

Clinical and Tomographic Characteristics of Keratoconus Progression in an East Asian Cohort: A Retrospective Study in Taiwan

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Research Article

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Abstract

Background

To identify clinical and tomographic characteristics of keratoconus (KC) progression in an East Asian cohort and to evaluate the discriminative performance of various corneal parameters in characterizing disease instability.

Methods

A total of 164 eyes from 164 patients diagnosed with KC between 2005 and 2025 were included. Patients were categorized into the progression and non-progression groups based on tomographic criteria (Kmax increase > 1.0 D annually). Baseline clinical characteristics, Pentacam HR parameters and systemic comorbidities were compared. Multivariate logistic regression with Benjamini-Hochberg false discovery rate correction was performed to investigate the association with progression.

Results

Univariate analysis revealed that the progression group had significantly steeper baseline Kmax ($P = 0.009$), higher cylinder ($P = 0.002$), lower Rmin ($P < 0.001$) and shorter cone decentration distance ($P = 0.03$). Furthermore, baseline symmetric indices of IHD (OR = 16.09, $P < 0.001$), IVA (OR = 5.90, $P < 0.001$) and ISV (OR = 1.02, $P < 0.001$) demonstrated significant correlation with progression even after multivariable model adjustment.

Conclusion

In this East Asian cohort, localized morphological asymmetry and focal apex decentration (notably IHD and IVA) demonstrated significant correlation with keratoconus progression beyond single baseline elevation or systemic comorbidities. Clinicians should prioritize monitoring these asymmetric indices and focal apex coincidences to facilitate early identification and timely intervention for progressive keratoconus.

Background

Keratoconus (KC) is a bilateral and asymmetric corneal disorder characterized by progressive thinning and ectasia of the cornea, leading to irregular astigmatism and decreased visual acuity. More importantly, progressive corneal distortion ultimately affects vision-related quality of life if left untreated. Although classified as a rare disease, KC is an important contributor to visual debilitation in the young population.[1, 2]

The diagnosis of KC is established through clinical examinations,[3] slit-lamp findings, pachymetry, keratometry and corneal imaging techniques. In particular, corneal imaging such as computerized corneal topography and tomography, enables detailed assessment of corneal surfaces and becomes a crucial tool for diagnosis and monitoring of KC progression. Several classification systems are proposed to stage disease severity, including the Amsler–Krumeich classification, the Belin ABCD grading system, and the Dutch Crosslinking for Keratoconus (DUCK) criteria.

The progression of KC, traditionally defined as a significant increase in keratometric power or corneal steepening over time, is a key determinant in treatment planning.[4] Optical correction with spectacles or rigid contact lenses is often sufficient for stable or slowly progressing cases, whereas corneal cross-linking (CXL) is the standard treatment for halting rapid progression. Early and reliable detection of progression is needed so that clinicians can determine who may benefit from CXL or further intervention. Therefore, the identification of risk factors predictive of worsening disease appears to be a major clinical objective.

Though the exact causes and underlying pathogenesis of KC are still unknown, several factors are generally recognized to contribute to the development of the disease, including chronic eye rubbing, atopy, UV ray exposure, and different geographical locations.[5] Previous studies have also highlighted several parameters potentially associated with KC progression, including onset age and baseline corneal curvature. Large-scale meta-analyses have found that younger patients and those presenting with steeper Anterior maximum curvature (Kmax) face a significantly higher risk of progression.[6, 7] Furthermore, specific clinical thresholds have been proposed to predict keratoconus progression, such as the index of surface variance (ISV) and the index of height asymmetry (IHA).[8] An elevated Inferior-superior index (IS index) is also found to be related to an increased risk for progressive keratoconus.[9, 10]

Concerning pachymetry, lower corneal thickness values are associated with an increased risk of keratoconus progression.[11] An annual thinnest corneal thickness (TCT) decrease also represents an advance of the pathology.[8] Other parameters such as the regularity index, spherical equivalent, and irregular astigmatism appear to be useful in predicting keratoconus progression.[8, 10–12] Recent evidence suggests that many KC cases exhibited documented progression earlier, with the ABCD progression display than that detected by standard Kmax changes, revealing that the Belin ABCD grading system may help in early identification of progression cases.[13, 14]

Despite these advancements, the interplay between many proposed predictive factors and KC progression remains insufficiently characterized across diverse populations. To address these gaps, our study retrospectively reviewed KC cases diagnosed over the past two decades. By comparing corneal imaging parameters and systemic comorbidities between progression and non-progression groups, this study aims to identify clinical and systemic factors associated with disease progression, thereby contributing to a more comprehensive understanding of KC pathophysiology and facilitating strategies in early intervention.

Methods

Study Design and Study Population

This retrospective study focused on individuals diagnosed with KC who had visited the Chang Gung Memorial Hospitals, Taiwan, between 2005 and 2025.

Inclusion criteria included: diagnosis of keratoconus by cornea specialists based on complete ophthalmic exam, corneal tomography and topography; at least two comprehensive eye examinations, corneal imaging, and regular follow-up for at least 2 years.

Exclusion criteria included: incomplete clinical records, refractive maps of insufficient quality, prior ocular trauma or surgery, such as cross-linking, cataract surgery, keratoplasty, and refractive laser surgery. Eyes with extreme baseline values of $K_{max} > 75$ D or corneal thickness < 350 μ m were also excluded.

In this study, KCN progression was defined as an increase of more than 1.00 diopter (D) in K_{max} within 12 months.[15] Eyes were classified into two group, based on KC progression or not. For statistical independence, only one eye per patient (index eye) was included in the analysis, following the recommendations by Armstrong.[16] The index eye was selected according to the following hierarchy: (1) if one eye met the progression criteria and the other eye did not, the progressing eye was chosen; (2) if both eyes were eligible for the same group, the index eye was selected by simple randomization.

Variables of interest

Complete ophthalmological examination data including spherical, cylindrical refractive errors, CDVA, slit-lamp biomicroscopy, and keratometry reading (K) were evaluated for all eyes. The tomographic data were derived from Scheimpflug imaging (Pentacam) (Oculus, Wetzlar, Germany), with three recordings performed for each eye every time. All images were reevaluated by cornea specialists first, then the one with the best quality status was chosen to ensure optimal quality. Systemic comorbidities were also collected by reviewing electronic medical records. Follow-up appointments were advised every 3 to 6 months based on individual risk assessment for disease progression. As a standard practice, patients should discontinue use of soft, hard, or scleral contact lenses 2 weeks before each appointment and examinations.

Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics software version 29.

All reported P values were two-sided, and a value of $P < 0.05$ was considered significant.

For univariate analysis, categorical variables were compared with Fisher's exact test. For continuous variables, the normality of data distribution was first assessed using the Shapiro-Wilk test. Continuous

variables following normal distribution were compared using Student's t-test, while non-normally distributed variables were analyzed using Mann–Whitney U test.

Subsequently, multivariate analysis was conducted to identify independent risk factors. A series of binomial logistic regression models was constructed, where each tomographic parameter was entered independently as the primary predictor, adjusted for baseline characteristics including onset ages, baseline Kmax and Belin grading. To account for multiple comparisons, P-values from multivariate analyses were further adjusted using the Benjamini–Hochberg false discovery rate (FDR) method. $P < 0.05$ after FDR correction was considered significant.

Results

Patient characteristics

A total of 164 eyes from 164 patients with keratoconus were included, of which 69 showed progression (32 were right eye, and 37 were left eye). In the demographic data analysis between two groups, there were no significant differences in onset age, sex ratio and baseline visual acuity (LogMAR). Both groups had a mean BMI within the borderline overweight range (overweight definition: $24 \leq \text{BMI} < 27$), with no significant difference between two groups ($P = 0.95$).

For baseline KC severity grading, Belin ABCD grading system between the two groups demonstrated significant differences ($P < 0.001$), while the distribution of Amsler–Krumeich grading and TKC staging by Pentacam were non-significant (Table 1).

Table 1
Baseline demographics of the progressive and non-progressive groups

Case number	progression group	non-progression group	P value
	n = 69(42.1%)	n = 95(57.9%)	-
Index eye ratio, OD:OS	32:37	49:46	0.51
Onset age(year)	22.78 ± 6.67	24.01 ± 7.97	0.30
Sex ratio, M:F	51:18	59:36	0.11
BMI	23.90 ± 5.05	24.00 ± 6.27	0.95
LogMAR	0.46 ± 0.31	0.38 ± 0.41	0.23
IOP (mmHg)	11.19 ± 4.03	13.24 ± 3.76	0.001
TKC staging			0.38
1	5(7.2%)	19(20.0%)	
2	30(43.5%)	24(25.3%)	
3	21(30.4%)	38(40.0%)	
4	13(18.8%)	14(14.7%)	
Amsler-Krumeich grading			0.15
1	6(8.7%)	21(22.1%)	
2	24(34.8%)	28(29.5%)	
3	21(30.4%)	26(27.4%)	
4	18(26.1%)	20(21.1%)	
Belin ABCD grading			< .001
0	0	3(3.2%)	
1	1(1.4%)	16(16.8%)	
2	19(27.5%)	31(32.6%)	
3	20(29.0%)	20(21.1%)	
4	29(42.0%)	25(26.3%)	

Data are presented as mean ± standard deviation or frequency (percentage).

BMI body mass index, *LogMAR* logarithm of the minimum angle of resolution, *IOP* intraocular pressure, *K* keratometry, *TKC* topographic keratoconus classification.

Association of clinical parameters with progression risk

The progression group had a significantly higher mean cylinder ($P = 0.002$) and steeper baseline Kmax ($P = 0.009$). Longitudinal corneal measurements also revealed marked differences, with the progression group showing significantly greater annual reduction in cylinder, thinnest corneal thickness, and greater annual increase in Kmax (all $P < 0.001$).

Baseline intraocular pressure (IOP) was slightly lower in the progression group ($P = 0.001$), while baseline thinnest corneal thickness (TCT) of the two groups showed no significant differences ($P = 0.45$) (Table 2).

Table 2
Comparison of baseline clinical characteristics across the two groups

Sphere (D)	progression group	non-progression group	Univariate <i>P</i> value	Multivariate <i>P</i> value	OR (95% CI)
	-5.93 ± 5.13	-5.18 ± 5.86	0.41	0.38	1.03 (0.97 to 1.10)
Cylinder (D)	-5.44 ± 3.14	-4.03 ± 2.55	0.002	0.04	0.89 (0.80 to 0.98)
average annual Cylinder change	-1.27 ± 1.64	-0.3 ± 1.42	< .001	0.003	0.58 (0.43 to 0.78)
Spherical Equivalent	-8.29 ± 5.85	-7.09 ± 6.28	0.23	0.52	0.97 (0.92 to 1.01)
Thinnest corneal thickness (TCT) (µm)	470.94 ± 48.38	472.15 ± 61.94	0.45	0.14	0.94 (0.91 to 1.02)
average annual TCT change (µm)	-16.56 ± 12.10	-2.36 ± 7.69	< .001	0.003	0.83 (0.77 to 0.88)
K1 (D)	47.44 ± 5.10	47.35 ± 6.19	0.46	0.10	1.00 (0.96 to 1.05)
K2 (D)	50.56 ± 5.93	50.82 ± 7.02	0.51	0.12	0.91 (0.82 to 1.00)
Kmax (D)	57.47 ± 7.32	54.96 ± 8.18	0.009	0.15	1.03 (0.97 to 1.12)
average annual Kmax change (D)	2.86 ± 3.28	-0.39 ± 1.10	< .001	0.003	93.62 (10.82 to 808.46)

Baseline systemic conditions

Analysis of underlying systemic and allergic conditions revealed no statistically significant differences between progression and non-progression groups. Factors such as asthma, systemic allergies, Down's syndrome, G6PD deficiency, and other comorbidities were distributed similarly across both cohorts (all $P > 0.05$) (Table 3).

Table 3
Distribution of systemic comorbidities across study cohorts

Case number	progression group	non-progression group	P value
	n = 69	n = 95	
Asthma, n (%)	9 (13.0%)	7 (7.4%)	0.29
Atopy, n (%)	5 (7.2%)	2 (2.1%)	0.13
Allergic rhinitis, n (%)	24 (34.8%)	21 (22.1%)	0.08
Diabetes mellitus, n (%)	1 (1.4%)	2 (2.1%)	1.00
Hypertension, n (%)	0	4 (4.2%)	0.14
Down's syndrome, n (%)	0	2 (2.1%)	0.51
G6PD deficiency, n (%)	1 (1.4%)	1 (1.1%)	1.00
Obesity(BMI $\geq$ 27 kg/m ²), n (%)	14 (20.3%)	12 (12.6%)	0.20
itchy and eye rubbing, n (%)	24 (34.8%)	19 (20.0%)	0.11
Allergy to drug or food, n (%)	Total: 5 (7.2%)	Total: 7 (7.4%)	1.00
Antibiotics	0	2	
Analgesic agent	0	1	
pyrin	0	1	
NSAID	3	1	
Sulfonamides	1	0	
others	1	2	
Thyroid disorder, n (%)	3 (4.3%)	5 (5.3%)	1.00
Mental disorder, n (%)	Total: 5 (7.2%)	Total: 5 (5.3%)	0.74
ADHD	3	3	
Depression/Anxiety	1	2	
schizophrenia	1	0	
Skin disease, n (%)	Total: 3 (4.3%)	Total: 3 (3.2%)	0.70
Lichen Simplex Chronicus	2	0	
Superficial layer infection	1	2	
Vitiligo	0	1	

Comparative analysis of baseline corneal parameters associated with progression

Several baseline indices maintained significant association with KC progression after multivariate adjustment and FDR correction: Indices representing corneal irregularity and asymmetry, including IS ($P < 0.001$, OR = 1.13), ISV ($P < 0.001$, OR = 1.02), IVA ($P < 0.001$, OR = 5.90), and IHD ($P < 0.001$, OR = 16.09) were significantly higher in the progression group. The progression group also exhibited a significantly lower Rmin ($P < 0.001$, OR = 0.40).

Beside the above findings, several baseline parameters also showed statistical significance in univariate analysis, although failed to reach significance level after adjusting for multiple comparisons: A lower Back Rm ($P < 0.001$) and shorter cone decentration distance ($P = 0.03$) were seen in progressive keratoconic corneas (Table 4).

Table 4
Comparison of baseline corneal parameters between the two groups

Anterior elevation (μm)	progression group	non-progression group	Univariate <i>P</i> value	Multivariate <i>P</i> value	OR (95% CI)
	24.10 ± 15.15	21.78 ± 16.97	0.42	0.65	1.02 (0.98 to 1.08)
Posterior elevation (μm)	49.79 ± 28.81	46.87 ± 32.06	0.59	0.61	1.00 (0.98 to 1.01)
Q-value	-0.96 ± 0.72	-0.82 ± 0.58	0.20	0.94	1.02 (0.57 to 1.83)
Rmin (mm)	5.53 ± 0.77	6.02 ± 0.93	< .001	0.03	0.40 (0.19 to 0.81)
Front Rm (mm)	6.79 ± 0.69	7.00 ± 0.75	0.07	0.75	0.89 (0.44 to 1.81)
Back Rm (mm)	5.37 ± 0.64	5.63 ± 0.78	0.03	0.57	0.69 (0.36 to 1.34)
IS index	13.43 ± 6.57	8.95 ± 7.13	< .001	0.02	1.13 (1.05 to 1.22)
ISV	115.5 ± 41.70	89.98 ± 45.67	< .001	0.02	1.02 (1.01 to 1.03)
IHA	53.64 ± 36.70	48.97 ± 35.15	0.42	0.88	1.00 (0.98 to 1.01)
IVA	1.08 ± 0.41	0.80 ± 0.45	< .001	0.02	5.90 (1.89 to 18.47)
IHD	0.14 ± 0.07	0.09 ± 0.06	< .001	0.01	16.09

Anterior elevation (μm)	progression group	non-progression group	Univariate <i>P</i> value	Multivariate <i>P</i> value	OR (95% CI)
	24.10 $\pm$ 15.15	21.78 $\pm$ 16.97	0.42	0.65	1.02 (0.98 to 1.08)
					(6.15 to 31.78)
Distance between Thinnest location and Kmax location (mm)	0.91 $\pm$ 0.57	1.16 $\pm$ 0.88	0.14	0.67	0.89 (0.85 to 1.02)
Cone decentration distance (mm)	1.05 $\pm$ 0.68	1.28 $\pm$ 0.72	0.03	0.51	0.84 (0.53 to 1.34)

Rmin minimum radius of sagittal corneal curvature, *Rm* mean radius of anterior corneal curvature, *Q-value* corneal asphericity, *IS index* inferior-superior index, *ISV* index of surface variance, *IHA* index of height asymmetry, *IVA* index of vertical asymmetry, *IHD* index of height decentration, *Cone decentration distance* distance between cone location and geometric center of cornea.

Influence of onset age and baseline Kmax on progression rate

Figure 1 presents the correlation between onset age and annual Kmax change: A clear downward trend was observed in the progression group, where younger patients demonstrated higher annual Kmax increase. In contrast, the non-progression group maintained a consistently flat profile across all age groups.

Figure 2 illustrates the relationship between baseline Kmax and annual Kmax change. As the steepening intensified, the variation of annual Kmax change increased, especially found in the progression group that patients presenting with higher baseline Kmax values exhibited a more aggressive increase in annual Kmax change.

Discussion

This study identifies key characteristics associated with keratoconus progression, revealing that localized corneal morphological irregularity and geometric decentration exhibit stronger associations with disease instability than systemic comorbid conditions. Baseline asymmetric markers—specifically ISV, IVA, IHD and IS— showed significant independent associations with progression. Among these, IVA and IHD emerged as the most reliable indicators for characterizing patients with a high risk of clinical

deterioration. These results are consistent with previous literature highlighting the diagnostic value of IS, ISV, IVA and IHD in the KC progression.[8–10, 13, 17–19] Notably, while Duncan et al.[8] identified IHA as a strong predictor, our data showed it to be non-significant, aligning with recent observations by Jamali et al.[20], suggesting that IHA may possess limited discriminative power in certain clinical phenotypes.

Despite the baseline differences in Belin ABCD grading, our multivariate analysis indicates that ISV, IVA and IHD remained independent factors after adjusting for onset ages, baseline Kmax and Belin grading. This may suggest that corneal geometric asymmetry potentially offers additional discriminative performance beyond single-point severity staging. Further studies are warranted to validate whether these topographic indices consistently outperform conventional staging in predicting progression.

Besides asymmetry indices, our study identified several significant trends that provide a holistic view of corneal deterioration. The progression group was characterized by a steeper baseline Kmax, higher cylinder and lower Rmin. These results reinforce the established risk profiles identified by previous studies, which highlight higher baseline Kmax as a significant risk factor for deterioration.[6–8, 13] Furthermore, the progression group exhibited markedly aggressive annual change in refractive cylinder and TCT, validating the role of TCT decline as a critical biomarker for disease activity.[8] Collectively, these findings suggest that rapid thinning and increasing irregular astigmatism are functional hallmarks of active ectasia.

Regarding patient demographics, while onset age did not differ significantly ($P = 0.30$), scatterplot analysis (Fig. 1) revealed a trend that younger onset age is associated with a steeper trajectory of annual Kmax increase. This observation aligns with the present view that juvenile-onset keratoconus often exhibits higher disease activity and a more aggressive clinical course, as evidenced by several studies.[6, 7, 17, 21] Martínez et al.[10] also identified age under 30 as a critical threshold for increased progression risk. However, the lack of absolute statistical significance in our cohort possibly reflects the inherent unpredictability of the disease. This variability corroborates Jamali et al.[20], who challenged the traditional dogma of adult stabilization by demonstrating that keratoconus can progress or fluctuate at any age.

Lastly, in our study, the progression group showed significantly lower baseline mean IOP. Corneal thinning—characteristic of advanced ectasia—are known to confound Goldmann-applanation-based readings, leading to systematic underestimation[22]. To enhance diagnostic accuracy, tools less influenced by corneal biomechanical variability, such as the Corvis ST, may provide a more accurate reflection of true IOP in the keratoconus population. Nonetheless, these findings also raise the possibility that altered biomechanical properties of the cornea, rather than IOP reduction, may be more relevant to ectatic progression.

Despite our efforts to ensure cohort comparability, the present study encountered several limitations. First, an inherent baseline imbalance in disease severity between the two groups, with the progression group presenting at more advanced Belin ABCD grading. While our multivariate analysis

attempted to adjust for baseline severity, the relatively small sample size of this cohort precluded more granular stratification by disease severity.

Second, due to the retrospective nature, data were collected from existing medical records. The presence of systemic conditions may be subject to underdiagnosis or underreporting, potentially leading to a measurement bias in underlying disease status.

Though our study did not identify statistically significant associations between systemic conditions and keratoconus progression, routine inquiry into a broad scope of systemic evaluations remains clinically relevant. Future multi-center prospective studies with larger, balanced cohorts that combine systemic evaluations will further empower ophthalmologists to validate these associated factors through stage-specific analysis and refine risk stratification models.

Conclusion

In conclusion, baseline localized corneal irregularity and morphological asymmetry—specifically the IHD, IVA, and ISV—demonstrated significant correlation with keratoconus progression beyond systemic status and traditional elevation metrics. Other baseline parameters, including steeper Kmax, higher cylindrical error, and shorter cone decentration distance are also features of progressive Keratoconus. Furthermore, aggressive longitudinal shifts in Kmax and thinnest corneal thickness serve as functional hallmarks of active ectasia. The above characteristics in progressive Keratoconic corneas may hold potential prognostic value in identifying patients at risk of progression. Clinicians should prioritize monitoring these corneal parameter shifts to identify patients at risk of progression and candidates for early intervention.

Abbreviations

KC

Keratoconus

TCT

Thinnest corneal thickness

Kmax

Anterior maximum curvature

IOP

Intraocular pressure

IHD

Index of height decentration

ISV

Index of surface variance

IVA

Index of vertical asymmetry

IHA
Index of height asymmetry
Rmin
Minimum radius of sagittal corneal curvature
Rm
Mean radius of anterior corneal curvature
IS index
Inferior-superior index

Declarations

Ethical approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board of Chang Gung Memorial Hospital (CGMH IRB; approval number: 202501262B0, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Consent for publication:

Not applicable.

Competing interests:

The authors declare no competing interests.

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Author Contribution

The study was conceptualized by Jin-Jhe Wang. Zhu-Yun Chen performed material preparation, data collection, statistical analysis and wrote the main manuscript. Jin-Jhe Wang contributed resources, provided intellectual support, and revised the manuscript. All authors read and approved the final manuscript.

Data Availability

The datasets generated and analyzed during this study are not publicly available due to ethical policy, but are available from the corresponding author on reasonable request.

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Figures

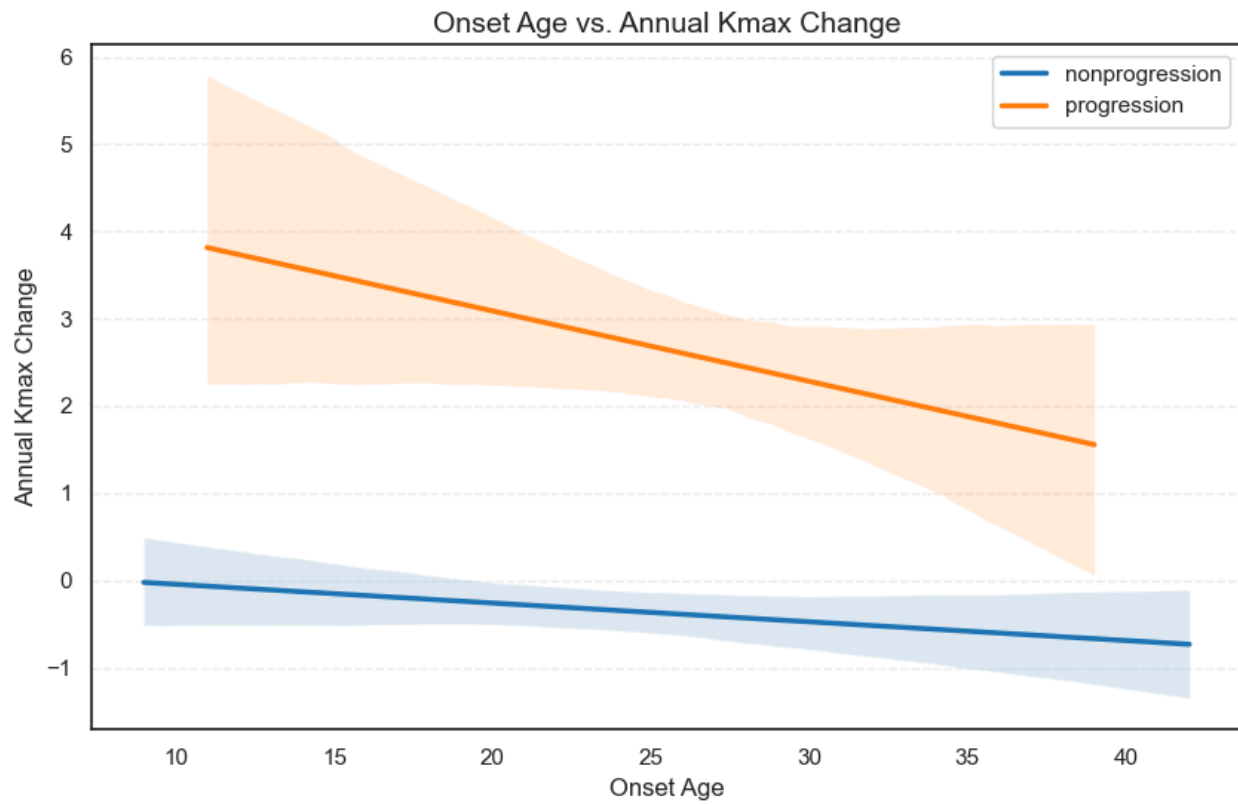


Figure 1

The pattern of Kmax changes across the two groups at various ages

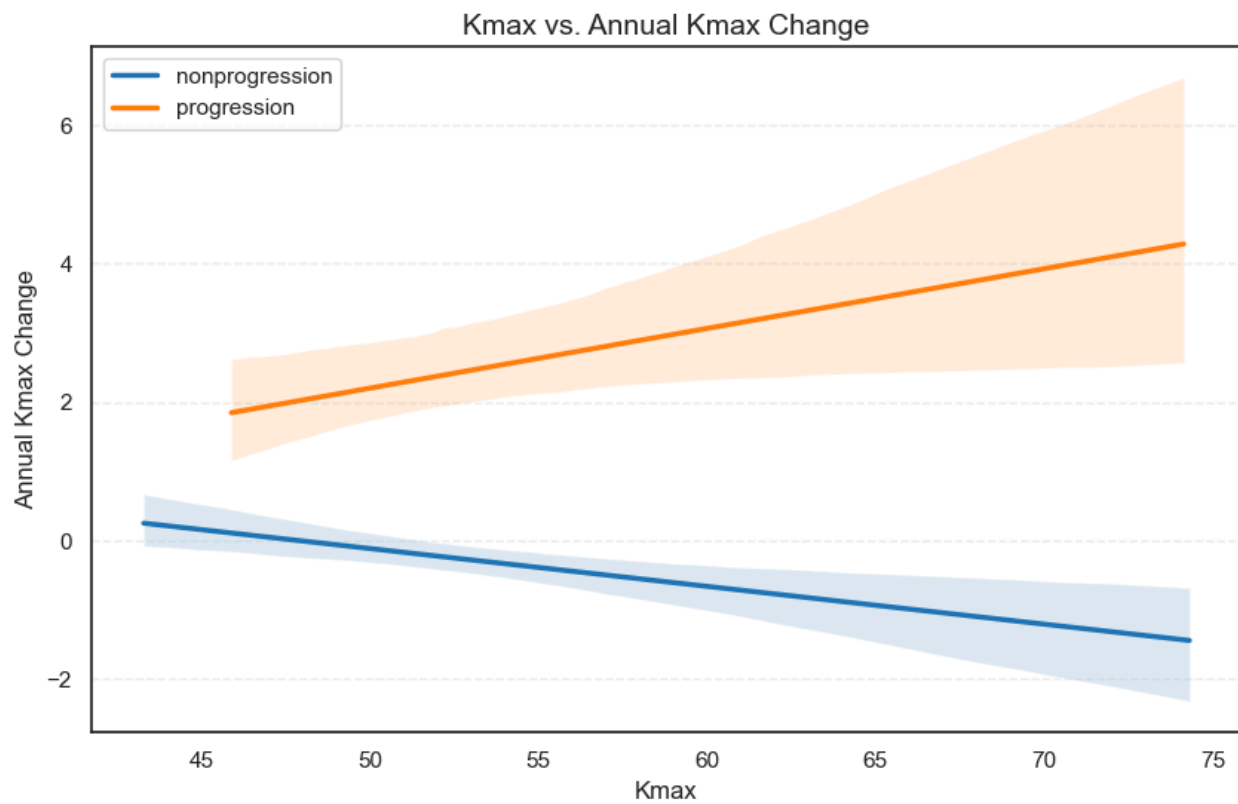


Figure 2

The pattern on Kmax changes across baseline Kmax for the two groups studied