Keratoconus staging by decades: a baseline ABCD classification of 1000 patients in the Homburg Keratoconus Center

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ABSTRACT

Background This retrospective cross-sectional study aims to analyse the keratoconus (KC) stage distribution at different ages within the Homburg Keratoconus Center (HKC).

Methods 1917 corneae (1000 patients) were allocated to decades of age, classified according to Belin's ABCD KC grading system and the stage distribution was analysed.

Results 73 per cent (n=728) of the patients were males, 27% (n=272) were females. The highest KC prevalence occurred between 21 and 30 years (n=585 corneae, 294 patients). Regarding anterior (A) and posterior (B) curvature, the frequency of A was significantly higher than B in all age groups for stage 0, 1 and 2 (A0>B0; A1>B1; A2>B2; p<0.03, Wilcoxon matched-pairs test). There was no significant difference between the number of A3 and B3, but significantly more corneae were classified as B4 than A4 in all age groups (p<0.02). The most frequent A|B combinations were A4|B4 (n=451), A0|B0 (n=311), A2|B4 (n=242), A2|B2 (n=189) and A1|B2 (n=154). Concerning thinnest pachymetry (C), most corneae in all age groups were classified as C0>C1>C2>C3>C4 (p<0.04, Wilcoxon matched-pairs test). For the best distance visual acuity (D), a significantly higher number of corneae were classified as D1 compared to D0 (p<0.008; D1>D0>D2>D3>D4).

Conclusion The stage distributions in all age groups were similar. Early KC rather becomes manifest in the posterior than the anterior corneal curvature whereas advanced stages of posterior corneal curvature coincide with early and advanced stages of anterior corneal curvature. Thus, this study emphasises the necessity of posterior corneal surface assessment in KC as enabled by the ABCD grading system.

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INTRODUCTION

Keratoconus (KC) is usually a bilateral asymmetric corneal ectasia of a still unclear aetiology with progressive thinning of the cornea[1] resulting in an irregular astigmatism and visual impairment.[2] Different therapy options are available depending on the progression of the disease and include contact lens fitting, surgical treatment via corneal cross linking, implantation of corneal ring segments, deep anterior lamellar keratoplasty or penetrating keratoplasty.[3] The disease often becomes clinically apparent in young adulthood, and most patients showing up in departments of ophthalmology are between 20 and 30 years of age.[4] Different approaches have been developed in the past to classify KC including the Amsler classification (1950) based on clinical signs, which was supplemented in 1984 by Muckenhirn, who added the parameter of corneal eccentricity. Another classification was created by Krumeich, who included induced myopia, corneal radius, thickness and corneal slit-lamp findings in stages 0–4 as additional parameters.[5] The latest classification was introduced by Belin and Duncan in 2016,[6 7] who proposed a new KC grading system based on the analyses of the anterior (A) and posterior (B) curvature (at 3 mm from the thinnest point on the anterior (A) or posterior (B) corneal surface) of the cornea, the thinnest corneal pachymetry (C) and the distance best-corrected visual acuity (D) including stages 0–4 for each parameter (table 1).[6 8]

In contrast to the Amsler-Krumeich classification, it allows an individual grading of each component including the posterior corneal curvature, where early ectatic changes can often be found prior to anterior changes.[8 9] The ABCD grading system was found to be useful in discriminating progressive from nonprogressive KC eyes,[10] and it can be used for evaluation of topographic corneal changes after corneal cross linking[11] or implantation of corneal ring segments.[12] The purpose of the current study was to analyse the KC stage distribution at different ages in the Homburg Keratoconus Center (HKC) based on the ABCD KC grading system and to elucidate how these parameters vary in different age groups.

PATIENTS AND METHODS

Patients

This retrospective cross-sectional study is based upon data of patients with KC registered in the HKC, which was founded in 2010 and, up to now, comprises more than 1500 patients with KC. The study includes the first 1000 patients registered by the HKC. Pentacam high-resolution Scheimpflug imaging (Oculus, Wetzlar, Germany[13]) was performed, and the Belin/Ambrósio enhanced ectasia display, which combines anterior elevation, posterior elevation and pachymetric data[8] was analysed. The enhanced reference surface enables a greater separation between the ectatic and the reference surface, and KC was diagnosed (1) based on clinical slit-lamp findings (corneal thinning and steepening, Vogt striae, Fleischer ring, scar formation), (2)

Table 1 ABCD keratoconus grading system according to Belin and Duncan (2016,[6] with permission of the publisher, Thieme Group, Stuttgart, Germany)

ABCD stages	A, anterior radius of curvature	B, posterior radius of curvature	C, thinnest pachymetry	D, best-corrected visual acuity
0	>7.25 mm (<46.5 D)	>5.90 mm	>490 µm	≥20/20
1	>7.05 mm (<48.0 D)	>5.70 mm	>450 µm	<20/20
2	>6.35 mm (<53.0 D)	>5.15 mm	>400 µm	<20/40
3	>6.15 mm (<55.0 D)	>4.95 mm	>300 µm	<20/100
4	≤6.15 mm (≥55.0 D)	≤4.95 mm	≤300 µm	<20/400

posterior elevation at the thinnest point ≥13 µm (based on a best fit sphere from 8.0 mm optical zone), (3) a minimal corneal thickness <550 µm and (4) a spherical equivalent <0 D (myopic). The measurement was repeated every time the quality score in the Pentacam showed red because of blinking artefacts, fixation errors or lost images. In advanced KC stages, however, measurements with a poor quality score also had to be accepted for evaluation, as the error 'model deviation' occurred more frequently in these cases.

In order to exclude corneal measurements influenced by contact lens-induced corneal warpage,[14 15] only Pentacam measurements after a period of at least 3 days without contact lens wear were included in the current study. For patients without contact lenses, the measurement of the initial presentation was included. Patients with contact lenses were asked to remove their contact lenses 3 days before their first appointment in our department. If this was not possible, the first follow-up measurement without wearing contact lenses was used for this study. Each eye was classified according to Belin and Duncan's ABCD KC grading system,[6 8] which is incorporated in the Pentacam software.

As only eyes without previous operations or other ocular diseases could be included, a total of 1917 eyes of 1000 patients treated at the HKC were allocated to nine age groups sorted by decades of life (table 2). The remaining 83 eyes were excluded because of previous surgical procedures, which were performed prior to the inclusion in the HKC such as implantation of corneal ring segments (n=1), corneal cross linking (n=7), penetrating keratoplasty (n=71) or unreliable Pentacam results despite repeated measurements (n=4).

Subsequently, the absolute numbers of corneae and the different parameters of the ABCD KC grading system were put into relation to the age of the patients.

Table 2 Patients and eyes in the Homburg Keratoconus Center according to age

	Male	Female	Total (patients)	Total (eyes)
n (patients)	728	272	1.000	1.917
n (≤10 years)	0	0	0	0
n (11–20 years)	102	26	128	255
n (21–30 years)	239	55	294	585
n (31–40 years)	181	70	251	481
n (41–50 years)	130	51	181	336
n (51–60 years)	52	50	102	178
n (61–70 years)	16	15	31	56
n (71–80 years)	8	4	12	24
n (81–90 years)	0	1	1	2

The study (trial number NCT03923101, U.S. National Institutes of Health, ClinicalTrials.gov) was approved by the regulatory body, the local ethics committee of Saarland (Ethikkommission bei der Ärztekammer des Saarlandes, reference number 121/20). Written informed consent was provided by each patient with KC in the HKC for the analysis of data.

Statistical analysis

A draft of figures and statistical analysis were performed using SPSS software (version 20.0; International Business Machines Corporation, Armonk, NY, USA). The statistical analysis was carried out based on the absolute numbers of corneae in each stage of the ABCD KC grading system and the two-tailed Wilcoxon matched-pairs test assuming significant differences with $p<0.05$.

RESULTS

In this study, 73% (n=728) of the patients were males and 27% (n=272) were females. Of the 1000 patients, the vast majority were native Germans (78%, n=784), 9.5% (n=95) originated from other European countries and 12% (n=121) from non-European countries (71 Asians, 30 North Americans, 10 Latin Americans, 10 Africans according to the world regions as proposed by the United Nations Statistic Division). While 52% of the patients (n=515) did not wear contact lenses, 36% (n=364) wore rigid, gas-permeable contact lenses and 4% (n=43) wore soft contact lenses (8%, n=77, not specified). Eight per cent (n=80) of the patients reported to suffer from atopic dermatitis and 40% (n=398) from allergies. None of the patients fell into the age group ≤10 years of age and only one patient belonged to the group of 81–90 years; therefore, these groups were excluded from further analysis. The highest KC prevalence occurred in the age range from 21 years to 30 years (n=585 corneae, 294 patients, figure 1).

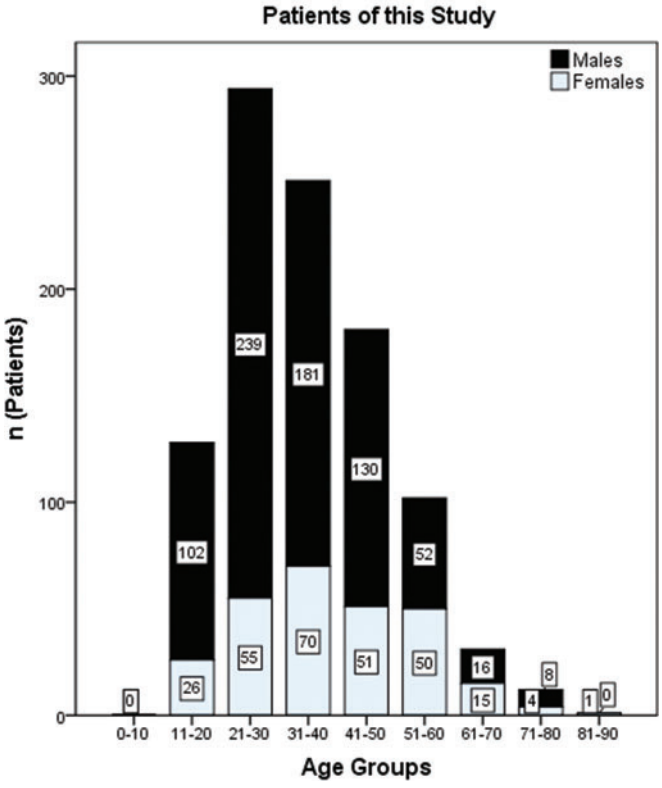

Figure 1 Age groups (x-axis) of patients of this study. Grey column, number of female patients in each age group; black column, number of male patients in each age group.

After the application of the ABCD KC grading system on each eye included in this study, the grading parameters were compared. With regard to the anterior (A) and posterior (B) curvature, there were significantly more corneae classified as A0 than B0 ($p<0.02$) in all age groups. The same was applied for A1>B1 ($p<0.03$) and A2>B2 ($p<0.02$, Wilcoxon two-tailed matched-pairs test, figure 2, table 3).

In stage 3, there was no significant difference between the number of corneae classified A3 or B3 ($p>0.5$). Analysis of stage 4, however, revealed that there were significantly more corneae classified as B4 than A4 in all age groups (B4>A4, $p<0.02$, Wilcoxon two-tailed matched-pairs test, figure 2, table 3).

The number of corneae in the different stages of anterior and posterior curvatures were further put into relation to each other, and revealed a total of 24% (n=451) of corneae with stage A4 which were also classified as B4 (figure 3, table 4), and represented the most frequent A|B combination within the entire study group.

The second most frequent A|B combination was A0|B0 (16%, n=311), with the numbers significantly lower than A4|B4 (figure 3, table 4). The number of corneae in the second, third (A2|B4, 13%, n=242), fourth (A2|B2, 10%, n=189) and fifth (A1|B2, 8%, n=154) most frequent combinations did not differ significantly from the preceding, more frequent group (figure 3). These 5 of 25 possible A|B combinations (A0–A4×B0–B4=25) represented more than 70% (n=1347) of the corneae included in this study (n=1917, figure 3).

The thinnest corneal pachymetry is defined as parameter C in the ABCD KC grading system. With regard to parameter C, the number of corneae across all age groups was significantly higher

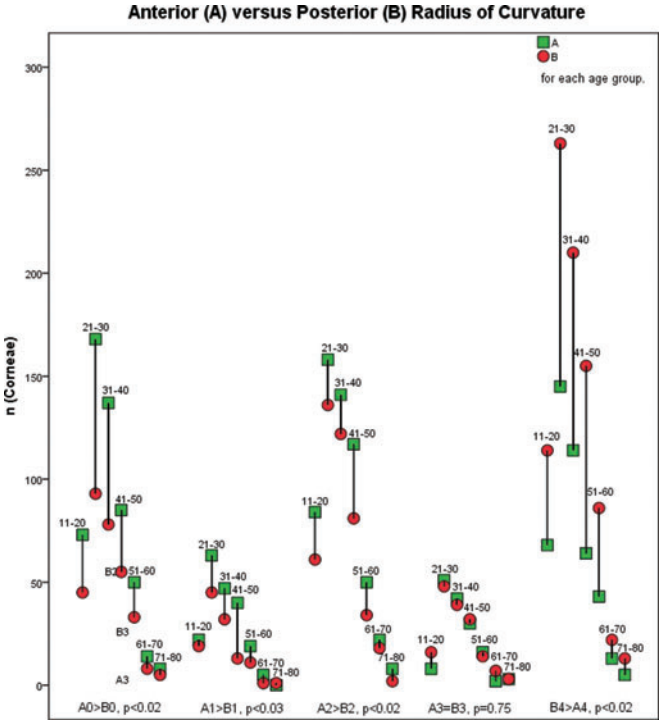

Figure 2 Comparison of anterior (green) and posterior (red) radius of curvature. Significantly more corneae were classified as A0>B0 ($p<0.02$), A1>B1 ($p<0.03$) and A2>B2 ($p<0.02$) in all age groups (as indicated above the measuring points). No significant difference between the absolute number of corneae classified as A3 and B3 ($p=0.75$) and significantly more corneae were classified as B4>A4 ($p<0.02$) in all age groups (as indicated above the measuring points). P values calculated by Wilcoxon two-tailed matched-pairs test.

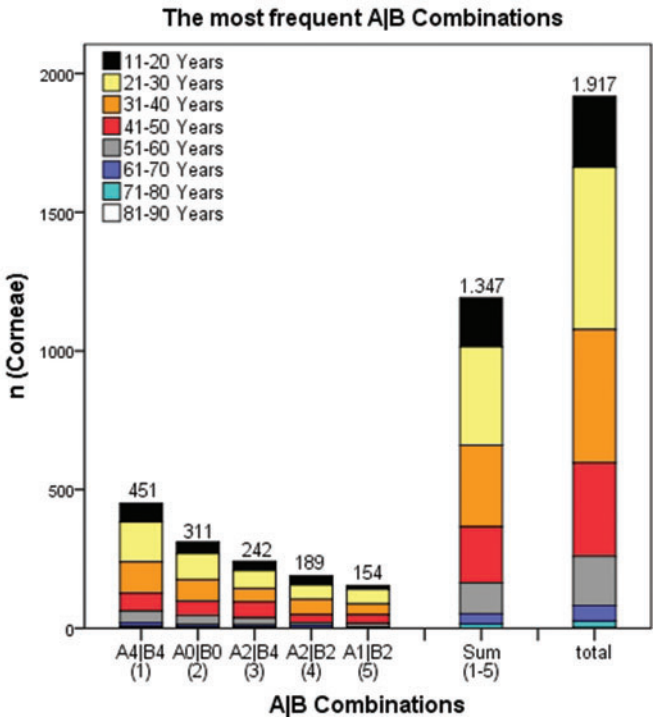

Figure 3 (1)–(5), most frequent A|B combinations in all age groups. Significantly larger number of corneae classified (1) than (2) ($p<0.02$). No significant difference between the number of corneae classified as (2) vs (3) ($p<0.08$). Significantly larger number of corneae classified as (2) vs (4) ($p<0.03$). No significant difference between the number of corneae classified as (3) vs (4) ($p=0.15$). Same for (4) and (5) ($p<0.4$). P values calculated by Wilcoxon two-tailed matched-pairs test.

Table 3 Absolute numbers as shown in figure 2

	Age groups								
AB stages	**11–20**	**21–30**	**31–40**	**41–50**	**51–60**	**61–70**	**71–80**	**81–90**	**P value**
A0>B0	**73**|45	**168**|93	**137**|78	**85**|55	**50**|33	**14**|8	**8**|5	0|0	<0.02
A1>B1	**22**|19	**63**|45	**47**|32	**40**|13	**19**|11	**5**|1	0|1	0|0	<0.03
A2>B2	**84**|61	**158**|136	**141**|122	**117**|81	**50**|34	**22**|18	**8**|2	0|0	<0.02
A3=B3	8|16	51|48	42|39	30|32	16|14	2|7	3|3	0|0	0.75
A4<B4	68|**114**	145|**263**	114|**210**	64|**155**	43|**86**	13|**22**	5|**13**	2|2	<0.02

Data in bold represents significantly larger number of corneae in A0>B0, A1>B1, A2>B2 in all age groups (except A1|B1 in age group 71–80 years). There was no significant difference between the number of corneae in A3 and B3 in all age groups. In bold, significantly larger number of corneae in B4>A4 in all age groups. P values calculated by Wilcoxon two-tailed matched-pairs test.

Table 4 Absolute numbers of corneae according to age in the most frequent A|B combinations (1) –(5) as shown in the columns in figure 3

	Age groups								
AB stages	11–20	21–30	31–40	41–50	51–60	61–70	71–80	81–90	Total
(1) A4 and B4	67	145	113	63	43	13	5	2	451
(2) A0 and B0	42	94	77	52	33	8	5	0	311
(3) A2 and B4	34	64	49	57	26	7	5	0	242
(4) A2 and B2	33	52	55	30	10	8	1	0	189
(5) A1 and B2	13	53	39	32	12	5	0	0	154

in C0 than C1 (p<0.04, Wilcoxon two-tailed matched-pairs test, figure 4, table 5) and the same applied to the further stages (C1>C2, p<0.03; C2>C3, p<0.01; C3>C4, p<0.02; Wilcoxon two-tailed matched-pairs test, except in age groups >60 years, figure 4, table 5).

Twenty per cent (n=379) of the corneae classified as A0 within the entire study group were also classified as C0, 13% (n=252) as B0 and C0 (table 5). Progressive thinning of the cornea is

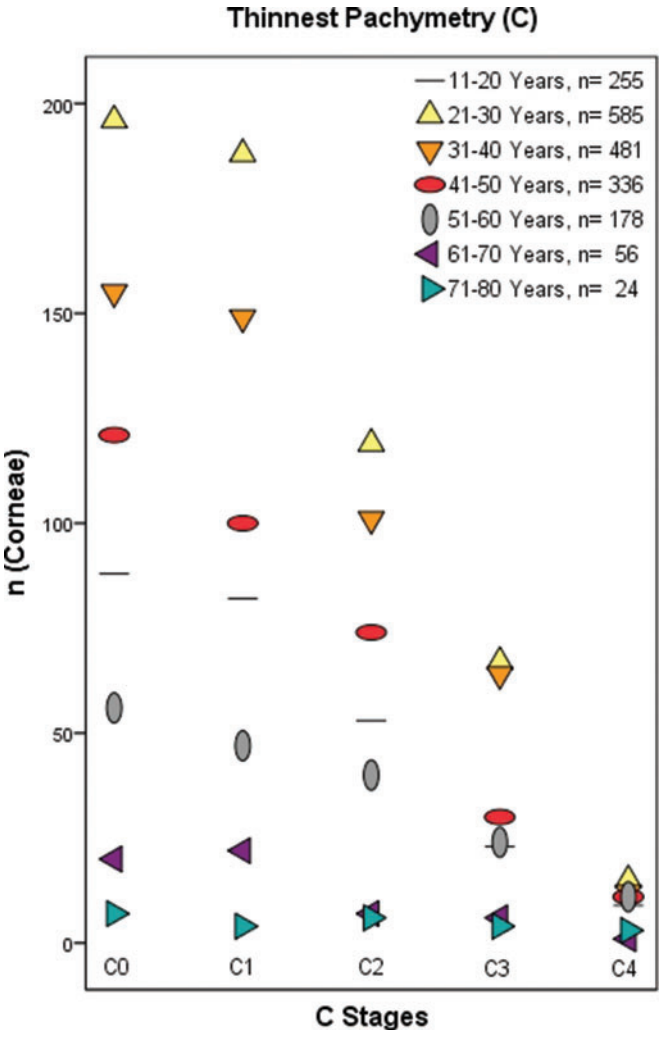

Figure 4 Absolute numbers of corneae at stages C0, C1, C2, C3 and C4 (thinnest corneal pachymetry, x-axis) in the different age groups (legend). Significantly more corneae were classified as C0>C1 (p<0.04), C1>C2 (p<0.03), C2>C3 (p<0.01) and C3>C4 (p<0.02) in all age groups except age groups >60 years. P values calculated by Wilcoxon two-tailed matched-pairs test.

Table 5 Classification of A|C and B|C based on the absolute numbers of corneae in the entire study group

Stages	C0	C1	C2	C3	C4
A0|B0	**379|252**	121|52	16|7	8|1	9|1
A1|B1	88|72	85|43	19|26	3|0	1|1
A2|B2	150|192	**263|207**	136|43	27|11	5|0
A3|B3	11|45	53|71	67|47	17|4	3|0
A4|B4	15|82	71|220	**163|278**	**163|202**	**44|60**
Total	643|643	593|593	401|401	218|218	62|62

Numbers in bold show the associations between anterior curvature (A), posterior curvature (B) and pachymetry (C).
Low A|B stages (A0|B0) are associated only in part with a normal corneal pachymetry (C0), intermediate A|B stages (A2|B2) with a slightly reduced corneal pachymetry (C1) and late A|B stages (A4|B4) with a further decreasing corneal pachymetry (C2–C4).

associated with increasing anterior or posterior corneal curvature: 62 corneae of the entire study group were classified as C4, 71% (n=44) of which also classified as A4, 96% (n=60) as B4 (figure 4, table 5).

Considering parameter D, which represents the best distance visual acuity, a significantly higher number of corneae were classified as stage D1 in comparison to D0 (p<0.008; D0>D2, p<0.08; D2>D3, p<0.008; D3>D4, p<0.02; Wilcoxon two-tailed matched-pairs test, figure 5).

DISCUSSION

This retrospective cross-sectional study summarises the KC parameters according to Belin and Duncan's ABCD grading system in 1917 eyes of 1000 patients who were treated at the HKC. The gender distribution of the patients with KC was not balanced with almost three quarters (73%, n=728) of male patients and 27% (n=272) of female patients (figure 1, table 2). Previous and recent studies—with however differing inclusion criteria—including the Collaborative Longitudinal Evaluation of KC (CLEK) study (1209 patients with KC) reported a preponderance of males ranging from 56%[16] to 63%.[17] Other recent publications also showed a male to female ratio of 1.43 in patients with KC in the USA[18] and 2.02 in Denmark.[19]

The proportion of patients wearing rigid, gas-permeable contact lenses (36%, n=364) and patients with allergies (40%, n=398) was lower in our study than in the CLEK study (65% wearing rigid contact lenses, 53% with allergies[16]) while the proportion of patients with atopic dermatitis was the same in both studies (8%). Nevertheless, the prevalence of allergies among our patients with KC remains higher in comparison to the resident German adult population (30%, including atopic dermatitis[20]). It is still unclear, whether there is a coincidence between atopic diseases and KC in general or whether eye rubbing because of atopic diseases accelerates KC progression.[21] The presence of eye rubbing, however, is accepted widely as an

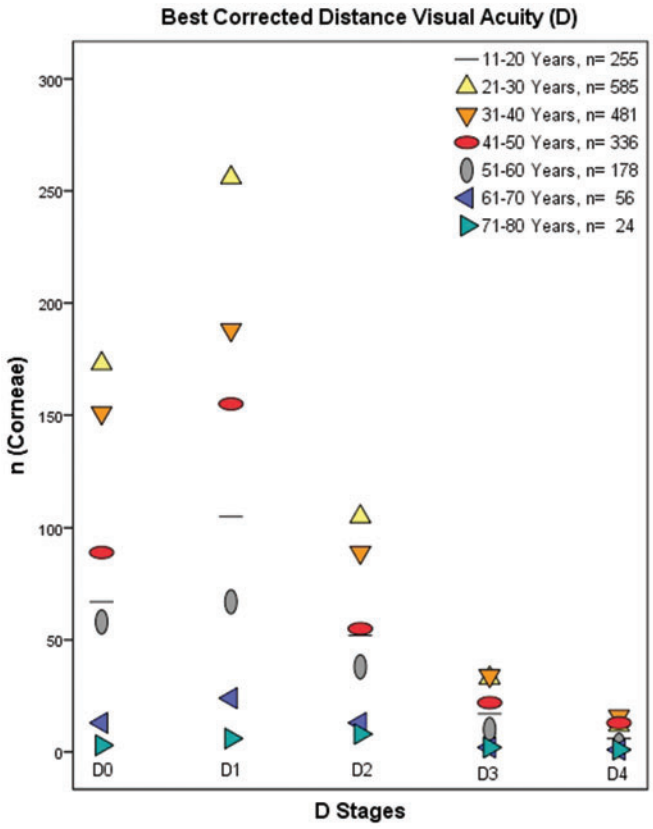

Figure 5 Absolute numbers of corneae at stages D0, D1, D2, D3 and D4 (best distance visual acuity, x-axis) in the different age groups. Significantly more corneae were classified as D1>D0 (p<0.008), D0>D2 (p<0.08), D2>D3 (p<0.008) and D3>D4 (p<0.02) in all age groups except age group >70 years. P values calculated by Wilcoxon two-tailed matched-pairs test.

environmental stressor, which contributes to KC progression and progressive corneal thinning.[21 22]

The smaller proportion of patients with KC in our study wore rigid, gas-permeable contact lenses (36%, n=364). The HKC also includes its own contact lens department. After a 3-day period without contact lenses for patients with KC and the subsequent ophthalmological examinations, further follow-up examinations in the contact lens department were conducted on the same day, when the best-corrected visual acuity with contact lenses was assessed. This can only be carried out for 36% (n=364) of the patients with KC who wore contact lenses. The remaining 64% (n=636) of the patients with KC in this study may not be as perfectly refracted with their glasses as they could have been with contact lenses, which might explain the number of patients in the distance visual acuity classification (D1>D0>D2>D3>D4, respectively, in all age groups except age group 71–80 years, figure 5).

An 'off contact lens' waiting period of 2 weeks in healthy individuals was suggested prior to the evaluation for refractive surgery[15] because of the potential bias caused by contact lens-induced warpage. This waiting period is often unacceptable for the mostly young and working patients with KC who have to attend regular follow-up examinations. Consequently, this study required a period without contact lenses of at least 3 days before follow-up examinations. This enables patients with KC to remove their contact lenses over the weekend without major restrictions prior to a follow-up examination.

The HKC, from which the patients with KC of this study were recruited, was founded in 2010 at the Department of Ophthalmology of Saarland University Medical Center in Homburg, Germany, and it is a renowned reference centre for corneal diseases and corneal transplantation as it belonged to the four most active corneal transplantation centres in Germany in 2016.[23] Consequently, many patients with advanced KC stages are referred to this centre for penetrating keratoplasty, which may in turn result in a distortion of the actual distribution of KC stages. As inter-eye asymmetry increases with KC severity in the worse eye,[24] this effect is mitigated by including the less affected partner eye of these patients. Although there is a general consensus that KC is a bilateral disease, colleagues from our department found 20 patients with so-called tomographically unilateral KC among 1280 patients in the HKC and examined their corneal biomechanics based on the Ocular Response Analyzer (ORA, Reichert Technologies, Buffalo, NY, USA) and the Corneal Visualization Scheimpflug Technology (Corvis ST, Oculus, Wetzlar, Germany). The biomechanics of these primarily considered 'healthy' partner eyes differed from those of healthy controls ('Unilateral' keratoconus: a biomechanical analysis, submitted, under review). A long-term observation of these patients is still pending.

In the present study, most corneae across all age groups were classified to have a normal corneal thickness (C0), which decreased depending on the stage of the disease (C0>C1>C2>C3>C4, respectively, except in age groups >60 years, figure 4, table 5). Early anterior and posterior curvature stages (A0, B0) were only partially associated with a normal thinnest corneal pachymetry (C0) in the different age groups (20% (n=379) of the A0 and 13% (n=252) of the B0 corneae). With decreasing corneal thickness, the anterior corneal curvature does increase: 71% (n=44) of the corneae classified as A4 were also classified as C4 (table 5). This finding is in line with reports in the literature hypothesising, based on the lower keratocyte density in the anterior part of the stroma, that KC is primarily an anterior corneal disease.[25] However, this phenomenon could be observed to an even larger extent at the posterior corneal curvature within our study group: 96% (n=60) of the corneae classified as B4 were also classified as C4 (table 5), which indicates that the posterior curvature might be even more affected by the disease at advanced KC stages than the anterior curvature. This theory is supported by the finding that there were significantly more corneae in stage B4 than A4 in the entire study group (figure 2, table 3). Posterior corneal curvature[8 9 26] and corneal endothelium[27] have been documented to be affected in early KC stages. Isolated analysis of A and B in our study group shows that there is a large number of KC (n=545) classified as A0 indicating a normal anterior corneal curvature at 3 mm from the thinnest point in these corneae (<46.5 D, table 1). In these cases, KC was diagnosed based on the analysis of parameter B (corneal curvature at 3 mm from the thinnest point of the posterior corneal surface) or C (thinnest pachymetry). Thus, clinical examination, corneal curvature changes beginning on the posterior surface and reduced corneal pachymetry led to KC diagnosis in more than a quarter (n=545) of the included corneae (n=1917). In stages A1 and A2, which represent clinically manifested KC, the disease seems to become more apparent at the anterior part of the cornea (A1>B1 (A1, n=196; B1, n=122), A2>B2 (A2, n=580; B2, n=454), figure 2, table 3). The number of corneae classified as A3 (n=152) and B3

(n=159) did not differ significantly (table 3), so that one may hypothesise that the relation between anterior and posterior affection of the cornea reverses at this stage in favour of an increasing posterior corneal curvature in more advanced KC stages (B4>A4 (B4, n=865; A4, n=454), figure 2).

Analysis of the most frequent A|B combinations (figure 3, table 4) revealed that the most advanced stage (A4|B4) was the most frequent A|B combination within the entire study group (n=451, 24%), and there were significantly more corneae classified as B4 than A4 (figure 2). The second most frequent A|B combination was A0|B0 (n=311, 16%, figure 3, table 4).

The question arises whether the eyes classified as A0|B0 are actually eyes with KC. In these cases, KC was also diagnosed based on the Belin/Ambrósio enhanced ectasia display implemented in the Pentacam software, corneal pachymetry, but also in dependance on the partner eye. The large majority of these 311 (16%) A0|B0 classified corneae had partner eyes with more advanced KC stages (n=183 with A≥1 and B≥1; n=28 with A0 and B0 and C≥1; n=13 with A0 and B≥1; n=13 with A0 and B≥2; n=6 with A0 and B≥1 and C≥1). Finally, only 34 pairs of corneae with A0|B0|C0 on both sides remained, which showed very subtle deviations from the norm, so that the final ABC grading did not show any pathological values. Although the ABCD grading system usually allows an assessment of KC progression based on the most important corneal parameters at one glance during follow-up examinations, this aspect represents a limitation. Deviations from the norm smaller than stage 1 are indicated for each parameter A, B or C in graduations from 0.1 to 0.9. Although these deviations are detected, they do not appear in the final grading, because according to M Belin (personal communication, 2019), they are rounded down and thus, for example, A0.9 is considered A0 instead of A1. Since conspicuous corneae can also show a normal final ABC grading, the ABC grading must always be considered only as a supplement to the ophthalmologist's assessment of the Pentacam and not as a replacement.

The third most frequent A|B combination was A2|B4, the fourth A2|B2 and the fifth A1|B2 (figure 3, table 4). In these frequent intermediate stages, earlier stages of anterior corneal surface curvature also seem to coincide with more advanced posterior corneal surface curvature stages. These 5 of 25 possible A|B combinations (A0|1|2|3|4×B0|1|2|3|4=25) represent more than two-thirds (n=1347 eyes) of the corneae included in this study (n=1917 eyes, figure 3, table 4).

CONCLUSIONS

This age-dependent ABCD classification is meant to be the basis for a longitudinal assessment of the development of KC during the next 10 years in the HKC. The frequency of the distribution of KC stages within the current study was comparable in almost every decade of life. Early or subclinical KC rather becomes manifest in the posterior than anterior corneal curvature as well as in reduced corneal thickness. Advanced stages of posterior corneal curvature do coincide with early and advanced stages of anterior corneal curvature. Consequently, the beginning of the KC disease seems to be attributable rather to the posterior than to the anterior curvature of the cornea. Finally, by taking into account the analysis of the posterior corneal curvature, the ABCD grading system improves diagnosis and assessment of the progression in KC disease.

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Ethics approval The study (trial number NCT03923101, U.S. National Institutes of Health, ClinicalTrials.gov) was approved by the regulatory body, the local ethics committee of Saarland (Ethikkommission bei der Ärztekammer des Saarlandes, reference number 121/20). Written informed consent was provided by each patient with KC in the HKC for the analysis of data.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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REFERENCES

1 Gomes JAP, Tan D, Rapuano CJ, *et al.* Global consensus on keratoconus and ectatic diseases. *Cornea* 2015;34:359–69.
2 Goebels S, Eppig T, Wagenpfeil S, *et al.* Staging of Keratoconus indices regarding tomography, topography, and biomechanical measurements. *Am J Ophthalmol* 2015;159:733–738.e3.
3 Goebels S, Seitz B, Langenbucher A. Diagnostics and stage-oriented therapy of keratoconus: introduction to the Homburg Keratoconus Center (HKC). *Ophthalmologe* 2013;110:808–9.
4 Galvis V, Sherwin T, Tello A, *et al.* Keratoconus: an inflammatory disorder? *Eye* 2015;29:843–59.
5 Krumeich J, Daniel J. Lebend-Epikeratophakie und Tiefe Lamelläre Keratoplastik zur Stadiengerechten chirurgischen Behandlung des Keratokonus (KK) I-III. *Klin Monbl Augenheilkd* 1997;211:94–100.
6 Belin MW, Duncan JK. Keratoconus: the ABCD grading system. *Klin Monbl Augenheilkd* 2016;233:701–7.
7 Belin MW, Duncan J, Ambrósio R, *et al.* A new tomographic method of staging/classifying keratoconus: the ABCD grading system. *Int J Kerat Ect Cor Dis* 2015;4:85–93.
8 Duncan JK, Belin MW, Borgstrom M. Assessing progression of keratoconus: novel tomographic determinants. *Eye* 2016;3:6.
9 de Sanctis U, Loiacono C, Richiardi L, *et al.* Sensitivity and specificity of posterior corneal elevation measured by Pentacam in discriminating keratoconus/subclinical keratoconus. *Ophthalmology* 2008;115:1534–9.
10 Kosekahya P, Caglayan M, Koc M, *et al.* Longitudinal evaluation of the progression of keratoconus using a novel progression display. *Eye Contact Lens* 2019;45:324–30.
11 Sağlık A. Progression analysis with ABCD grading system following corneal collagen cross-linking in keratoconus. *Beyoglu Eye J* 2019.
12 Sedaghat M-R, Momeni-Moghaddam H, Belin MW, *et al.* Changes in the ABCD keratoconus grade after intracorneal ring segment implantation. *Cornea* 2018;37:1431–7.
13 Scheimpflug T. Method of distorting plane images by means of lenses and mirrors for photography and for other purposes. 1904. Available https://patents.google.com/patent/US751347A/en (accessed 9 Feb 2019)
14 Holladay JT. Keratoconus detection using corneal topography. *J Refract Surg* 2009;25:958–62.
15 Alipour F, Letafatnejad M, Beheshtnejad AH, *et al.* Corneal biomechanical findings in contact lens induced corneal warpage. *J Ophthalmol* 2016;2016:5603763.
16 Zadnik K, Barr JT, Edrington TB, *et al.* Baseline findings in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study. *Invest Ophthalmol Vis Sci* 1998;39:2537–46.
17 Fatima T, Acharya MC, Mathur U, *et al.* Demographic profile and visual rehabilitation of patients with Keratoconus attending contact lens clinic at a tertiary eye care centre. *Cont Lens Ant Eye* 2010;33:19–22.

18 Woodward MA, Blachley TS, Stein JD. The association between sociodemographic factors, common systemic diseases, and keratoconus. *Ophthalmology* 2016;123:457–465.e2.
19 Bak-Nielsen S, Ramlau-Hansen CH, Ivarsen A, *et al.* Incidence and prevalence of keratoconus in Denmark: an update. *Acta Ophthalmol* 2019;97:752–5.
20 Langen U, Schmitz R, Steppuhn H. Häufigkeit allergischer Erkrankungen in Deutschland: Ergebnisse der Studie zur Gesundheit Erwachsener in Deutschland (DEGS1). *Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz* 2013;56:698–706.
21 Barbara R, Turnbull AM, Hossain P, *et al.* Epidemiology of Keratoconus. In: *Keratoconus: recent advances in diagnosis and treatment*. Cham, Switzerland: Alió JL, Editor, Springer International Publishing AG, 2017: 13–23.
22 Gatinel D. Eye rubbing, a sine qua non for keratoconus? *Int J Kerat Ect Cor Dis* 2016;5:6–12.
23 Flockerzi E, Maier P, Böhringer D, *et al.* Trends in corneal transplantation from 2001 to 2016 in Germany: a report of the dog-section cornea and its keratoplasty registry. *Am J Ophthalmol* 2018;188:91–8.
24 Eppig T, Spira-Eppig C, Goebels S, *et al.* Asymmetry between left and right eyes in keratoconus patients increases with the severity of the worse eye. *Curr Eye Res* 2018;43:848–55.
25 Sherwin T, Ismail S, Loh I-P, *et al.* Histopathology (from keratoconus pathology to pathogenesis). In: *Keratoconus: recent advances in diagnosis and treatment*. Cham, Switzerland: Alió JL, Editor, Springer International Publishing AG, 2017: 25–41.
26 Tomidokoro A. Changes in anterior and posterior corneal curvatures in keratoconus. *Ophthalmology* 2000;107:1328–32.
27 Goebels S, Eppig T, Seitz B, *et al.* Endothelial alterations in 712 keratoconus patients. *Acta Ophthalmol* 2018;96:e134–9.