tomographic ABCD ectasia/keratoconus (KC) staging.**

Methods: **The Corvis Biomechanical Factor (CBiF) represents the modified linear term of the Corvis Biomechanical Index (CBI) developed based on 448 KC corneas from the Homburg Keratoconus Center (HKC). The CBiF range was divided into five stages (E0 to E4) to create a grading system according to the ABCD stages. Stage E0 was characterized by values smaller than the 2.5 percentile. The thresholds were created by dividing the CBiF range between the 2.5 and 97.5 percentiles into four groups of equal values (E1–E4). The frequency distribution of 'E' was analysed and independently validated based on another 860 KC corneas dataset from Milano and Rio de Janeiro (MR). The relationship between 'E' and the ABCD staging was analysed by cross-tabulation. The specificity of 'E' was assessed based on healthy controls (112|851) from both datasets (HKC|MR).**

Results: **'E' was normally distributed with E0 = 37|30, E1 = 86|200, E2 = 155|354, E3 = 101|206, E4 = 69|70 in the KC group and 96.4%|90.5% of the controls classified E0 in the HKC|MR dataset, respectively. Cross-tabulation revealed that 'E' was most comparable to posterior corneal curvature ('B') in both datasets, while showing a trend towards more advanced stages in comparison to anterior corneal curvature ('A') and thinnest corneal thickness ('C').**

Conclusion: **The novel Corvis-derived parameter 'E' provides a biomechanical staging for ectasia/KC potentially enhancing the ABCD staging and may detect abnormalities before tomographic changes, which requires further studies.**

Key words: ABCD grading – biomechanics – Corvis Biomechanical Index – correlation – Corvis – keratoconus – tomography

Elias Flockerzi and Riccardo Vinciguerra contributed equally to this work and should be considered as equal first authors.

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Introduction

Keratoconus (KC) is a bilateral asymmetric corneal ectasia characterized by a biomechanical corneal destabilization (Ambrósio et al. 2017). This results in decreased corneal resistance to deformation, which has been attributed to a reduced corneal volume with altered proteoglycan content, reduced keratocyte (Ali et al. 2014) and nerve fibre density (Flockerzi et al. 2020), less collagen lamellae (Chan et al. 2018) and endothelial alterations (Goebels et al. 2018).

One available tomographic KC analysis is based on the Belin/Ambrósio-enhanced ectasia display and the ABCD KC classification according to Belin and Duncan (Belin et al. 2015, 2017; Belin & Duncan 2016; Flockerzi et al. 2021a). This classification includes the stages 0 to 4 for each of the parameters: 'A' for anterior, 'B' for posterior radius of curvature (taken from a 3.0 mm optical zone centred on the thinnest corneal point), 'C' for thinnest corneal thickness and 'D' for best spectacle-corrected distance visual acuity ('D').

The Corneal Scheimpflug Visualization Technology (Corvis ST®, CST, Oculus, Wetzlar, Germany) measures the corneal deformation after the application of a standardized air puff

(Vinciguerra et al. 2016; Ambrósio et al. 2017) and has been shown to detect biomechanical abnormalities in early or subclinical KC (Elham et al. 2017; Vinciguerra et al. 2017). Although recent studies reporting on correlations between biomechanical and tomographic indices raised the question about a KC classification based on corneal biomechanical indices (Shen et al. 2019; Koh et al. 2020), a concomitant tomographic and biomechanical staging of KC grades has not been established yet (Shetty et al. 2015).

The Corvis Biomechanical Index (CBI) incorporates a number of different biomechanical parameters and is useful in differentiating KC from normal corneas (Reisdorf 2019; Langenbucher et al. 2020). The study that introduced the CBI stated a 100% specificity and 94.1% sensitivity of the CBI in diagnosing KC in the training dataset (n = 329 corneas of 227 healthy controls and 102 KC patients) and a 98.4% specificity and 100% sensitivity in the validation dataset (n = 329 corneas of 251 healthy and 78 KC patients, Vinciguerra et al. 2016; Reisdorf 2019). However, they did not include subclinical KC forms. One previous study analysed the CBI in relation to the topographical KC classification (TKC): The CBI was close to 0 in healthy controls (mean ± SD: 0.12 ± 0.16) and close to 1 in TKC2 (0.92 ± 0.21), TKC3 (0.97 ± 0.14) and TKC4 (1.0 ± 0.0). There was a wider spreading in TKC1 (0.46 ± 0.4) and TKC1-2 (0.62 ± 0.39) making the binary decision system of the CBI less informative for these earlier KC stages (Flockerzi et al. 2021b). The Tomographic Biomechanical Index (TBI), that combines the CBI with tomographic data ensured better detection of early KC forms because it was close to 0 in controls and close to 1 in all TKC stages (Flockerzi et al. 2021b). The CBI, however, does not provide information about KC severity. Information on KC severity can be obtained from its linear form, the CBI beta (Koh et al. 2020). The Corvis Biomechanical Factor (CBiF) is a modification of the CBI beta, which was linearly transformed to achieve an intuitive scaling developed based on a collective of 448 KC corneas from 448 Homburg Keratoconus Center (HKC) patients (Flockerzi et al. 2021c).

The purpose of this study was (1) to create a novel biomechanical KC staging parameter 'E' based on the CBiF analogous to the tomographic parameters in the ABCD KC classification and (2) to validate this parameter based on a second KC dataset derived from another location (ophthalmological departments in Milano and Rio de Janeiro (MR)).

Methods

This retrospective cross-sectional study is based upon two independent datasets of KC patients. The first dataset comprises 448 corneas of 448 KC patients and is derived from the HKC in Germany (Flockerzi et al. 2021c). The HKC is a clinical observational trial (trial number NCT03923101, U.S. National Institutes of Health, https://ClinicalTrials.gov) that was approved by the regulatory body, the local ethics committee of Saarland (Ethikkommission bei der Ärztekammer des Saarlandes, reference number 121/20). Each patient in the HKC provided written consent for the analysis of data. The second dataset, which served for validation, comprises 860 corneas of 860 KC patients from two independent centres including KC corneas from the Vincieye Clinic in Milano, Italy, and from the Rio de Janeiro Corneal Tomography and Biomechanics Study Group, Rio de Janeiro, Brazil (MR dataset). The institutional review boards in Milano and Rio de Janeiro decided that the study was exempt; however all participants provided informed consent for using their data and the study was conducted according to the tenets of the Declaration of Helsinki.

In both datasets, patients with previous operations, ocular diseases other than KC and diabetes mellitus were excluded. Keratoconus grading was analysed separately in both datasets based on the ABCD KC classification (Belin & Duncan 2016) and the eye with the more advanced KC stage was included in the KC group. KC was diagnosed (1) based on clinical slit lamp findings (corneal thinning and steepening, Vogt Striae, Fleischer ring, scar formation), (2) posterior elevation at the thinnest point ≥13 µm (based on an 8 mm reference sphere), (3) a thinnest corneal thickness <550 µm and (4) a spherical equivalent <0 (myopic)(Belin et al. 2017). Criteria (2) to (4) had to be met in KC without clinically visible signs. All KC corneas also met the criteria established in the 2015 consensus document on KC and ectatic corneal disease (Gomes et al. 2015).

Pentacam and CST measurements were repeated each time the quality score (QS) showed red. Measurements with a low-quality score, in spite of repeated attempts, were accepted for advanced disease as it is often impossible to obtain acceptable QS in these cases. The Pentacam and CST measurements were exported.

For each cornea, the CBI was transformed to its linear form, the CBI beta (CBI beta = $k_0 + k_1$ x A1 velocity + k_2 x DA ratio 2 mm + k_3 x ARTh + k_4 x SP-A1 + k_5 x integrated radius with $k_0 = 12.693$, $k_1 = -60.556$, $k_2 = 0.639$, $k_3 = -0.011$, $k_4 = -0.0699$, $k_5 = 0.5407$), followed by a linear transformation of the CBI beta resulting in the CBiF (CBiF = −0.24294226 × CBI beta + 6.02) as reported previously (Flockerzi et al. 2021c).

The 2.5 and 97.5 percentiles of the CBiF values were calculated and severity stages of 'E' (E1, E2, E3 and E4) were defined as CBiF ranges of equal partitions ranging from the 2.5 percentile to the 97.5 percentile to achieve a biomechanical staging parameter 'E' analogous to the tomographic parameters 'A', 'B' and 'C' included in the ABCD KC classification system (Belin et al. 2015). All CBiF values smaller than the 2.5 percentile were defined as stage E0. This new grading system developed based on the HKC dataset was then applied to the MR dataset.

The frequency distribution of 'E' was assessed within both datasets independently and thereafter compared (1) between both datasets and (2) to the respective distributions of the established tomographic 'A', 'B' and 'C' grading. The relationship between the biomechanical staging parameter 'E' and the tomographic parameters 'A', 'B' and 'C' was examined based on cross-tabulation.

The specificity of the biomechanical staging parameter 'E' in detecting normal corneas was assessed based on the data of healthy controls from the HKC and the MR departments. One eye per healthy individual was randomly chosen for analysis. The drafts of the

figures and the statistical analyses were performed using SPSS software (version 20.0; International Business Machines Corporation, Armonk, NY, USA).

Results

The HKC dataset included 448 KC corneas from 448 KC patients (mean age 38 ± 12.4 years) and the Milano/Rio de Janeiro (MR) dataset included 860 KC corneas from 860 KC patients (mean age 29.6 ± 6.7 years). Both datasets cover a wide spectrum of KC severity and the ratio between the right and left eyes was balanced (HKC: 47.5% left eyes, 52.5% right eyes; MR: 49.2% left, 50.8% right eyes).

Table 1. Gates for stages E0, E1, E2, E3 and E4 based on the values of the Corvis Biomechanical Factor (CBiF) in the Homburg Keratoconus Center (HKC) dataset.

Stages of 'E'	CBiF gates	Interval spacing
0	≥5.94	-
1	<5.94–≥ 5.36	0.58
2	<5.36–≥ 4.78	0.58
3	<4.78–≥ 4.20	0.58
4	<4.20	-

In the first step, the CBiF thresholds were calculated in the HKC dataset based on the 2.5 and 97.5 percentiles to define the biomechanical KC stages E1, E2, E3 and E4. CBiF values smaller than the 2.5 percentile were defined as stage E0. An interval spacing of 0.58 was calculated in order to achieve CBiF gates with equal spacing. Table 1 shows the CBiF gates for E0, E1, E2, E3 and E4.

The frequencies of these stages of 'E' were calculated in both datasets (HKC, MR). Figure 1 shows the frequency distributions of the established tomographic ABC stages and the newly developed biomechanical parameter 'E' in both KC datasets.

The 'E' stage was normally distributed in both datasets (Fig. 1a,b). Only 36 KC corneas (8.0%) in the HKC dataset and 30 (3.5%) KC corneas in the MR dataset were classified as stage E0 based on the biomechanical score 'E', respectively (Fig. 1a,b). Based on the tomographic stages, 18.5% of the HKC KC corneas were as classified A0 (MR: 21.4%), 10.3% as B0 (MR: 7.1%) and 22.5% as C0 (MR: 16.9%).

When compared with the tomographic stages 'A' and 'C', the biomechanical parameter 'E' showed a trend towards more severe stages (Fig. 1a,b) in both datasets. Although there were more cases with stage B0 than E0 in each dataset (Fig. 1a,b), the posterior

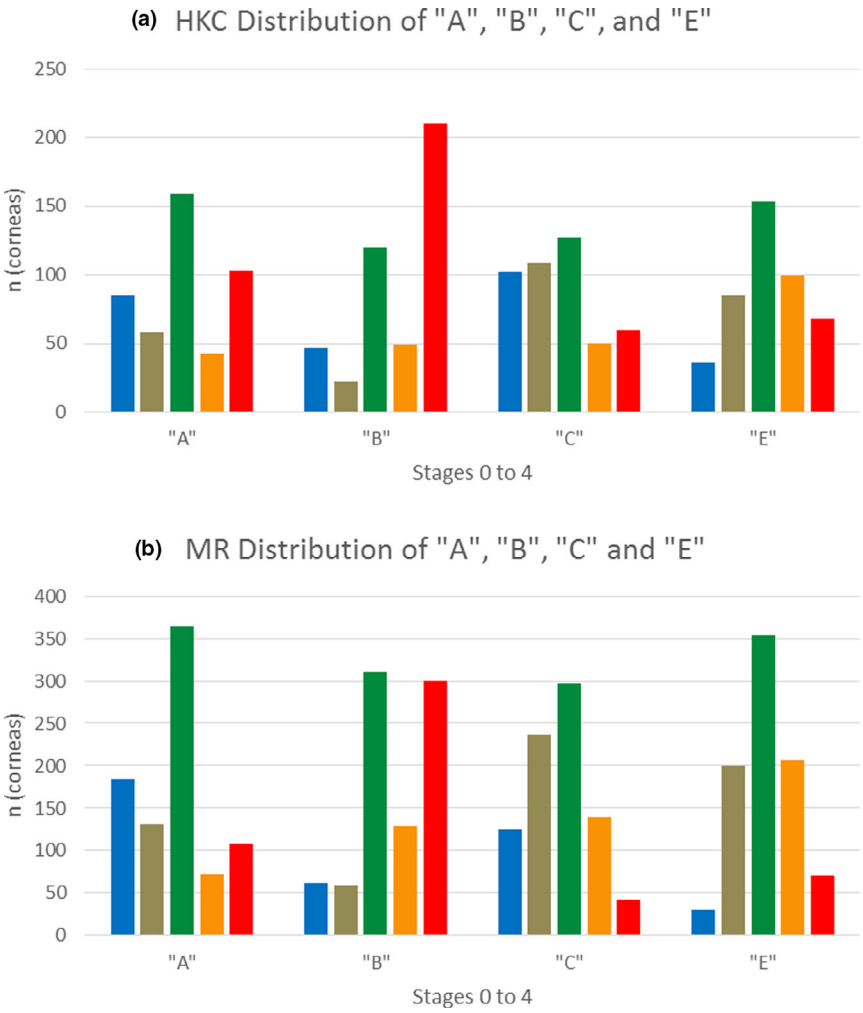

Fig. 1. ABCE KC severity distribution in this study. (a) HKC dataset (n = 448 KC corneas) and (b) Milano/Rio de Janeiro (MR) dataset (n = 860 KC corneas). Blue, stage 0; brown, stage 1; green, stage 2; yellow, stage 3; red, stage 4. 'A', anterior radius of curvature; 'B', posterior radius of curvature; 'C', thinnest corneal thickness; 'E' new biomechanical grading.

corneal surface staging 'B' showed an overall trend towards even more severe stages than the biomechanical staging 'E'.

Cross-tabulation between biomechanical stages and tomographic stages

Next, a cross-tabulation between the stages of 'E' and the stages of 'A', 'B' and 'C' was performed to analyse the relationship between the biomechanical staging 'E'and the tomographic ABC classification. Figure 2 shows the frequency distribution for 'E' in dependency of each stage of 'A' (Fig. 2a,b), each stage of 'B' (Fig. 2c,d) and each stage of 'C' (Fig. 2e,f).

The relative frequencies of (1) similar stages of 'E' compared with 'A', 'B' and 'C', (2) more severe stages of 'E' compared with 'A', 'B' and 'C' and (3) less severe stages of 'E' compared with 'A', 'B' and 'C' were calculated to summarize the results of the cross-tabulation.

The results of this analysis are summarized in Table 2.

The biomechanical staging 'E' showed the highest agreement with

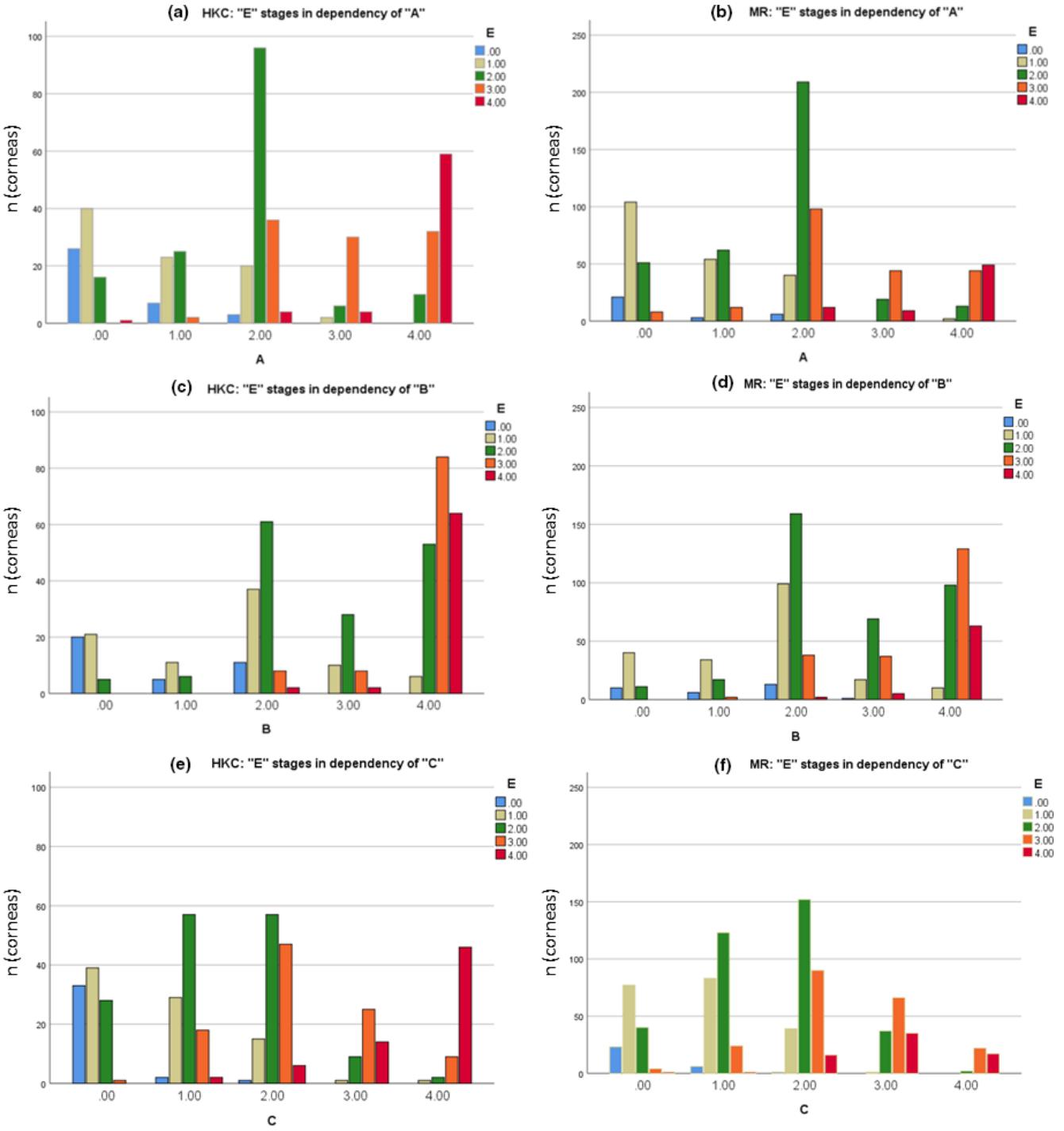

Fig. 2. Stages of 'E' in dependency of the tomographic parameters A0–A4, B0–B4 and C0–C4 in the Homburg Keratoconus Center (HKC) dataset (n = 448 KC corneas; a, c, e) and in the Milano/Rio de Janeiro (MR) dataset (n = 860 KC corneas; b, d, f).

the anterior radius of curvature staging ('A', HKC: 52.9%, MR: 43.8%, Table 2). However, 'E' was more often indicating a higher stage than 'A' (HKC: 28.9%, MR: 41.4%, Table 2) and least frequently indicating a lower stage than 'A' (HKC: 18.2%, MR: 14.8%, Table 2). Similarly, 'E' indicated far more frequently a more severe stage than 'C' (HKC: 48%, MR: 47.8%, Table 2). This was in contrast to 'B', which showed a remarkable trend towards higher scores than 'E' (HKC: 52.9%, MR: 51.4%, Table 2).

Although the biomechanical parameter 'E' was not intended to diagnose KC or to separate between KC and healthy corneas, a sensitivity and specificity analysis was performed to check its capability of detecting abnormalities.

Sensitivity analysis

Table 3 shows the frequency distribution of 'E' for corneas that were classified either as 'A0', 'B0', 'C0' or a combination of 'A0B0C0'. This does not mean that 'A0B0C0' corneas were tomographically completely innocuous, but rather that the detected tomographic abnormalities were so small that they did not appear in the final ABC staging (which is rounded down, e.g. A0.9 is considered A0 instead of A1).

18.5% ($n = 83$) of the HKC and 21.4% ($n = 184$) of the MR KC corneas were classified 'A0' despite clinically diagnosed KC (Table 3). The majority of these cases (HKC: 67% ($n = 56$) and MR: 88% ($n = 162$)) showed abnormalities within the biomechanical 'E' staging.

Considering 'B', 10.3% (HKC, $n = 46$) and 7.1% (MR, $n = 61$) were classified 'B0' (Table 3). Also in these cases, the majority (HKC: 56.5% ($n = 26$) and MR: 83.6% ($n = 51$)) were classified 'E1' or even higher.

With regards to 'C', 22.5% (HKC, $n = 101$) and 16.9% (MR, $n = 145$) were classified 'C0' and the majority of them (HKC: 67.3% ($n = 68$) and MR: 84.1% ($n = 122$)) were classified 'E1' or higher (Table 3).

Because the tomographic staging is based on the comprehensive analysis of 'A', 'B' and 'C', the biomechanical assessment is of even greater interest in cases that were normal on all three tomographic grading parameters ('A0B0C0'): 6.3% (HKC, $n = 28$) and 2.1% (MR, $n = 18$, Table 3) were classified 'A0B0C0', which indicates, that they did not reveal any tomographic abnormalities in the ABC staging. Further analysis revealed, that 9 (HKC) and 12 cases (MR) showed biomechanical abnormalities and were accordingly classified 'E1' or higher.

Considering stage 'E0', biomechanical assessment provided this preclinical stage in only 8.0% (HKC, $n = 36$) and 3.5% (MR, $n = 30$, Table 4). Table 4 shows the frequencies of the tomographic stages in these biomechanically innocuous cases.

This analysis confirmed that the tomographic stages 'A', 'B' and 'C' were also indicating stage 0 in the majority of KC corneas that were classified 'E0'. However, some of these 'E0' cases were classified as stage 1 or higher in one of the three tomographic scores (Table 4).

Specificity analysis

The new biomechanical staging was also tested on healthy control corneas in order to analyse its specificity. For specificity analysis, 112 healthy control corneas (112 healthy patients presenting for evaluation of refractive surgery, HKC) were included with a mean age of 39.9 ± 14.9 years and a balanced distribution of left (43%) and right eyes (57%).

In addition to the HKC dataset, healthy control corneas from the MR ophthalmology departments were included as an independent validation dataset. This dataset consisted of 851 healthy corneas (851 patients) with a mean age of 34.9 ± 13.5 years and a balanced distribution of left (50.9%) and right eyes (49.1%). The frequency distribution of 'E' in healthy controls is shown in Fig. 3.

Table 2. Comparison of 'E' stages to tomographic stages 'A', 'B' and 'C'. Relative frequencies of 'E' providing similar ('E = A/B/C'), more severe ('E > A/B/C') or less severe ('E < A/B/C') stages than the tomographic stages.

	Relative frequencies	
Comparison of scores	Homburg dataset (%)	Milano/Rio dataset (%)
E compared to A		
E = A	52.9	43.8
E > A	28.9	41.4
E < A	18.2	14.8
E compared to B		
E = B	37.1	35.2
E > B	10.0	13.4
E < B	52.9	51.4
E compared to C		
E = C	43.0	39.7
E > C	48.0	47.8
E < C	9.0	12.5

Table 3. Frequency of 'E' in cases that were classified 'A0', 'B0', 'C0' or a combination of 'A0B0C0'.

	Frequency %		E0		E1		E2		E3		E4	
	HKC (%)	MR (%)	HKC (%)	MR (%)	HKC (%)	MR (%)	HKC (%)	MR (%)	HKC (%)	MR (%)	HKC (%)	MR (%)
A0	18.5	21.4	5.8	2.4	8.9	12.1	3.6	5.9	0.0	0.9	0.2	0.0
B0	10.3	7.1	4.5	1.2	4.7	4.7	1.1	1.3	0.0	0.0	0.0	0.0
C0	22.5	16.9	7.4	2.7	8.7	9.0	6.3	4.7	0.2	0.5	0.0	0.1
A0B0C0	6.3	2.1	4.3	0.7	2.0	1.2	0.0	0.2	0.0	0.0	0.0	0.0

Table 4. Frequency distribution of tomographic stages 'A0–A4', 'B0–B4' and 'C0–C4' in cases with the biomechanical staging 'E0'.

	Frequency		A0		A1		A2		A3		A4	
Stage	HKC	MR	HKC	MR	HKC	MR	HKC	MR	HKC	MR	HKC	MR
E0	8.0%	3.5%	5.8%	2.4%	1.6%	0.3%	0.7%	0.7%	0.0%	0.0%	0.0%	0.0%
			B0		**B1**		**B2**		**B3**		**B4**	
			HKC	**MR**	**HKC**	**MR**	**HKC**	**MR**	**HKC**	**MR**	**HKC**	**MR**
			4.5%	1.2%	1.1%	0.7%	2.5%	1.5%	0.0%	0.1%	0.0%	0.0%
			C0		**C1**		**C2**		**C3**		**C4**	
			HKC	**MR**	**HKC**	**MR**	**HKC**	**MR**	**HKC**	**MR**	**HKC**	**MR**
			7.4%	2.7%	0.4%	0.7%	0.2%	0.1%	0.0%	0.0%	0.0%	0.0%

Within the HKC dataset, 108 of 112 cases (96.4%) were classified 'E0' and four cases (3.6%) were classified 'E1' (Fig. 3). In the MR dataset, 771 of 851 cases (90.7%) were classified 'E0', 75 (8.8%) were classified 'E1' and 4 cases (0.5%) were classified 'E2' (Fig. 3).

In the HKC dataset, the tomographic staging revealed 'false positive' stages in no case for 'A' (MR: 1.2%), in 0.9% of cases for 'B' (MR: 2.8%) and 0.9% of cases for 'C' (MR: 5.1%).

Discussion

The diagnosis and classification of KC and ectatic corneal diseases have been refined in recent years by the advent of tomographic and biomechanical analysis of the cornea by different devices. Measurement of biomechanical dynamic corneal response parameters can be performed using the CST (Vinciguerra et al. 2016, 2017; Ambrósio et al. 2017; Elham et al. 2017; Zhao et al. 2019; Langenbucher et al. 2020). The Pentacam provides tomographical measurements and generates an ABC stage according to the ABCD KC classification (Belin et al. 2015, 2017; Belin & Duncan 2016). The uniqueness of the ABCD KC classification lies in the additional analysis of the posterior corneal curvature, which has not been evaluated in older grading systems (e.g. Amsler-Krumeich, Topographical Keratoconus Classification (TKC) or Placido-based classifications) and which is considered to be the earliest

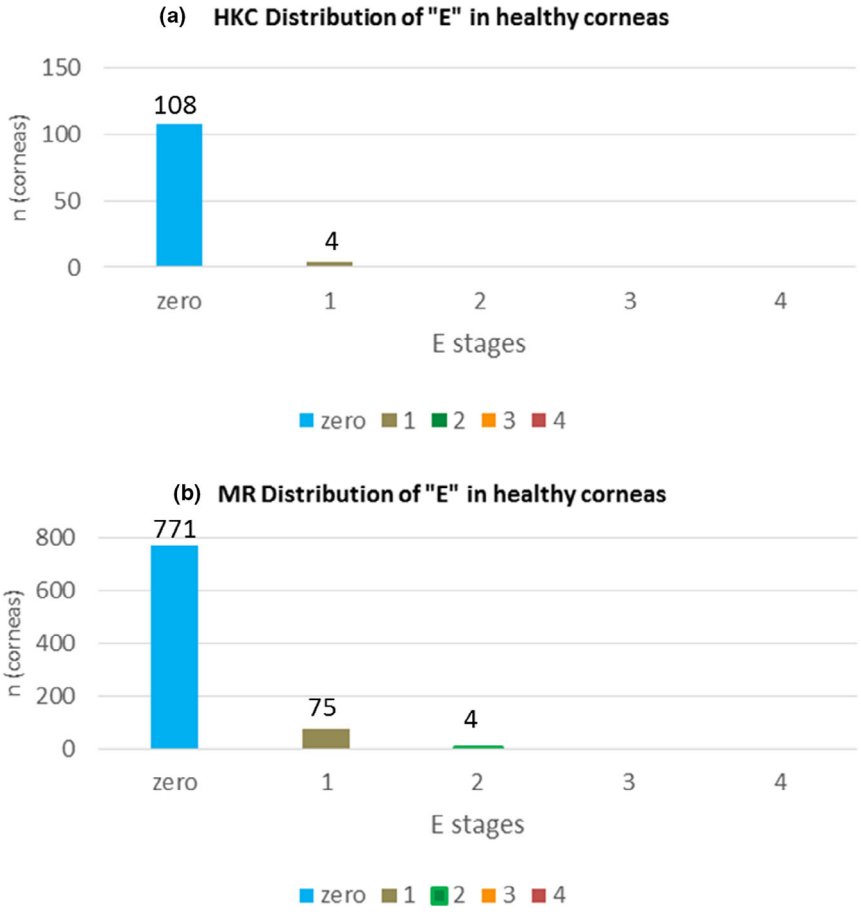

Fig. 3. Distribution of 'E' in healthy control corneas in (a) the Homburg Keratoconus Center (HKC) dataset and (b) in the Milano/Rio de Janeiro (MR) dataset.

marker for ectatic changes (Belin et al. 2017; Chan et al. 2018; Goebels et al. 2018; Flockerzi et al. 2021a) together with changes in epithelial maps (Reinstein et al. 2015; Temstet et al. 2015; Li et al. 2016; Pavlatos et al. 2020).

Biomechanical destabilization of the cornea may even precede changes on the posterior corneal curvature (Ambrósio et al. 2017; Elham et al. 2017) and, therefore, the biomechanical corneal analysis has gained an important role in the early detection not only of KC but also of other ectatic corneal diseases (Lenk et al. 2016; Yang et al. 2020). The introduction of the CBiF as a modification of the linear CBI beta provided a measure for different stages of the biomechanical destabilization of the cornea (Flockerzi et al. 2021c). The purpose of this study was to establish a link between the ABCD KC classification and corneal biomechanics by adding this biomechanical grading parameter as 'E' to augment the ABCD ectasia/KC staging.

The tomographic parameters A and B included in the ABCD KC classification are measured independently over a 3-mm zone centred on the thinnest corneal point, which should correspond to the location of the cone and be more representative than apical measurements. Based on those tomographic parameters, it has been demonstrated in previous studies, that they are significantly correlated with corneal biomechanical indices derived from the CST (Koh et al. 2020).

This study introduced a biomechanical grading parameter 'E' based on CST examination thus supplementing the tomographic ABCD KC classification. The application of this new biomechanical grading parameter 'E' in two independent representative KC collectives provided comparable results in terms of KC severity grading (Fig. 1a,b).

However, KC staging has to be differentiated from KC detection. The intention of the ABCDE staging is not to biomechanically diagnose KC solely based on these parameters (which is the aim of the CBI) but to further refine the severity classification. A staging system should classify the vast majority of KC cases higher than stage 0, but should indicate stage 0 in a high amount of healthy corneas.

It is therefore particularly noticeable that the biomechanical grading parameter 'E' shows abnormal values in some HKC cases earlier than the tomographic parameters of the ABCD KC classification. Although it has to be taken into account that this result depends on how 'E' was defined, a similar result was obtained in the second, independent MR dataset. Especially the lower frequency of 'false negative' stages of 'E0' compared with the tomographic stages 'A0', 'B0' and 'C0' in both KC datasets reveals the importance of a biomechanical assessment in early KC cases. In this study, the biomechanical staging indicated biomechanical abnormalities even in cases considered as normal in all three tomographic parameters ('A0B0C0') according to the ABCD KC classification. This finding is limited by the fact that an 'A0B0C0' staging does not imply the absence of ectatic corneal disease, because it was developed for staging instead of diagnosing KC. In these cases, the tomographic abnormalities may be so small that they are sufficient for KC diagnosis, without, however, appearing in the final ABC staging. The apparent contrast of early tomographic abnormalities but an innocuous 'A0B0C0' staging could thus be resolved by the addition of a conspicuous biomechanical 'E' staging in these cases.

This study found a trend that the most severe KC stage was set by parameter 'B' followed by 'E', 'A' and 'C' in both datasets. However, it is not possible to infer from this in principle that stages of 'B' are generally more advanced than stages of 'A' in every KC, as these are only frequency data as raised in this study. Because posterior elevation and thinnest corneal thickness were diagnostic criteria during selection of KC corneas for this study, it could be expected that they would play an important role in KC staging.

This study therefore emphasizes again the importance of posterior corneal curvature analysis but adds the importance of biomechanical analysis in the evaluation of KC. The results are also in line with the current theory that KC pathogenesis is based on a local biomechanical decompensation that leads to tomographic changes followed by further biomechanical decompensation (Roberts & Dupps 2014; Eliasy et al. 2019). Further, biomechanical decompensation would ultimately lead to changes on the anterior corneal surface and the appearance of the clinical changes seen in more advanced disease (Vinciguerra et al. 2016; Chan et al. 2018).

Two independent datasets of healthy control corneas were also evaluated for specificity analysis. The percentage of cases that were classified 'E1' or higher in healthy patients was relatively low. However, the tomographic parameters 'A', 'B' and 'C' showed a slightly higher specificity on these healthy cases compared with 'E'. It will be interesting to observe, whether any of the biomechanically slightly abnormal healthy control corneas will develop signs of tomographic abnormalities in future.

A predisposition for the application and interpretation of these results is a high reliability of the CST measurements, which has been proven in recent studies: The CST measurements have been shown to be of excellent reliability in mild to moderate KC (Yang et al. 2019), in three different KC severity stages (Herber et al. 2020) and in one study assessing every KC stage according to the topographical KC classification (TKC, Flockerzi et al. 2021b). Based on this high reliability of the CST measurements in all KC stages and the fact that the biomechanical staging was developed without using biomechanical information for initial diagnosis of KC, it can be assumed that the new biomechanical parameter 'E' introduced in this study is a robust parameter for a biomechanical KC grading.

Conclusion

This study introduced a biomechanical staging parameter 'E' as an addition to the tomographic ABCD ectasia/KC staging based on the separation of the CBiF into five stages (E0 to E4). The combination of tomographic and biomechanical parameters may offer certain clinical advantages over either the use of either alone. Further clinical utilization of the augmented staging system is needed to ultimately determine its clinical applicability.

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References

Ali NQ, Patel DV & McGhee CNJ (2014): Biomechanical responses of healthy and keratoconic corneas measured using a non-contact scheimpflug-based tonometer. Invest Ophthalmol Vis Sci **55**: 3651–3659.

Ambrósio R, Lopes BT, Faria-Correia F et al. (2017): Integration of scheimpflug-based corneal tomography and biomechanical assessments for enhancing ectasia detection. J Refract Surg **33**: 434–443.

Belin MW & Duncan JK (2016): Keratoconus: the ABCD grading system. Klin Monbl Augenheilkd **233**: 701–707.

Belin MW, Duncan J, Ambrósio R & Gomes JAP (2015): A new tomographic method of staging / classifying keratoconus: the ABCD grading system. Int J Kerat Ect Cor Dis **4**: 85–93.

Belin MW, Meyer JJ, Duncan JK, Gelman R & Borgstrom M (2017): Assessing progression of keratoconus and cross-linking efficacy: the belin ABCD progression display. Int J Kerat Ect Cor Dis **6**: 1–10.

Chan TC, Wang YM, Yu M & Jhanji V (2018): Comparison of corneal dynamic parameters and tomographic measurements using Scheimpflug imaging in keratoconus. Br J Ophthalmol **102**: 42–47.

Elham R, Jafarzadehpur E, Hashemi H, Amanzadeh K, Shokrollahzadeh F, Yekta A & Khabazkhoob M (2017): Keratoconus diagnosis using Corvis ST measured biomechanical parameters. J Curr Ophthalmol **29**: 175–181.

Eliasy A, Chen K-J, Vinciguerra R et al. (2019): Determination of corneal biomechanical behavior in-vivo for healthy eyes using CorVis ST tonometry: stress-strain index. Front Bioeng Biotechnol **7**: 105.

Flockerzi E, Daas L & Seitz B (2020): Structural changes in the corneal subbasal nerve plexus in keratoconus. Acta Ophthalmol **98**: e928–e932.

Flockerzi E, Häfner L, Xanthopoulou K, Daas L, Munteanu C, Langenbucher A & Seitz B (2021b): Reliability analysis of successive Corneal Visualization Scheimpflug Technology measurements in different keratoconus stages. Acta Ophthalmol [Epub ahead of print].

Flockerzi E, Vinciguerra R, Belin MW, Vinciguerra P, Ambrósio R Jr & Seitz B (2021c): Correlation of the Corvis Biomechanical Factor CBiF with tomographic parameters in keratoconus. J Cataract Refract Surg [Epub ahead of print].

Flockerzi E, Xanthopoulou K, Goebels S et al. (2021a): Keratoconus staging by decades - a baseline ABCD classification of 1,000 patients in the Homburg Keratoconus Center (HKC). Br J Ophthalmol **105**: 1069–1075.

Goebels S, Eppig T, Seitz B, Szentmàry N, Cayless A & Langenbucher A (2018): Endothelial alterations in 712 keratoconus patients. Acta Ophthalmol **96**: e134–e139.

Gomes JAP, Tan D, Rapuano CJ et al. (2015): Global consensus on keratoconus and ectatic diseases. Cornea **34**: 359–369.

Herber R, Vinciguerra R, Lopes B, Raiskup F, Pillunat LE, Vinciguerra P & Ambrósio R (2020): Repeatability and reproducibility of corneal deformation response parameters of dynamic ultra-high-speed Scheimpflug imaging in keratoconus. J Cataract Refract Surg **46**: 86–94.

Koh S, Inoue R, Ambrósio R, Maeda N, Miki A & Nishida K (2020): Correlation between corneal biomechanical indices and the severity of keratoconus. Cornea **39**: 215–221.

Langenbucher A, Häfner L, Eppig T, Seitz B, Szentmáry N & Flockerzi E (2020): Keratoconus detection and classification from parameters of the Corvis®ST: a study based on algorithms of machine learning. Ophthalmologe **118**: 697–706.

Lenk J, Haustein M, Terai N, Spoerl E & Raiskup F (2016): Characterization of ocular biomechanics in pellucid marginal degeneration. Cornea **35**: 506–509.

Li Y, Chamberlain W, Tan O, Brass R, Weiss JL & Huang D (2016): Subclinical keratoconus detection by pattern analysis of corneal and epithelial thickness maps with optical coherence tomography. J Cataract Refract Surg **42**: 284–295.

Pavlatos E, Chen S, Yang Y, Wang Q, Huang D & Li Y (2020): A coincident thinning index for keratoconus identification using OCT pachymetry and epithelial thickness maps. J Refract Surg **36**: 757–765.

Reinstein DZ, Archer TJ, Urs R, Gobbe M, RoyChoudhury A & Silverman RH (2015): Detection of keratoconus in clinically and algorithmically topographically normal fellow eyes using epithelial thickness analysis. J Refract Surg **31**: 736–744.

Reisdorf S (2019): Artificial intelligence for the development of screening parameters in the field of corneal biomechanics. Klin Monbl Augenheilkd **236**: 1423–1427.

Roberts CJ & Dupps WJ (2014): Biomechanics of corneal ectasia and biomechanical treatments. J Cataract Refract Surg **40**: 991–998.

Shen Y, Han T, Jhanji V, Shang J, Zhao J, Li M & Zhou X (2019): Correlation between corneal topographic, densitometry, and biomechanical parameters in keratoconus eyes. Trans Vis Sci Tech **8**: 12.

Shetty R, Nuijts RMMA, Srivatsa P, Jayadev C, Pahuja N, Akkali MC & Sinha Roy A (2015): Understanding the correlation between tomographic and biomechanical severity of keratoconic corneas. Biomed Res Int **2015**: 1–9.

Temstet C, Sandali O, Bouheraoua N et al. (2015): Corneal epithelial thickness mapping using Fourier-domain optical coherence tomography for detection of form fruste keratoconus. J Cataract Refract Surg **41**: 812–820.

Vinciguerra R, Ambrósio R, Elsheikh A, Roberts CJ, Lopes B, Morenghi E, Azzolini C & Vinciguerra P (2016): Detection of keratoconus with a new biomechanical index. J Refract Surg **32**: 803–810.

Vinciguerra R, Ambrósio R, Roberts CJ, Azzolini C & Vinciguerra P (2017): Biomechanical characterization of subclinical keratoconus without topographic or tomographic abnormalities. J Refract Surg **33**: 399–407.

Yang K, Xu L, Fan Q et al. (2020): Evaluation of new Corvis ST parameters in normal, Post-LASIK, Post-LASIK keratectasia and keratoconus eyes. Sci Rep **10**: 5676.

Yang K, Xu L, Fan Q, Zhao D & Ren S (2019): Repeatability and comparison of new Corvis ST parameters in normal and keratoconus eyes. Sci Rep **9**: 15379.

Zhao Y, Shen Y, Yan Z, Tian M, Zhao J & Zhou X (2019): Relationship among corneal stiffness, thickness, and biomechanical parameters measured by Corvis ST, pentacam and ORA in keratoconus. Front Physiol **10**: 740.

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