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Continuous Intracorneal Ring Implantation in Keratoconus; Efficacy and Complications, Impact on Vision-Related Quality of Life and Machine-Learning for Surgical Decision Making

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1. Publication

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ORIGINAL RESEARCH

Continuous Intracorneal Ring Implantation in Keratoconus: Efficacy, Predictive Factors, and Complications

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Purpose: To examine the clinical outcomes, predictors of visual improvement and complications of continuous intracorneal ring (ICCR) implantation in patients with keratoconus and confirmed contact-lens intolerance (CLI).

Methods: This nonrandomized, multi-centric, retrospective cohort study examined visual, keratometric and clinical outcomes evaluated after a minimum follow-up of 2 months. Among the inclusion criteria for the standard treatment group (STG) were corrected distance visual acuity (CDVA) <20/25 Snellen, no central corneal scars, minimum corneal thickness >350µm, and central mean keratometry reading (meanK) <55 diopters. All other eyes were classified as non-standard treatment group.

Results: A total of 118 eyes of 118 patients with aged 32 ± 11 years were included in this study. At a median follow-up of 161 days (interquartile range: 111–372 days) ICCR implantation improved the CDVA from a mean of 0.38 to 0.15 logMAR ($p<0.0001$). Our correlation analysis showed lower preoperative CDVA to be the single best predictor of CDVA improvement, with eyes of a CDVA of 20/80 or lower improving by 4.3 ± 2.0 lines on average. Eyes with a meanK >55 diopters gained 9.04±4.83 lines in UDVA and 2.86±3.09 lines in CDVA. However, postoperatively these eyes had a CDVA of 0.32±0.21 logMAR which is significantly inferior to the STG outcome ($p=0.001372$). Fifteen eyes (12.7%) had to undergo a ring exchange procedure because of refractive under- (9 eyes) or overcorrection (6 eyes). Two eyes (1.7%) experienced medical complications.

Conclusion: This study confirms the inclusion criteria of ICCR implantation in KC eyes with CDVA <20/25 and CLI. Particularly in eyes with a preoperative CDVA <20/80 and a meanK <55 diopters, ICCR implantation should be considered due to its reversibility and low rates of serious complications. The main challenge remains in the low predictability of the magnitude of this improvement in eyes with CDVA >20/30.

Keywords: keratoconus, MyoRing, continuous intracorneal ring, intracorneal continuous ring

Introduction

In the last 20 years, the range of treatment modalities for Keratoconus (KC) has vastly expanded. Novel contact-lens types[1] can significantly improve visual acuity by correcting both lower- and higher-order aberrations. A central problem, however, is that, due to irregularities of the corneal surface, many patients begin to experience CL intolerance (CLI) and surgical measures become necessary.[2]

Classical corneal crosslinking (CXL) is an established surgical first step to halt KC by stabilizing the cornea and thereby prevents further ectasia and decreases in visual acuity.[3–6]

To improve vision in a clinically significant manner, the minimally invasive embedding of intracorneal implants have become increasingly popular. Intracorneal ring segments (ICRS) and 360° intracorneal continuous rings (ICCR) have been developed by different manufacturers and have shown their efficacy in significantly improving visual acuity in eyes with KC and in postponing or completely eliminating the need for keratoplasty.[7–9] The reported advantages of ICCR

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compared to ICRS are the more robust improvement of spherical aberrations,[7] increased biomechanical stability[10,11] and their sustained effectiveness in progressive KC.[8,12–15]

However, a recent systematic review and meta-analysis on ICCR implantation in KC highlighted the need for high-powered studies, mainly due to heterogeneity in corrected distance visual acuity (CDVA) outcome.[9] Furthermore, only few studies have reported on the surgical complications occurring after ICCR implantation and even less have reported on the need for repeated surgery to address over or under correction.[16,17]

To provide further insight into the efficacy of this treatment option and its complications for patients with KC, we retrospectively examined the data collected at three different centers. All treatments were planned in coordination with the manufacturer's reading center, and all patients met the same inclusion and exclusion criteria for ICCR implantation.

Materials and Methods

This retrospective case-series was performed in accordance with the tenets of the Declaration of Helsinki and was approved by the ethics committee of the Hamburg medical association in April 2019 with the approval number PV6017. All patients provided informed consent for anonymized data analyses.

Patient Selection

Patients were diagnosed with KC based on their medical history, slit-lamp examination results, and corneal topography and tomography findings (irregular astigmatism displayed by one or more of the following findings: a steepest K value ≥47 diopters (D); an inferior-superior K-value difference (I-S value) of >1.5 D and/or a skewed topographical axis. Patients aged 16 years or older with a thinnest pachymetry reading >350 µm, a CDVA <20/25, and without central corneal scarring were considered for ICCR implantation. Only patients with persistent contact-lens intolerance after multiple fitting attempts, one of which must have been done at specialized contact lens institute were included in the study. To prevent aniseikonia, patients with a projected postoperative anisometropia >4 D were considered ineligible for surgery. The "keratometric limit" beyond which we expected an ICCR to be insufficient for visual rehabilitation was set to a mean central simulated keratometry reading ($meanK = \frac{SIMK1+SIMK2}{2}$) of 55 D.[14] When patients met these criteria, the decision to perform ICCR implantation was based on the degree of subjective visual impairment. In some cases, we deviated from this treatment algorithm and included patients that did not meet all the aforementioned criteria. The eyes of these patients were defined as the non-standard treatment group (NSG). Surgery was performed for these patients when the alternative treatment (laser-assisted therapeutic keratectomy with CXL[18] or keratoplasty) was not feasible for the patient.

The primary aim of the surgery was visual rehabilitation, ie an improvement of the best spectacle-corrected distance visual acuity (CDVA). Additional aims can be halting the progression of KC by stabilizing the corneal after unsuccessful CXL and to reduce anisometropia, thereby improving functional binocular CDVA. In this trial, however, eyes with previous CXL were not included.

Postoperatively, beside a consult on the first postoperative day, patients were scheduled for a follow-up 2–3 months after ICCR implantation. At this follow-up visit, a definitive evaluation of the surgical effect can be made and the need for potential ring-exchange can be assessed.[19] Only patients who realized their follow-up at least 2 months after surgery were included in the study. If, at follow-up, both the physician in charge and the manufacturer's reading center considered the visual rehabilitation to have been maximized with the ring size employed, the patient was enrolled in the study. When a second surgery was performed to exchange a ring due to refractive over- or under-correction or due to complications, we included the preoperative values of the first surgery and the postoperative values of the last surgery in the analysis. A subgroup analysis was done to compare eyes undergoing single and those undergoing two surgeries. Patients scheduled for a ring exchange at the time of data collection were excluded. We also excluded all eyes that had previously undergone ocular surgery including CXL. To avoid biasing our analysis by treating two eyes within the same patient as independent, we only included one of two eyes (selected at random) when patients had undergone surgery for both eyes.

Instruments and Procedures

Topography and tomography were performed on all patients using two different Scheimpflug-Placido camera systems (Pentacam HR, Oculus and Galilei G6, Ziemer Ophtalmic Systems AG). To implant the ICCR (MyoRing), an intra-corneal

pocket with a diameter of 8.7 mm was created at a corneal depth of 300 µm. Pocket creation was carried out either using mechanical dissection with a microkeratome (Pocketmaker®, DIOPTEX GmbH, Austria) or a femtosecond laser (Femto LDV Z8®, Ziemer Ophthalmic Systems AG, Port, Switzerland) at the surgeon's discretion. The correct MyoRing dimensions were provided by the manufacturer (DIOPTEX GmbH, Linz, Austria) based on a mathematical corneal model after uploading the relevant parameters to an online database. The treatments were performed by one of three surgeons (AD, SL, JS). All steps have been described in previous publications.[11,13]

Main Outcome Measures

Our primary outcome measures were the improvement of uncorrected distance visual acuity (UDVA) and CDVA as measured in logMAR chart lines. UDVA and best spectacle-CDVA were measured using a decimal scale and transformed into logMAR values for statistical analysis. As previous authors have done, the safety Index was defined as follows: the quotient between the postoperative CDVA and the preoperative CDVA.[20]

The rate of intraoperative and/or postoperative complications were also cataloged. Simulated central K values (SIM K1=steep, SIM K2=flat and meanK) were determined in the central 1–4-mm zone with a refractive index of n=1.3375 with the axial (sagittal) curvature map. Kmax and thinnest Pachymetry were determined on an 8-mm zone of the anterior surface.

Follow-Up

Follow-up examinations included slit-lamp examinations, assessments UDVA and CDVA, corneal topography and tomography, and corneal optical coherence tomography (OCT) examinations to assess the implantation depth of the ring. KC progression was assessed using tangential (instantaneous) anterior curvature maps and manifest refraction.

Statistical Analysis

We calculated the median, mean, standard deviation (SD) and interquartile range of all continuous variables for the included eyes. Where applicable, the data are presented as the mean ± standard deviation (SD) while non-normally distributed data are represented using the median and interquartile range (Q25:Q75).

All available variables were tested for normality using a conjunction of a graphical quantile–quantile test, and the Shapiro–Wilk test. We used the two variations of the *t*-test to assess for significant differences between variables sampled from a Gaussian distribution. Non-normally distributed data were analyzed using the Wilcoxon signed rank test for matched pairs (before and after) and the Mann–Whitney *U*-Test for independent samples.

Correlational analyses were computed with the appropriate parametric (Pearson) or non-parametric (Spearman) test using Bonferroni correction. The threshold for statistical significance was set at $p < 0.05$. All statistical analyses were performed using the programming language Python 3.7 run on PycharmEdu2019 (JetBrains, Czech Republic) for Microsoft Windows.

For statistical analysis, all visual acuities were converted to logarithm of minimum angle of resolution (logMAR). The visual acuities of counting finger, hand motion, and light perception were converted to 0.014, 0.005 and 0.001 in decimal notation respectively as described in previous studies.[21]

Results

In total, 140 eyes of KC patients with full preoperative data were considered for the study. We excluded four eyes that were still scheduled for a ring exchange; one eye had previous penetrating keratoplasty; seven eyes of patients with bilateral surgery were randomly excluded to avoid overestimating the statistical power of our analysis. Finally, we excluded 10 eyes in which the final follow-up was performed before the completion of 60 days. We therefore included 118 eyes in our analysis. No patient was lost to follow-up.

Overall, the median age of patients was 32 ± 11 years with 17 eyes (14%) having to undergo additional surgeries. Visual acuity improvements postoperatively were 6.0 ± 4.8 lines in UDVA and 2.3 ± 2.1 lines in CDVA. The median follow-up period was 161 days (111:372).

Descriptive statistics on pre- and postoperative parameter values are displayed in Table 1. The statistics on the differences between pre- and postoperative values are displayed in Table 2.

Table 1 Descriptive Statistics

Parameter	Preoperative Values		Postoperative Values		p
	n	Mean ± SD	n	Mean ± SD	
UDVA (logMAR)	118	0.99 ± 0.45	118	0.39 ± 0.3	<0.0001
CDVA (logMAR)	118	0.38 ± 0.23	118	0.15 ± 0.15	<0.0001
Sph (D)	106	-2.5(−4.94:-0.06)*	107	0.82 ± 2.32	<0.0001
Cyl (D)	106	−3.82 ± 2.32	107	−1.5(−3.0: −0.75)	<0.0001
SE (D)	106	−4.0(−7.0: −2.03)	107	−0.19 ± 2.2	<0.0001
K1 preop (D)	118	47.38 ± 4.18	111	42.35 ± 2.58	<0.0001
K2 preop (D)	118	50.59 ± 4.85	111	45.75 ± 3.16	<0.0001
meanK (D)	118	48.98 ± 4.23	111	44.05 ± 2.66	<0.0001
topoAsti (D)	118	3.82 ± 2.49	111	2.9(1.96: 4.39)*	0.1195
Kmax preop (D)**	118	57.58 ± 7.67	112	53.70(48.68: 57.32)*	<0.0001
min. Pachy (μm)	117	445.18 ± 41.22	110	450.24 ± 45.67	0.3837

Notes: *Denotes median (interquartile range) for variables that are not normally distributed as **Preoperative and postoperative values for Kmax could be located at completely different points in the cornea.
Abbreviations: logMAR, logarithm of the minimum angle of resolution; D, Diopter; SD, standard deviation; Sph, refractive sphere; Cyl, refractive cylinder; SE, spherical equivalent; K1, flat meridian of anterior simulated keratometry, K2, steep meridian of anterior simulated keratometry min. Pachy, thinnest pachymetry reading; Kmax, maximum keratometry reading; topo Asti, topographical astigmatism.

Table 2 Difference Between Preoperative and Postoperative Values

Parameter	n	Mean ± SD	p
Δ UDVA (logMAR)	118	−0.6 ± 0.48	<0.0001
Δ CDVA (logMAR)	118	−0.22 ± 0.21	<0.0001
Δ Sph (D)	97	3.74 ± 3.78	<0.0001
Δ Cyl (D)	97	1.84 ± 2.58	<0.0001
Δ SE (D)	97	3.88(1.75 to 7.0)*	<0.0001
Δ K1 preop (D)	111	−4.93 ± 3.25	<0.0001
Δ K2 preop (D)	111	−4.62 ± 3.61	<0.0001
Δ meanK (D)	111	−4.78 ± 3.1	<0.0001
Δ topoAsti (D)	111	−0.28 ± 2.44	0.1195
Δ Kmax preop (D)**	112	−3.91 ± 6.75	<0.0001
Δ min. Pachy (μm)	109	4.73 ± 25.53	0.3837

Notes: *Denotes values that are not normally distributed in the format median (interquartile range) *Preoperative and postoperative values for Kmax could be located at completely different points in the cornea. **Preoperative and postoperative values for Kmax could be located at completely different points in the cornea. Δ is the difference between the postoperative and the preoperative value of the same parameter.
Abbreviations: logMAR, logarithm of the minimum angle of resolution; D, Diopter; SD, standard deviation; Sph, refractive sphere; Cyl, refractive cylinder; SE, spherical equivalent; K1, flat meridian of anterior simulated keratometry, K2, steep meridian of anterior simulated keratometry min. Pachy, thinnest pachymetry reading; Kmax, maximum keratometry reading; topo Asti, topographical astigmatism.

Figure 1 depicts the postoperative changes in distance visual acuity lines for each eye. Figure 2 shows the CDVA improvement in all eyes with respect to the day of follow-up at which this was measured.

Subgroup Analyses – Multiple Surgeries and Non-Standard Treatment Group

Among the eyes that underwent multiple surgeries, 17 underwent one additional treatment. One eye had three surgeries overall. The reasons for reoperation are listed under the subheading Complications.

The outcomes comparing eyes that only underwent one surgery and the ones undergoing multiple surgeries are listed in Table 3.

We performed another subgroup analysis for the 14 eyes in the NSG. Alternative treatments were not feasible for those patients. Eight of 14 eyes were classified as non-standard for their meanK being above our threshold of 55 d with meanK at 59.18 ± 3.29 and Kmax at 73.48 ± 11.82. These eyes gained 9.04±4.83 lines in UDVA and 2.86±3.09 lines in CDVA with a postoperative vision of 0.32±0.21 CDVA significantly worse than STG eyes (p=0.001372). One patient had a min. pachy of 346µm and had a femto-laser assisted pocket creation at 290µm. Five eyes only had mild KC findings with preoperative CDVA >20/25 and Kmax values below 47D. Three of those patients were treated with the main objective of improving UDVA in myopic patients. Two of the mild KC patients underwent ICCR implantation to relieve anisometropia due to asymmetrical KC. All comparisons between STG and NSG can be found in Table 4.

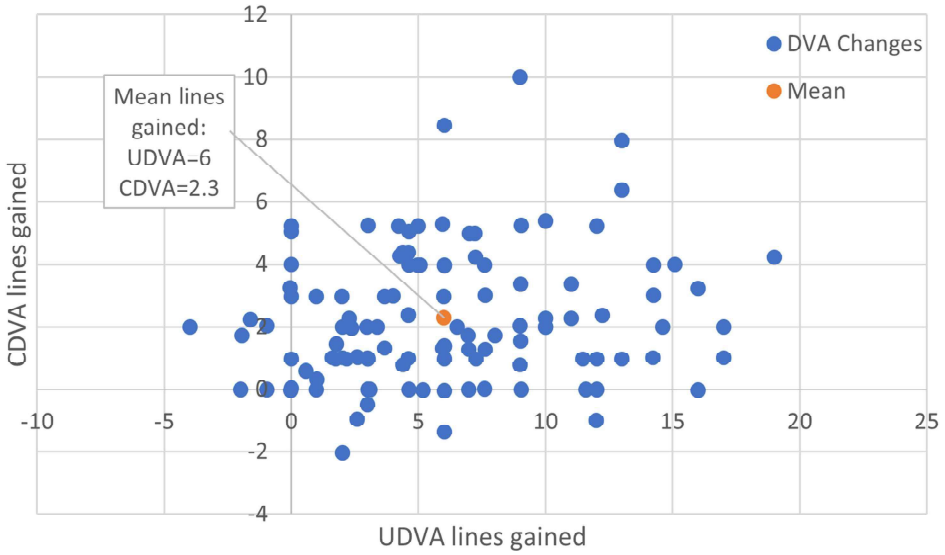

Figure 1 Simultaneously displayed changes in UDVA and CDVA. Mean: Denotes the simultaneous representation of mean changes in UDVA (6 lines) and mean changes in CDVA (2.3 lines).

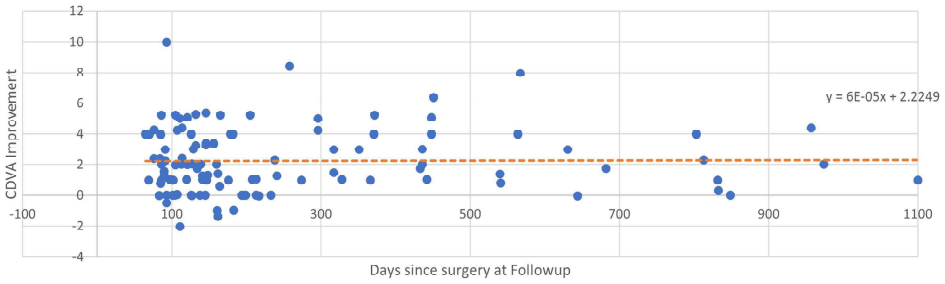

Figure 2 CDVA changes across time. The relationship between the day of last follow-up and the CDVA change after surgery of different eyes included in the study is displayed. The upper right corner shows the mathematical equation of the trendline in scientific notation: $y = 6 * 10^{-5} * x + 2.2$.

Table 3 Subgroup Comparison Multiple Surgeries versus Single Surgery Eyes

Parameter	Single Surgery Eyes		Multiple Surgeries (Compounded Outcome)		p
	n	Mean ± SD	n	Mean ± SD	
Age (years)	101	32.27 ± 10.78	17	32.59 ± 10.81	0.9106
Surgeries	101	1.0 (1.0: 1.0)*	17	2.0 (2.0: 2.0)*	<0.0001
Safety Index	101	1.59 (1.25: 2.5)*	17	1.55 ± 0.76	0.0465
Follow-up (days)	101	156.0 (107.0: 351.0)*	17	213.0 (142.0: 564.0)*	0.0845
UDVA Lines gained	101	6.3 ± 4.8	17	3.0 (1.7: 5.0)*	0.012
CDVA Lines gained	101	2.4 ± 2.0	17	1.6 ± 2.0	0.1396
Preoperative values					
UDVA (logMAR)	101	1.0 ± 0.42	17	0.7 (0.7: 1.3)*	0.1518
CDVA (logMAR)	101	0.38 ± 0.23	17	0.3 (0.2: 0.4)*	0.3967
Sph (D)	90	−3.39 ± 4.01	16	−0.12 (−3.12: 0.26)*	0.0214
Cyl (D)	90	−3.5 (−5.75: −2.0)*	16	−3.66 ± 1.99	0.7614
SE (D)	90	−5.32 ± 4.19	16	-2.12 (−5.09: −1.44)*	0.0316
K1 preop (D)	101	47.62 ± 4.24	17	45.97 ± 3.47	0.1343
K2 preop (D)	101	50.4 (47.3: 53.41)*	17	48.9 ± 3.29	0.0608
meanK (D)	101	49.24 ± 4.31	17	47.44 ± 3.28	0.1047
topoAsti (D)	101	3.95 ± 2.6	17	3.06 ± 1.41	0.1737
Kmax preop (D)	101	57.3 (52.4: 61.6)*	17	55.67 ± 4.31	0.1486
min. Pachy (µm)	100	443 ± 40	17	458 ± 47	0.1722
Postoperative values					
UDVA (logMAR)	101	0.37 ± 0.25	17	0.53 ± 0.47	0.0372
CDVA (logMAR)	101	0.15 ± 0.15	17	0.2 ± 0.18	0.1532
Sph (D)	90	0.91 ± 2.4	17	0.32 ± 1.7	0.3447
Cyl (D)	90	−1.98 ± 1.8	17	−2.13 ± 1.87	0.7496
SE (D)	90	−0.08 ± 2.27	17	−0.74 ± 1.64	0.2591
K1 preop (D)	95	42.4 ± 2.48	16	42.08 ± 3.06	0.6435
K2 preop (D)	95	45.79 ± 3.13	16	45.52 ± 3.32	0.7559
meanK (D)	95	44.1 ± 2.59	16	43.8 ± 3.04	0.683
topoAsti (D)	95	2.9 (1.9: 4.32)*	16	3.45 ± 1.94	0.3941
Kmax preop (D)	96	53.86 ± 6.13	16	52.73 ± 6.15	0.4998
min. Pachy (µm)	95	450 ± 46	15	450 ± 46	0.983

Notes: This table compares eyes having had one surgery (group 1) and those having had multiple surgeries (group 2). Postoperative values for eyes in group 2 are the outcomes after all surgeries. *Non-normally distributed data are displayed as median (25th percentile:75th percentile).

Abbreviations: logMAR: logarithm of the minimum angle of resolution; D: Diopter; SD: standard deviation; Sph: refractive sphere; Cyl: refractive cylinder; SE: spherical equivalent; K1: flat meridian of anterior simulated keratometry, K2: steep meridian of anterior simulated keratometry min. Pachy: thinnest pachymetry reading; Kmax: maximum keratometry reading; topo Asti: topographical astigmatism.

Table 4 Standard Treatment Group Vs Non-Standard Treatment Group

Parameter	STG		NSG		p
	n	Mean ± SD	n	Mean ± SD	
Age (years)	104	32.65 ±10.94	14	29.79 ±9.95	0.35438
Safety Index	104	1.91 ±1.21	14	2.29 ±1.82	0.29502
Follow-up (days)	104	362.2 ±511.41	14	313.57 ±274.38	0.72831
UDVA Lines gained	104	5.68 ±4.75	14	8.05 ±4.73	0.08217
CDVA Lines gained	104	2.3 ±1.95	14	1.85 ±2.92	0.44447
Preoperative values					
UDVA (logMAR)	104	−3.04 ±4.11	14	−4.6 ±4.54	0.10173
CDVA (logMAR)	104	−3.96 ±2.28	14	−2.71 ±2.6	0.95539
Sph (D)	94	−5.02 ±4.22	12	−5.96 ±5.25	0.22119
Cyl (D)	94	46.8 ±3.4	12	51.68 ±6.68	0.07968
SE (D)	94	49.94 ±3.64	12	55.39 ±8.95	0.48187
K1 preop (D)	104	48.37 ±3.16	14	53.54 ±7.6	0.00002
K2 preop (D)	104	3.84 ±2.18	14	3.71 ±4.28	0.00005
meanK (D)	104	56.89 ±5.48	14	62.75 ±16.23	0.00001
topoAsti (D)	104	445.85 ±37.39	14	440.21 ±65.54	0.85997
Kmax preop (D)	104	−3.04 ±4.11	14	−4.6 ±4.54	0.00700
min. Pachy (μm)	104	−3.96 ±2.28	14	−2.71 ±2.6	0.63450
Postoperative values					
UDVA (logMAR)	104	0.39 ±0.3	14	0.37 ±0.31	0.74838
CDVA (logMAR)	104	0.15 ±0.14	14	0.2 ±0.22	0.26807
Sph (D)	94	0.86 ±2.37	13	0.48 ±2.08	0.58280
Cyl (D)	94	−2.06 ±1.87	13	−1.6 ±1.38	0.39278
SE (D)	94	−0.17 ±2.25	13	−0.32 ±1.98	0.82006
K1 preop (D)	98	42.17 ±2.41	14	43.77 ±3.45	0.03546
K2 preop (D)	98	45.58 ±3.1	14	47.04 ±3.54	0.12008
meanK (D)	98	43.87 ±2.53	14	45.4 ±3.42	0.05224
topoAsti (D)	98	3.48 ±2.22	14	3.27 ±1.4	0.75159
Kmax preop (D)	98	53.8 ±6.05	14	52.99 ±7.2	0.64962
min. Pachy (μm)	97	450.89 ±43.48	14	445.38 ±62.94	0.68664

Notes: This table compares eyes in the standard treatment group (STG) and non-standard treatment group (NSG). STG fit all the classical inclusion criteria, while NSG eyes received treatment when the alternative treatment keratoplasty or laser-assisted topography was not feasible for the patient or the primary aim was not to improve CDVA.

Abbreviations: logMAR, logarithm of the minimum angle of resolution; D, Diopter; SD, standard deviation; Sph, refractive sphere; Cyl, refractive cylinder; SE, spherical equivalent; K1, flat meridian of anterior simulated keratometry, K2, steep meridian of anterior simulated keratometry min. Pachy, thinnest pachymetry reading; Kmax, maximum keratometry reading; topo Asti, topographical astigmatism.

Correlation Analysis

Table 5 shows the correlation of preoperative parameters with the UDVA lines gained and CDVA lines gained. The Pearson *r* correlation coefficients are found in the columns of "UDVA lines correlation coefficient" and "CDVA lines correlation coefficient", respectively. The single best predictor of CDVA lines gained is preoperative CDVA. In Figure 3 one can observe the CDVA lines gained for each eye with respect to the preoperative CDVA in the same eye, further underlining the significant correlation between both variables.

Exemplary Case

To illustrate a typical outcome, we chose a typical patient with regards to UDVA and CDVA improvements. All his preoperative parameter values except age lie within half a standard deviation from the median. The patients' age is within one standard deviation from the median. In the concerned eye, the preoperative unaided vision was 20/200 with a CDVA of 20/70. UDVA improved by 4.6 lines (study average: 5.9) to 20/70 while his CDVA improved by 2.4 lines (study average: 2.1) to 20/40. Figure 4 shows a top-to-bottom comparison of the curvature maps one week before and 3.5 months after surgery in our exemplary case.

Complications

In all, 15 eyes (12.7%) had to undergo a ring exchange procedure because of refractive under- (9 eyes) or overcorrection (6 eyes). One eye developed a corneal herpes simplex infection, which warranted explantation 8 months post-operatively. Re-implantation of the ICCR as performed 4 months later. Nevertheless, the patient gained 6.0 lines in UDVA and 3.9 lines in CDVA as a combined result of all procedures.

Table 5 Correlation of Preoperative Parameters with UDVA Lines Gained and CDVA Lines Gained

Preoperative Parameter	UDVA Lines Correlation Coefficient	p	CDVA Lines Correlation Coefficient	p
Age (year)	0.15	0.1121	0.04	0.642
UDVA (logMAR)	0.79	<0.0001	0.09	0.3414
CDVA (logMAR)	0.06	0.5228	0.75	<0.0001
Sph (D)	−0.44*	<0.0001	−0.24*	0.0116
Cyl (D)	0.05	0.646	−0.16	0.0915
SE (D)	−0.44*	<0.0001	−0.3*	0.0016
K1 preop (D)	0.31	0.0006	0.27	0.0034
K2 preop (D)	0.14	0.1181	0.33	0.0002
meanK (D)	0.24	0.0101	0.32	0.0004
topoAsti (D)	−0.03	0.7739	0.15	0.0954
Kmax preop (D)	0.12	0.2109	0.35	0.0001
min. Pachy (µm)	−0.19	0.0442	−0.34	0.0002

Notes: This table displays how preoperative parameters correlate with the postoperative gains in UDVA and CDVA lines. The correlation coefficient denotes the Pearson r coefficient or in the case of non-normally distributed variables the Spearman rank ρ coefficient (*). A Bernoulli-adjusted alpha' would yield significant correlations for p-values equal or below: 0.0042.

Abbreviations: logMAR, logarithm of the minimum angle of resolution; D, Diopter; Sph, refractive sphere; Cyl, refractive cylinder; SE, spherical equivalent; K1, flat meridian of anterior simulated keratometry, K2, steep meridian of anterior simulated keratometry min. Pachy, thinnest pachymetry reading; Kmax, maximum keratometry reading; topo Asti, topographical astigmatism.

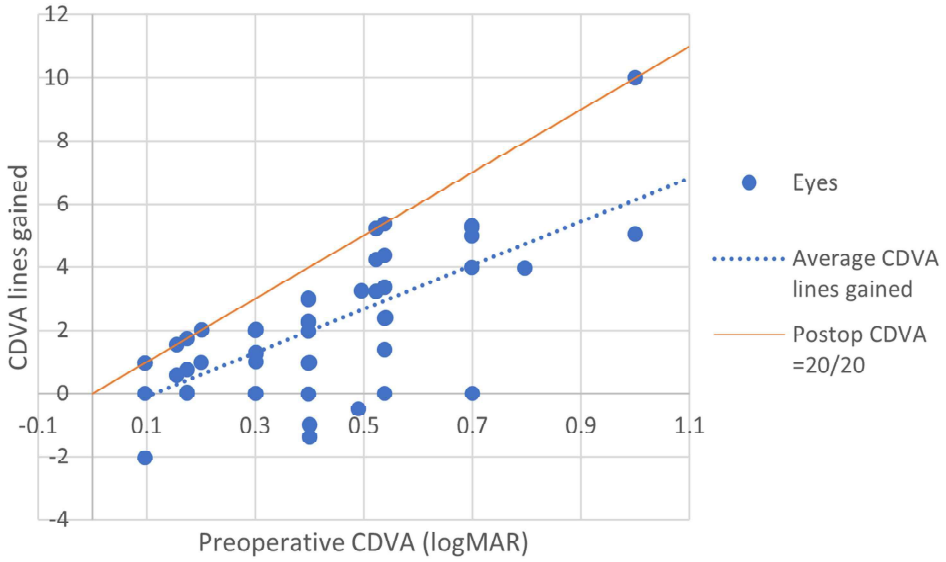

Figure 3 CDVA lines distribution and correlation with preoperative CDVA. The orange line denotes the number of lines necessary to achieve a postoperative vision of 20/20 Snellen. The blue dotted line is a trendline, achieved by linear regression with conventional least squares as loss function. This trendline can be understood as the average CDVA lines improvement for a given preoperative CDVA.

In one case, the surgical pocket created using the PocketMaker was too superficial. Initially, the patient had good postoperative vision; however, a month after surgery after minor trauma to the eye with a pillowcase, the patient started experiencing persistent epiphora. Four months after surgery, the ICCR was explanted due to the risk of extrusion. This eye gained 2.0 lines of UDVA but lost 2.0 lines of CDVA.

No eye included developed post-operative KC progression, epithelial ingrowth, or any signs of sterile inflammatory responses due to the implant or the surgical trauma.

Discussion

In this study, all analyzed visual acuity and topography parameters improved significantly ($p < 0.001$) with the exception of the thinnest pachymetry value (min. pachy) and topographical astigmatism (topoAsti).

The mean improvement in CDVA, was highly variable, with a standard deviation of 2.1 lines ranging from −2.0 to 10 Lines as can be seen in Figure 3. This underlines our further need for improving selection criteria by performing subgroup analyses.

Our subgroup analysis showed eyes with a higher SE were more likely to require reoperation (group 2). Eyes in group 2 had a tendency for inferior compounded CDVA gains compared to group 1 ($p=0.13958$).

Our correlation analysis showed preoperative vision to be the single most useful predictor of postoperative improvement in vision. In other words, high potential for improvement in CDVA was associated with a greater gain in CDVA lines. For instance, the eyes in the upper quartile of preoperative CDVA (as measured in logMAR) were eyes with a CDVA of 20/80 and lower, as measured in Snellen. These eyes gained 4.3 ± 2.0 lines in CDVA on average (Appendix A of Supplemental Data).

Our analyses further demonstrated that the degree of myopia predicts the average improvement in UDVA (Table 5), which is in line with the results in previous studies.[16,22] What has not been published before, is that preoperative myopia correlates weakly but significantly with the CDVA improvement (r_{SE}=−0.3 and p=0.0116) before applying an optional Bonferroni correction.[23] This further corroborates the link between our diverging outcomes in Group 1 and 2 and higher myopia in group 1.

The inverse correlation between SE and CDVA lines gained, could in part or entirely be explained by the correlation of myopia with advanced KC and hence, high potential for improvement. To investigate whether these correlations

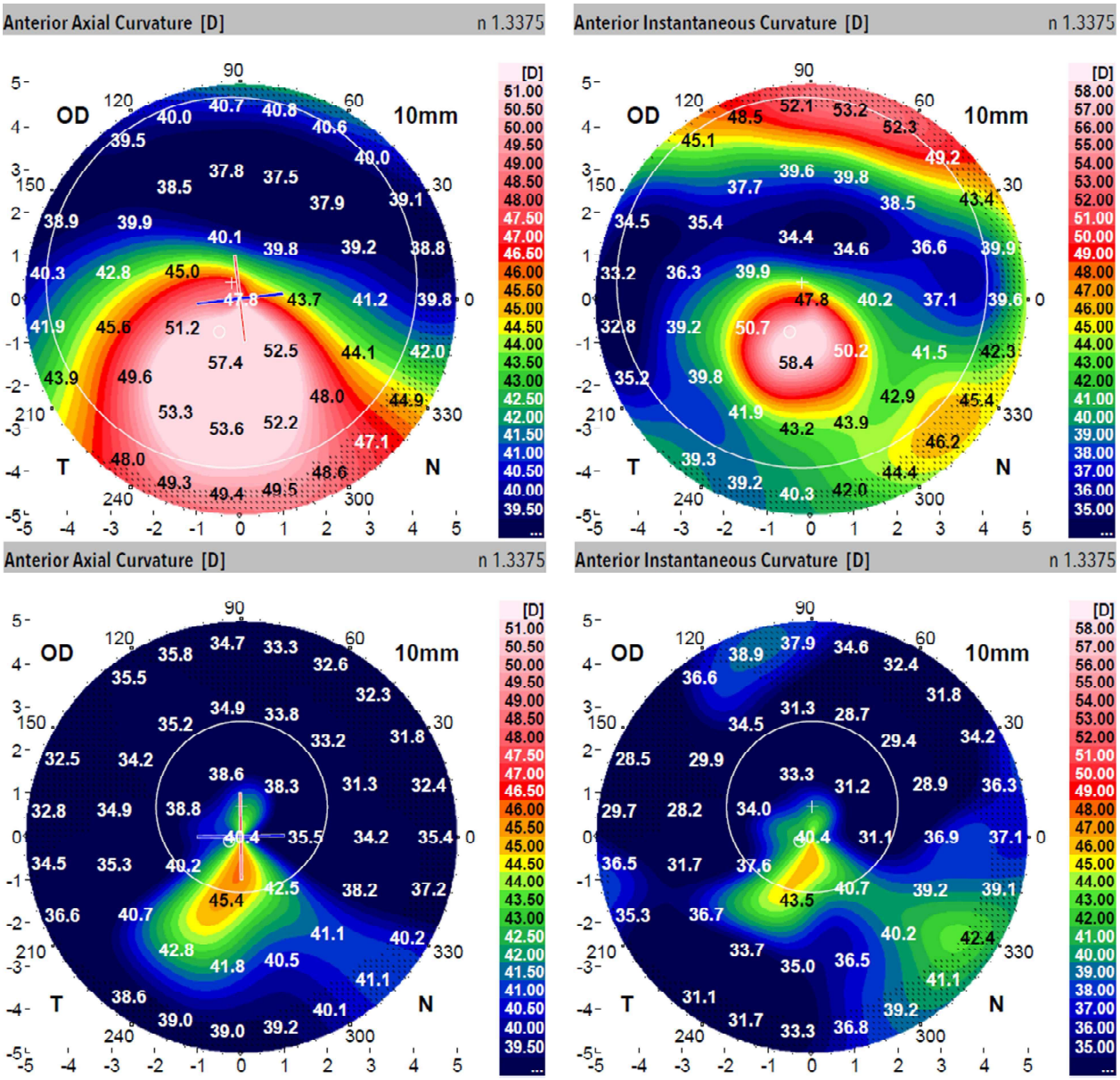

Figure 4 Curvature Maps before and after MyoRing implantation. Top-to-bottom comparison of the curvature of anterior axial and anterior instantaneous curvature maps one week before (top) and 3.5 months after MyoRing implantation (bottom) in an average patient.

reflected inherently positive biomechanical properties and held irrespective of potential for improvement, we did a post hoc correlation analysis between these variables and one we named the "achieved CDVA potential".

$$Achieved\ CDVA\ potential = \frac{CDVA\ Lines\ gained}{CDVA\ Lines\ to\ achieve\ 1.0}.$$

This post hoc analysis demonstrated a weak inverse correlation that was not statistically significant (Appendix B in Supplemental Data). Further research is therefore necessary to elucidate the role of SE and a host of other parameters, as predictive factors for postoperative CDVA outcomes.

As reported by a recent review,[22] reducing variability by improving inclusion criteria could yield considerably better outcomes for patients. The subgroup analysis between eyes undergoing standard and non-standard treatment showed a tendency for poorer postoperative vision (p= 0.26807). Particularly eyes with a meanK >55D had a significantly

inferior CDVA outcomes postoperatively (p= 0.001372) with their CDVA being under 20/40 Snellen. We therefore argue that for KC eyes classified as stage IV with Amsler–Krumeich classification, keratoplasty may be the more efficacious visual rehabilitation albeit with a different complications profile. The emergence of novel predictive models in the field of machine learning may be a worthwhile line of future research to further improve selection criteria.

There are large gaps in reporting the distribution of CDVA gains. Some publications with large sample sizes describe no eye losing a line and some report all eyes gaining vision and not a single eye losing a CDVA line.[14,16,24] With 20 eyes (17%) with CDVA lines change ≤0 at follow-up with 4 (3%) eyes losing one line or more in corrected vision, our findings suggest there may be large gaps in the reporting of CDVA gains distribution.

Very few publications have explicitly stated the percentage of eyes in which this enhancement surgery or ring centration was carried out. It has been reported that approximately 20% of eyes profit from a second procedure to adapt ring dimensions or positioning.[14] At 12.7%, our study found that eyes required these additional interventions less frequently.

In an attempt to compare studies analyzing results after complete ring (ICCR)- and ring segment-implantation, we found two reviews that were published since 2015. The first one, a systematic review by Izquierdo et al,[7] attributed improvements in UDVA and CDVA for all examined ICRS and ICCR after 1 year. However, they noted greater improvements in keratometry and more consistent correction of spherical aberration in patients treated with the ICCR compared with other ICRS. The second review, published by Park et al,[25] concluded that complete rings (ICCR) and near-complete ring segments of arc lengths of 340° and above achieved the most robust correction of spherical equivalent in comparison to regular ICRS.

Several comparative studies on this topic have been published since 2015 that were not included in either review.

A study by Yousif et al[26] comparing three intracorneal implant types found all three were effective at improving UDVA, CDVA, keratometry and corneal asphericity. They also reported a limited effect of 2-segment rings on advanced cases of KC at 6 months but a significant improvement with near-complete and complete rings.

A comparative study by Pashtaev et al[27] also demonstrated that ICCR treatment lead to a greater reduction in total corneal aberration, higher order aberrations (HOAs) and spherical aberration than the Keraring in KC eyes staged at Amsler–Krumeich III. Postoperative changes in Amsler–Krumeich II KC eyes were comparable in both groups.

Bamdad et al demonstrated superior reduction of asphericity and keratometry with MyoRing treatment as with the Keraring.[27]

Sammour et al[28] found that after 12 months the CDVA gains in eyes treated with the ICCR were significantly higher than those treated with the Ferrara Ring, mostly because of the regression of short-term (1 month) gains in the group treated with the Ferrara Ring.

Biomechanical considerations ascribing higher stabilization of the corneal by continuous rather than interrupted segments favor ICCR implantation.[10,11] This is particularly relevant since some publications report of regression to baseline of CDVA improvements 12 months after ICRS implantation, particularly in progressive KC.[12,26,28–31]

In light of the literature and our findings, we would suggest that the comparative advantages of ICCR to ICRS are its high suitability in advanced cases of KC, in eyes with low SE and possibly in progressive KC. Remaining purported advantages of some ICRS are possibly their particular suitability in KC with a highly asymmetric cone.

The current established modality to treat severe KC remains keratoplasty, with lamellar keratoplasty being the preferred option by many surgeons, because of the reduced risk of postoperative graft rejection compared with penetrating keratoplasty.[32] To our knowledge, only one study has intended to compare ICCR implantation with keratoplasty in KC.

A contralateral eye study by Yousif et al[33] with 30 patients comparing femtosecond assisted DALK and MyoRing implantation in patients with advanced to severe KC and a history of recent progression demonstrated that both techniques were effective at improving visual acuity and spherical and corneal aberrations with superior improvement of corneal asphericity and HOAs after DALK. The authors deemed it an acceptable substitute for keratoplasty in advanced KC. Yet, one needs to keep in mind that loss of visual acuity through central corneal scarring cannot be remediated by ICCR.

Further investigation is necessary to explore whether this comparability is reproducible, which could render ICCR a valid alternative in regions with insufficient capacities for corneal transplants.

A potential weakness of our study is that ICCR implantation was not thoroughly standardized as to the pocket creation method. Previous studies, however, have shown no significant differences in outcomes between femtosecond and manual dissection to create the stromal pocket.[34–36]

Despite the success demonstrated, a significant limitation is that patients were not systematically categorized using KC grading such as the Belin–Ambrosia ABCD classification. This renders comparison with the study population more arduous.

With 91% of eyes being followed up between 2 months and 3 years, only 29% of which were followed up 12 months or more, questions could remain as to the stability of the evaluated outcomes. Nonetheless, numerous other studies with follow-up periods of 1, 2, 3 and 5 years demonstrated stable refractive and keratometry outcomes with marginal improvement of HOAs beyond the first year.[9,14,15,37–39]

Furthermore, this work is also limited by the lack of its consideration of HOAs and qualitative photic phenomena, which play an important role in patients' quality of life.[15,32] Only one study to date has published any patient-centered outcomes such as satisfaction scores.[40] This is something that should be borne in mind in future studies.

The results of this study further confirm the efficacy of ICCR implantation as a treatment for KC. This promising technique comes with great benefits, particularly for KC patients with reduced preoperative vision (CDVA <20/70) and a low SE. The calculated safety index, low risk of complications and the reversibility of the treatment speak to its safety. The main challenge remains in the low predictability of the magnitude of this improvement in eyes with good spectacle corrected vision (CDVA >20/30).

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2. The Broader Context

2.1 Keratoconus & traditional therapeutic modalities

Keratoconus (KC) is the most prevalent non-infectious ectatic corneal disease worldwide. It is believed to be the single most common reason for a corneal transplant in the developed world (Davidson et al., 2014, America, 2013). The disease is characterized by a bilateral but mostly asymmetric progressive thinning and protrusion of the corneal stroma, rupture of the anterior limiting membrane and subsequent ectasia of the central and paracentral cornea. This results in an irregular corneal morphology, leading to a significant decrease in corrected and uncorrected visual acuity and a range of pic phenomena. These photic phenomena include halos, so-called “ghost images”, monocular double vision, increased light sensitivity, metamorphopsia and anisometropia (Macsek et al., 2018, Fournié et al., 2013).

KC can present at all ages; however, the peak incidence is usually reported between 20 and 30 years. Both sexes and all ethnicities are affected by the illness. An initial landmark review by Rabinowitz in 1998 estimated the prevalence in Western European populations at around 0.5 affected people in 1000 inhabitants (Rabinowitz, 1998). A recent systematic review and meta-analysis estimated the global prevalence at 1.38 in 1000 people (Hashemi et al., 2020). A genetic aetiology was suspected early on, in light of the varying prevalence figures in different countries, the associations with ethnic origin and the observed familial clustering. Yet, genetic studies have so far not been able to identify causative genes to explain most KC cases (Hashemi et al., 2020, Gordon-Shaag et al., 2015). Only one KC locus (5q21.2) has been reproduced throughout numerous linkage studies to date, indicating that the condition is most likely of polygenic origin (Bykhovskaya et al., 2016, Bisceglia et al., 2009).

Despite intense scientific research, the exact pathophysiology behind KC remains unknown. Although KC has historically been thought of as a non-inflammatory condition (Rabinowitz, 1998, Krachmer et al., 1984), several studies have found links with higher levels of circulating inflammatory mediators, suggesting that eyes with KC frequently are associated with some level of inflammation (Navel et al., 2022, McKay et al., 2016, Wisse et al., 2015). However, there are no well-established and sufficiently representative animal models (Zhang et al., 2021).

Treatment of progression in KC

Therapeutic modalities for KC span two goals. The first goal is stabilising the cornea and as such halting or preventing further progression of the ectasia. This impedes any further deterioration of vision and photic phenomena. The second goal is to improve visual acuity.

In the early 2000s, the only established modality to arrest KC progression was corneal collagen crosslinking (CXL). In CXL, corneal collagen fibres are first sensitised with riboflavin and then irradiated with ultraviolet A (UVA) light. This induces crosslinks between stromal collagen fibres and thus increases corneal rigidity and stiffness (Abrishamchi et al., 2021). The standard CXL protocol, also known as the Dresden Protocol, takes approximately 35 minutes and starts with the mechanical removal of the corneal epithelium before multiple series of applications of riboflavin and irradiation with UVA (Saad et al., 2020). Many accelerated CXL protocols with and without removal of the corneal epithelium using additional adjuvants such as oxygen have been devised, with mostly similar outcomes (Mazzotta et al., 2020). While progression halting is a well-documented and established outcome of CXL, vision improvements are moderate but often clinically insignificant (Parker et al., 2015, Rechichi et al., 2016, Mazzotta et al., 2017, Mazzotta et al., 2021). CXL is therefore mainly useful when eyeglasses or contact lenses still improve vision sufficiently.

Visual rehabilitation in KC

Visual rehabilitation has traditionally been attempted by correcting vision with spectacles, contact lenses and when necessary, by performing full-thickness keratoplasty.

Spectacles usually are only useful in very mild KC cases. Different contact-lens (CL) types, most notably the rigid gas-permeable type, can significantly improve visual acuity by correcting lower and higher-order aberrations. A central problem in moderate to advanced KC is that by way of an irregular corneal surface, many patients start suffering from a contact-lens intolerance. When specialised CL fitting including scleral lenses and piggy-back fitting is impossible, surgical methods become necessary (Negishi et al., 2007, Mohammadpour et al., 2018).

Corneal transplantation has long been the mainstay of surgical treatment for advanced KC. Before the advent of widespread crosslinking, perforating keratoplasty has been reported to be performed in 20% of eyes with KC in referral centres (Lass et al., 1990). The disadvantage of corneal transplants mainly lies in the limited availability of donor corneas, the often year-long recovery and the risk of complications such as transplant failure, rejection and infection (Javadi et al., 2010, Yuksel et al., 2017, Song et al., 2019).

More modern modalities that purport to improve visual acuity and quality are combined excimer laser ablation and CXL as well as corneal implants sometimes also combined with CXL. Combined topography-guided photorefractive keratectomy (tPRK) of the cornea followed by CXL to treat mild to moderate KC was first introduced by Kanellopoulos in what became known as the Athens protocol (Kanellopoulos and Binder, 2007, Kanellopoulos, 2009). Alterations to the Athens protocol have been proposed by other authors with varying results (Rechichi et al., 2021, Kymionis et al., 2010). The central limitation lies in the ablative and therefore mechanically weakening nature of tPRK. To avoid destabilization and consequently further ectasia, tPRK is feasible only when sufficient regularization can be achieved with a maximal ablation depth of 50-60µm in combination with crosslinking. In most reports, this yields a modest mean CDVA improvement of 1-2 lines (Kymionis et al., 2010, Grentzelos et al., 2017, Grentzelos et al., 2019, Kanellopoulos et al., 2019, Shetty et al., 2015, Al-Mohaimeed, 2019).

The first use of commercially available corneal implants to treat KC was reported in 2006 with intracorneal ring segments (ICRS) yielding heterogeneous results (Alió et al., 2006). Ever since the number of ICRS types and embedding techniques has vastly expanded. Nevertheless, many authors report receding gains a few months after implantation and progression despite ICRS implantation (Sammour et al., 2017, Park et al., 2019). This coincides with the purported mechanical inferiority of ring segments compared to fully circular continuous intracorneal rings(CIR) (Daxer, 2015, Izquierdo et al., 2019).
A more in-depth comparison of ICRS with CIR can be read in the discussion part of the publication in clinical ophthalmology.

2.2 The use of Continuous Intracorneal Rings

CIR implantation is an emerging technique used to treat moderate to advanced KC, particularly in patients with a marked decrease in corrected distance visual acuity (CDVA), as confirmed in multiple settings and trials (Naderi et al., 2021, Yousif and Said, 2018, Janani et al., 2019, Sedaghat et al., 2019, Alshammari and Al Somali, 2019, Jadidi et al., 2019, Khorrami-Nejad et al., 2019).

The main advantages lie in the minimal invasiveness of the procedure, the reversibility, the low complication rate and its potential to eliminate the need for a corneal transplant by regularizing and stabilizing the cornea. In comparison to ICRS implantation and to combined

tPRK and CXL, it seems particularly adequate to treat advanced KC without central corneal scars (Parker et al., 2015, Macsek et al., 2018, Park et al., 2019).

The Mechanics of CIR Implantation

The CIR used in all cases was the Myoring (DIOPTEX GmbH, Linz, Austria). This CIR is a 360° ring made of flexible polymethylmethacrylate (PMMA) that is inserted into a lamellar corneal stroma pocket. The CIR diameter ranges from 5-6 mm and its thickness ranges between 200 and 320 µm. The CIR dimensions were chosen using a nomogram based on the keratometry readings.

The CIR is inserted into a stromal pocket located at a depth of 300µm with a diameter of 8.5 - 8.7mm via a temporal insertion tunnel of 5-5.5mm.
Pocket creation can be accomplished using a microkeratome for mechanical dissection (Pocketmaker®, DIOPTEX GmbH, Austria) or a femtosecond laser
The microkeratome applanates the cornea and a micro-vibrating diamond blade incises the corneal stroma and thereby creates the insertion tunnel. Through this insertion tunnel, the blade forms the pocket of the aforementioned dimensions. In both pocket creation techniques, the aperture wound is self-sealing and requires no stitches. However, if a readjustment needs to be performed a spatula can reopen this tunnel up to a year after surgery.

A CIR acts as a spacer element between the bundles of corneal lamellae anteriorly and inferiorly to the stromal pocket. The central portion of the anterior corneal lamella is therefore stretched and flattened as the peripheral part of the anterior lamella is displaced forward. This arc-shortening effect is proportional to the thickness of the CIR (Wu et al., 2021, El-Husseiny et al., 2013, Andreassen et al., 1980).

The purported biomechanical advantage of a fully circular ring as described by Daxer (2015), is the increased stability of the cornea after implantation. The dome-shaped approximation of the inner area may explain why CIR has been shown to arrest progressive KC better than interrupted implants, as pressure loads are optimally distributed in a dome with an incompressible base (Sammour et al., 2017, Nabi et al., 1997). However, recent comparisons indicate that there could be no clinically meaningful difference between nearly circular and fully circular implants (Park et al., 2019, Yousif and Said, 2018).

Despite all the reported, benefits, mechanical advantages, ease of use and reversibility of the procedure, very few of the major academic hospitals in Germany use CIR implantation in their standard treatment algorithm.

2.3 Publication Hypotheses, Results and Contribution

We decided to take up this study because of the wide gap between our anecdotally positive results with patients and the still very low take-up of this novel technology. Our literature research revealed encouraging reports on CIR as a technique. Recent studies, however, showed the need for high-powered studies, mainly due to the heterogeneity of results on outcomes such as CDVA and major differences in the reporting of intra- and postoperative complications.

Furthermore, predicting individual improvement has been difficult, as underlined by different studies and a recent systematic review (Nobari et al., 2014, Park et al., 2019). Intending to further improve the current inclusion criteria, we hoped to identify risk factors for poor outcomes with traditional statistics and later machine-learning algorithms.

We, therefore, identified two falsifiable working research hypotheses. Firstly, the implantation of a CIR leads to an improvement in corneal morphology and thus to an improvement in the

spectacle-corrected visual acuity in patients with KC. Secondly, in KC patients with myopia or a high degree of astigmatism preoperatively, implantation of a CIR leads to an improvement in uncorrected visual acuity.
Moreover, we expected to identify statistically significant predictors for CDVA outcomes using univariate correlational analyses. More controversially, we also expected to find higher as previously reported rates of eyes without a CDVA gain and eyes with surgical complications (Jabbarvand et al., 2013, Daxer et al., 2017).

Results

In this section, I decided to only highlight the results and outcomes that, either respond to the main research hypotheses or are relevant to elucidate the contribution of the study.

This study included 118 eyes of 118 patients with a mean age of 32 ± 11 years. CIR implantation increased CDVA from a mean of 0.38 ± 0.23 as the logarithm of the minimum angle of refraction (logMAR) to 0.15 ± 0.15 logMAR ($p<0.0001$) after a median follow-up of 161 days (interquartile range: 111-372 days).

Both of our major research premises were corroborated by the results of our investigation.

Firstly, the implantation of a CIR led to a statistically and clinically significant improvement of nearly all corneal morphology parameters, as evidenced by keratometry ($p < 0.001$).
The only stable parameters were the thinnest pachymetry value (min. pachy) and topographical astigmatism (topoAsti). The consequent visual acuity improvements at follow-up were 2.3 ± 2.1lines in CDVA and 6.0 ± 4.8 lines in UDVA.
Secondly, myopia was strongly correlated with UDVA improvement as evidenced by a Spearman correlation coefficient of $\rho=0.44$ ($p<0.0001$). However, this did not hold for eyes with high preoperative astigmatism, since the preoperative manifest refraction cylinder did not correlate with UDVA change ($p=0.646$).

To improve prediction, univariate correlational analysis broadly revealed that all refractive, keratometric and tomographic factors indicating a more advanced disease correlated positively with CDVA lines gained. The only exceptions here were preoperative UDVA ($p=0.3414$), refractive cylinder ($p=0.0915$) and topoAsti ($p= 0.0954$). Our subgroup analysis of the non-standard treatment group (NSG) further demonstrated that eyes that received CIR, despite not fulfilling all stringent inclusion criteria, had a tendency for lower postoperative CDVA ($p=0.26807$). Among the NSG eyes, those with average simulated anterior keratometry reading (meanK) of 55D or more had significantly poorer postoperative vision than the STG ($p= 0.001372$) with their mean postoperative CDVA being under 0.5 in decimal notation.

Complications encountered in this study were mostly of temporary nature. In total, 15 eyes (12.7 %) underwent a ring exchange procedure because of refractive under- (9 eyes) or overcorrection (6 eyes). Two eyes (1.7%) however, had serious medical complications.

One patient developed a corneal herpes simplex infection and required a CIR explantation eight months after surgery. CIR re-implantation was carried out 4 months later. Still, the eye gained 3.9 lines in CDVA and 6.0 lines in UDVA, as a result of all operations.

In the other instance of a medical complication, the microkeratome-created corneal pocket was too superficial. Initial postoperative recovery and visual acuity were satisfactory.
A month after surgery, following a minor injury to the eye with a pillowcase, the patient began to experience recurrent epiphora. The CIR was removed four months after surgery because of the risk of impeding extrusion. This eye's UDVA increased by 2.0 lines while its CDVA decreased by 2.0 lines.

Contribution

Replication of previous results is a central tenet of scientific research and advancement. Therefore, one should regard outcomes that replicate previous studies' results as an important contribution to the body of science. Nonetheless, in this section, I will list the 6 main novel contributions for brevities' sake.

1) the large sample size clears up previous inconsistencies. After our 118 eyes from 118 persons, the second largest publication to date is by Bikbova in 2018 comprising 78 continuous rings where half of all eyes were implanted with concurrent crosslinking.

2) It is the first exhaustive and precise description of all surgical complications and repeated surgeries. Some previous publications including publications with large sample sizes; such as the 70 eyes study by Jadidi et al. (2019) or the 53 eyes included by Daxer et al. (2017) report no complications whatsoever. Many large case-series report no eye losing a line and some reports reveal all eyes gaining vision and not a single eye losing a CDVA line (Jabbarvand et al., 2013, Daxer et al., 2017). With 20 eyes (17%) with CDVA change ≤0 lines at follow-up and with 4 eyes (3%) losing one line or more in corrected vision, our results depart from these previous reports and might well explain the reluctance of some surgeons to adopt when reports don't seem entirely transparent.

3) Myopia not only correlates significantly with UDVA improvement, but it also correlates with CDVA improvement. This is possibly irrespective of the improvement potential as indicated by our post-hoc correlational analysis in the discussion part of the publication.

4) We confirmed and explained why meanK <55D with no upper limit on the largest anterior keratometry reading (kMax) is a valid upper threshold, especially for patients in which keratoplasty is a valid alternative.

5) We proposed achieved potential as a more useful central metric than postoperative vision or CDVA lines to compare study outcomes and to perform predictive modelling for continuous regressions.

6) Finally, we further supported the stability of outcomes across time, since we saw no significant effect of a longer follow-up in our case-series with follow-ups ranging from 65 to 3257 days. Our linear regression analysis rather revealed a tendency for improvement of outcomes as has been described in other publications (Bikbova et al., 2018, Daxer et al., 2017, Janani et al., 2019, Vega-Estrada et al., 2019, Studený et al., 2015, Mohammadpour et al., 2021).

2.4 Additional findings - Quality of Life and Visual Function

As dictated by the doctoral thesis guidelines, I will elaborate on further findings that were not included in the publication but were within the scope of the doctoral research. These findings centred around two approaches. The first was investigating the effect of CIR on quality of life (QOL), while the second approach aimed at improving outcomes prediction by using machine learning (ML) algorithms. None of these findings have been peer-reviewed yet. All additional findings were abridged so as to comply with the limitation of pages set by the doctoral thesis guidelines.

Background

In the last 20 years, the range of treatment modalities for KC has vastly expanded. CIR implantation is an emerging therapeutic alternative that has been shown to significantly improve corrected and uncorrected visual acuity by correcting both lower- and higher-order

aberrations. Yet, KC is known to cause a multitude of photic phenomena, ocular pain and discomfort, to name a few, which may not strongly correlate with main outcomes such as CDVA (Macsek et al., 2018, Shams et al., 2022).
To more globally encompass the changes brought on by KC and in a move towards patient-centred outcomes research, therapies that attempt to treat KC should include an assessment of the vision-related quality of life (QOL). The most frequently used tool to assess vision-related QOL in KC is the national eye institute 39-part visual function questionnaire (VFQ-39) (Kandel et al., 2020).
We, therefore, intended to evaluate the impact of CIR implantation in KC patients on their vision-related QOL and quality of vision as measured with the VFQ-39. To my knowledge, this is the first and only assessment of QOL in CIR-implanted patients.

Materials and Methods

We attempted to recruit all patients that received CIR implantation for KC in the zentrumsehstärke or at the Universitätsklinikum Hamburg-Eppendorf from June 2016 to January 2019. Inclusion and exclusion criteria are listed exhaustively in the main publication. Only changes to that protocol are listed here.

Patients were contacted by telephone or in-person appointments to ask for their consent and participation in the trial. Interviews pertaining to their pre- and postoperative vision-related QOL were conducted in person or by telephone. All preoperative interviews were made after the operation and required the patients to recall their preoperative mental and visual states. Both interviews on average took 15 minutes. When patients were incapable of or unwilling to remember, their data was excluded.
All patients gave written consent to the analysis of their pseudonymised data.

For vision outcomes we subsumed the bilateral CDVA line changes of both eyes to *Compounded CDVA Lines,* and the bilateral UDVA line changes to *Compounded UDVA lines.*
All VA Lines was defined as the addition *of compounded CDVA and UDVA lines* for one patient. We used the German translation of the VFQ-39 which has been validated in numerous previous studies (Biousse et al., 2021, Nickels et al., 2017, Hirneiss et al., 2010, Reimer et al., 2006).

The Hamburg Medical Association's ethics committee granted approval for this retrospective case-series in April 2019 under approval number PV6017. It was conducted in conformity with the principles of the Declaration of Helsinki.

To test the hypothesis that improving visual acuity improves vision-related QOL we attempted on one part, to correlate the different VFQ-39 category changes with visual acuity changes and on the other part to perform an independent t-test between the above mean Compounded CDVA lines performers and below mean CDVA lines performers.

Results

Of the 49 patients that had performed their minimum 2-month follow-up, only 6 were excluded, because of a planned ring exchange procedure. Of the remaining 43 one had received previous keratoplasty. 9 patients did not consent to the interview or only provided postoperative information.

In all, 33 patients were included in the study. The pre- and postoperative outcomes on the VFQ-39 subscores can be seen in Table 1.

Table 1:Visual Function before and after CIR Implantation

Visual Function Questionnaire Subscore	N	Preoperative Mean ± SD	Postoperative Mean ± SD	p (two-tailed)
General Health	33	67.2 ± 14.9	73.6 ± 14.8	0.001
General Vision	33	51.7 ± 16.9	70.3 ± 15.1	<0.001
Ocular pain	33	70.7 ± 26.6	78.9 ± 18.6	0.06
Near Vision	33	69.6 ± 18	80.3 ± 14.9	<0.001
Distance Vision	33	66.1 ± 18.7	81 ± 12.6	<0.001
Vision-Specific Social Functioning	33	82.8 ± 15.4	93.1 ± 8.9	<0.001
Vision-Specific Mental Health	33	62.8 ± 15.2	73.4 ± 13.4	<0.001
Vision-Specific Role Difficulties Health	33	72.8 ± 17.2	81.5 ± 16.7	0.008
Vision Specific Dependency	33	90.1 ± 13.9	95 ± 7.7	0.019
Driving	28	59.9 ± 26	67.8 ± 22	0.048
Colour Vision	33	95.7 ± 9.6	100 ± 0	0.023
Peripheral Vision	33	75 ± 22.2	87.1 ± 15.8	0.008

Abbreviations: SD: Standard Deviation; p: two-tailed predictive value of the paired T-Test comparing subscores before and after surgery

Patients that received a CIR on both eyes did not differ significantly with respect to their VFQ-39 subscores in 11 out of 12 categories.
Only when comparing the General Health subcategory did we find a significant difference between the subscore of unilaterally implanted eyes (67.8 ± 16.4) and bilaterally implanted eyes (84.2 ± 10.9) with a predictive value of p=0.012.

Correlation of Visual Acuity Outcomes with VFQ-39 Data

This section outlines our observations of the impact of the visual acuity changes in patients on the different VFQ subscores of each patient. Our primary analysis, an independent t-test comparing eyes with median Compounded CDVA Lines of less than 1.7 with those having median Compounded CDVA Lines greater than 1.7 showed a tendency for greater positive improvements in VFQ subscores in the group with greater Compounded CDVA improvements. These differences, however, were in no case statistically significant.

Additionally, in the correlation analysis between the VFQ-39 Score or the VFQ subscore changes and different bilateral visual acuity measure changes, only the change in General Health seems to be correlated with the Compounded UDVA Lines before Bonferroni correction (p=0.031). All correlation analysis outcomes can be read in Table 2.

Table 2: Correlational Analysis of Visual Function Changes

Visual Function Questionnaire Subscore Changes (After-Before)		Compounded CDVA Lines	Compounded UDVA Lines	All VA Lines
General Health	Pearson r	0.04	0.28	0.38*
	p (two-tailed)	0.834	0.118	0.031
General Vision	Pearson r	0.05	0.11	0.13
	p (two-tailed)	0.785	0.542	0.491
Ocular pain	Pearson r	0.21	0.28	0.25
	p (two-tailed)	0.254	0.124	0.161
Near Vision	Pearson r	0.07	0.17	0.20
	p (two-tailed)	0.700	0.346	0.274
Distance Vision	Pearson r	0.16	0.09	0.01

	p (two-tailed)	0.376	0.629	0.950
VS Social Functioning	Pearson r	-0.10	-0.11	-0.09
	p (two-tailed)	0.569	0.538	0.630
VS Mental Health	Pearson r	-0.03	0.02	0.05
	p (two-tailed)	0.867	0.909	0.773
VS Role Difficulties Health	Pearson r	-0.19	-0.19	-0.13
	p (two-tailed)	0.287	0.303	0.468
VS Dependency	Pearson r	0.32	0.24	0.12
	p (two-tailed)	0.076	0.188	0.525
Driving	Pearson r	-0.04	0.09	0.17
	p (two-tailed)	0.821	0.642	0.388
Colour Vision	Pearson r	-0.26	-0.07	0.09
	p (two-tailed)	0.152	0.702	0.642
Peripheral Vision	Pearson r	0.12	0.06	0.00
	p (two-tailed)	0.525	0.742	0.984

Abbreviations: Compounded CDVA Lines: bilateral CDVA changes; Compounded UDVA: bilateral UDVA Changes; All VA lines: addition of Compounded CDVA and UDVA; Pearson r: Pearson correlation coefficient; VS: vision-specific; p: two-tailed predictive value of the paired T-Test comparing subscores before and after surgery

Discussion

From the short review above, some key findings emerge. At baseline, the VFQ-39 showed how KC can impact each and all vision-related qualities including ocular pain. The ability to drive and general vision were particularly impacted. Postoperatively, we saw considerable and statistically significant improvements in nearly all subcategories, which we can safely assume is the consequence of CIR implantation. The average eight-point gain on the ocular pain score came close to but did not reach, statistical significance (p=0.060)

While we know from this and previous studies that the visual acuity of carefully selected KC patients is meaningfully improved through CIR implantation and visual acuity greatly impacts the quality of life, we could not prove a correlation between CDVA improvements and VFQ improvements. This, we posit, must mean that the VFQ improvements may be explained mostly by vision quality not rendered in CDVA rather than visual acuity changes. This further reinforces the idea of focusing on this and other patient-centred outcomes. Nevertheless, since we saw a clear (but not significant) tendency for improvement in all subcategories we would expect this correlation to reach statistical relevance with a sufficiently powered patient cohort. The overall correlation of keratometric and visual acuity improvements, particularly CDVA improvements, has not only been documented in the literature in KC but also in several other ophthalmological ailments (Balparda et al., 2020, Jelin et al., 2019, Hirneiss et al., 2010). Intriguingly, the subjective reduction of ocular pain and difficulties in peripheral vision is generally barely mentioned in reviews about KC (Macsek et al., 2018).

Despite the success demonstrated, this study suffers from two main weaknesses. The first is the possible bias introduced by the only partial response from patients. Indeed, one could imagine that unsatisfied patients might be less likely to accept taking part in our survey. A low response rate could hence cause us to overestimate the efficacy of our intervention. A response rate of 79%, however, is very much in line with most phone trials (Neve et al., 2021, MacLennan et al., 2014). Secondly, with this limited study, it is not known to which degree retrospective questioning might have impacted the outcome. The medical and broader scientific literature report numerous examples in which recollection can bias psychometric outcomes (Meduri et al., 2021, Groover et al., 2022, Thigpen, 2019). Nonetheless, we don't expect this shortcoming to undermine the main tenets of our findings,

since we demonstrated the robust statistical significance of considerable amplitude. Still, larger patient samples should be questioned prospectively to enhance both the generalisability and statistical power of our outcomes.

CIR positively impacts all affected VFQ categories and has a noticeable positive impact on patients' quality of life. The lack of a strong correlation between visual acuity changes and VFQ changes underlines the imperative of evaluating KC treatments with patient-centred outcomes such as the VFQ-39.

2.5 Additional findings – Machine-Learning-based Prediction

Background

The background behind the need for improved predictive modelling has already been discussed in the introduction and the discussion of the main publication and will only be summarised briefly.
The results in the publication demonstrated broadly encouraging, but very variable CDVA outcomes. With a mean CDVA improvement of 2.3 lines, an interquartile range from 1 to 4 lines and a total range from -2 to 10 lines, outcomes were quite difficult to predict. In a recent review, Park et al. (2019) described the high variability of results as a central problem of CIR implantation. With the aim of improving the prediction of CDVA outcomes, we endeavoured to use supervised ML algorithms on our retrospectively collected data.

Materials and Methods

Patient selection criteria were identical to our main study. Our primary outcome for ML was our categorical variable CDVA success. In light of our clinical experience, we posited that a three lines CDVA increase is in most cases a sufficient justification to undergo CIR implantation, regardless of UDVA and vision quality changes. Hence, CDVA success was defined as true, when the concerned eye gained 3 CDVA lines or more through surgery. When patients gained less than 3 lines in CDVA through surgery CDVA success was defined as false.
Feature engineering:
Features, as used in machine and statistical learning, are the inputs of an ML model used to predict the outcome of interest. These can be existing preoperative parameters but can also be constructed or engineered (Janjua et al., 2022).

Based on the authors' domain knowledge, preoperative features in Table 3 were engineered that might reflect important physical functions that may explain some of the variance in outcome.

Table 1: Feature Engineering and Rationale

Feature	Formula	Rationale
Glasses coefficient (GC)	$\frac{UDVA - CDVA}{2 - CDVA}$	GC was thought of as an indirect measure of corneal surface irregular astigmatism
Centrality coefficient (CeCo)	$\frac{meanK}{Kmax}$	Indirect measure of the cone's closeness to the optical axis
Natural logarithm of *min. pachy* (ln(min. pachy))	$\ln(\text{min. pachy})$	Thin corneas might be more pliable and amenable to regularization with diminishing returns

The mismatch between topoAsti and CDVA (topoAsti mismatch)	$\frac{topoAsti}{2 - CDVA}$ Where the numerator and denominator are normalized by being scaled between 0 and 1	A high topographical astigmatism compared to the CDVA might be easy to remediate
Ectasia Factor	$\frac{Kmax}{min.pachy}$ Where the numerator and denominator are normalized by being scaled between 0 and 1	A measure for the degree of KC irrespective of its impact on vision

Table 3 displays the engineered features their mathematical formulation as well as the rationale for their creation
Abbreviations: UDVA: uncorrected distance visual acuity; CDVA: spectacle-corrected distance visual acuity; min. pachy: thinnest pachymetry reading; topoAsti: topographical astigmatism; kMax: maximum keratometry reading.

Training, Validation and Testing Datasets

Out of the 118 used eyes we set aside 20% as a hold-out dataset. This hold-out dataset was only used as the final test set with which we would evaluate and score the quality of our already chosen model. To train and validate the remaining 80% (96 eyes) we chose a technique called 5-fold cross-validation. Here the dataset is split into 5 different groups where each unique group is selected as the validation set, to evaluate the model trained on the remaining 4 groups. This yields 5 different cross-validated training scores. The model and fine-tuned settings (hyperparameters) with the best cross-validated training scores were then chosen as the final model and hyperparameters.

Scoring Metrics

As the final algorithm was meant to assist in surgical decision-making, we deemed sensitivity and specificity to be of equal importance in this decision. We, therefore, chose a scoring metric that would incorporate both equally, namely the receiver operator characteristic area under the curve (ROC-AUC).

Our medically relevant performance metrics (sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated at a predetermined optimal threshold of the training set by maximizing the geometric mean between sensitivity and specificity.

Machine Learning Models

We chose to test the performance of two different classification methods.
Model 1 used Logistic regression as a learning model. As a preliminary step to logistic regression, we decided to use primary component analysis (PCA) to simplify the 17 preoperative parameters per eye to as few as possible all the while minimizing the information loss in that step. The number of components was determined by inspecting the cumulative explained variance ratio as a function of the number of components. In order to use PCA on our input we had to pre-process it, transforming the data into a standard normal distribution.

For Model 2 we used Random Forest Classification as a learning model. This model automatically selects the most important inputs using a metric called Gini impurity (Nembrini et al., 2018). No additional pre-processing was performed.

Feature importance
As used in other publications (Altmann et al., 2010), we evaluated the relative importance of features by calculating the permutation-derived importance on the hold-out set for each model with ROC-AUC as the guiding metric.

Results

Across all follow-ups, CDVA Success was 34% in our study. The best prediction on our testing set was achieved with our first method with a ROC-AUC of 85.2% or a sensitivity of 80% and a specificity of 84%.
The full ML metrics can be read in Table 4. Table 5 displays the feature importance in our best-performing model as derived by permutation importance.

Table 2: Model Performance Metrics

Model	Cross-Validated Performance	Testing Performance
Method 1: PCA & Logistic regression	ROC-AUC Score=0.810	ROC_AUC Score=0.852 Sensitivity=0.80; Specificity=0.84 PPV=0.57; NPV=0.94
Method 2: Random Forest	ROC-AUC Score=0.904	ROC_AUC Score=0.801 Sensitivity=0.80; Specificity=0.89 PPV=0.67; NPV=0.94

Table 4 displays the performance of our algorithms during the five-fold training and cross-validation process (Cross-Validated Performance) and the performance on our hold-out final test set (Testing Performance).
Abbreviations: ROC-AUC: receiver operator characteristic area under the curve; PPV: positive predictive value; NPV: negative predictive value.

Table 3: Feature Importance of Best Performing Model

Logistic regression parameter	Permutation Derived Importance
ln (min. pachy)	0.082105
min. pachy	0.08
CDVA	0.048421
Sph	0.010526
UDVA	0.004211
CeCo	0.004211
GC	0
meanK	-0.002105
topoAsti mismatch	-0.006316
EF	-0.010526
Follow-Up (Days)	-0.016842
topoAsti	-0.018947
kMax	-0.018947
Age	-0.025263
Cyl	-0.054737

Table 5 shows the features in Model 1 listed by descending permutation-derived importance score.
Abbreviations: ln(min. pachy): natural logarithm of min. pachy; min. pachy: thinnest pachymetry reading; CDVA: spectacle-corrected distance visual acuity; Sph: refractive sphere; UDVA: uncorrected distance visual acuity; CeCo: centrality coefficient; GC: glasses coefficient; meanK: average central keratometry reading; EF : ectasia factor; topoAsti: topographical astigmatism; kMax: maximum keratometry reading; Cyl: refractive cylinder

Discussion

For an outcome that only concerned a minority (34%) of our well-selected cohort, ML seems to gain valuable information on unseen data in our hold-out validation set with a testing sensitivity of 80%, a specificity of 84% and a negative predictive value of 94%.
The minor increase in our scoring metric from cross-validation to our hold-out test-set indicates low over-fitting and good generalisability (Tušar et al., 2017, Ying, 2019).

With a ROC-AUC Score of 0.85, our findings are on par with many machine-learning publication standards and clinical medical applications (Mansi et al., 2020, Dewulf et al., 2021). More generally ROC-AUC scores between 0.8-0.9 are considered as providing excellent problem discrimination (Hosmer Jr et al., 2013). Algorithms of that precision can readily be used in patient risk stratification (Oprea et al., 2020). Particularly the approach in Model 1 produces compelling results that could be tested prospectively and compared with surgical expert opinion.

A novel finding is the high predictive power attributed to our features $ln\ (min.pachy)$ and *min. pachy*. In the univariate correlation analysis of our original study with CDVA lines, preoperative CDVA had by far the most explanatory power followed closely by *kMax.* and *min. pachy*.
This may corroborate our rationale that thin corneas might be more pliable and hence amenable to regularization with diminishing returns. Further investigations are needed to adequately test and strengthen this hypothesis.

Our ROC-AUC of 0.85 indicates high discernment but also implies the biggest limitation of our study, namely the impossibility of direct clinical application as a robust surgical decision-making tool. The ROC-AUC threshold for popular applicable clinical decision-making tools is often set above 0.97 and generally uses more 10 000 -100 000 instances (Adlung et al., 2021, De Fauw et al., 2018, Gulshan et al., 2016) .
A second shortcoming of our study is the narrow binary classification goal set on a continuous outcome. Ideally, vision outcomes should be predicted using supervised regression algorithms. The constraint of the small dataset, however, made precise regression impossible in the ideation phase of this ML trial.
Finally, the last weakness one needs to bear in mind is that permutation derived importance (PDI) as performed above, does not reflect the intrinsic explanatory power of a feature by itself. PDI reveals how important a specific feature is for a particular model. One should therefore be cautious to extrapolate PDI outcomes to our general understanding of KC.

In summary, a prediction model of the CDVA improvement after CIR implantation was developed and validated retrospectively. In an effort to improve the clinical relevance of the algorithm we propose further studies using complete topographic and tomographic maps to predict continuous CDVA outcomes. This study shows the potential of artificial intelligence to enhance surgical decision-making in CIR implantation.

3. Summary

3.1 English

Background:
For patients with moderate to advanced keratoconus (KC), the implantation of a continuous intracorneal ring (CIR) is an emerging but not yet established treatment option. The goal of this study was to evaluate the clinical results and surgical complications of CIR in patients with moderate to severe KC and confirmed contact lens intolerance.

Methods:
In this multicentric retrospective consecutive case-series, we examined uncorrected and spectacle-corrected visual acuity (UDVA and CDVA) as well as keratometry parameters before and after a median follow-up of at least two months after CIR implantation. Treatments followed an established nomogram and were done in conjunction with a reading centre. The inclusion criteria included: CDVA < 0.8 in decimal notation; no central corneal scars; minimum corneal thickness > 350 microns and central mean keratometry reading (meanK) below 55 dioptres (D) in the standard treatment group (STG). Patients that did not meet all stringent inclusion criteria, but nevertheless requested treatment after informed and shared decision making, were allocated to the non-standard treatment group (NSG).

Results:
This study comprised 118 individuals with a mean age of 32 ± 11 years. CIR implantation increased the spectacle-corrected CDVA from a mean of 0.4 (interquartile range:0.3-0.6) to 0.7 (interquartile range: 0.6-1.0) ($p<0.0001$) after a median follow-up of 161 days (interquartile range: 111-372 days). Lower preoperative CDVA was found to be the strongest predictor of CDVA improvement in our correlation analysis, with eyes having a CDVA of 0.25 or lower improving by an average of 4.3 ± 2.0 lines. Eyes with a meanK > 55 D which were thusly allocated to the NSG, gained 2.86 ± 3.09 lines in CDVA and 9.04 ± 4.83 lines in UDVA. In contrast, postoperatively, these eyes' CDVA of 0.5 was substantially lower than the CDVA in the STG ($p=0.001372$). A ring exchange surgery was required for 15 eyes (12.7%) in case of refractive under- or overcorrections. Medical complications occurred in 2 eyes (1.7%).

Conclusion:
This study confirms both the generally positive impact of CIR implantation on CDVA and the wide range of outcomes. Owing to the reversibility and low rates of serious complications, CIR implantation should be taken into consideration, especially in eyes with a preoperative CDVA 0.25 and a meanK below 55 D. The remaining challenge lies in low predictability of individual outcomes, particularly in eyes with a CDVA >0.66

3.2 Deutsch

Hintergrund:
Für Patienten mit mittelschwerem bis fortgeschrittenem Keratokonus (KK) ist die Implantation eines kontinuierlichen intrakornealen Rings (KIR) eine aufstrebende, jedoch noch nicht etablierte Behandlungsoption. Ziel dieser Studie war es, die klinischen Ergebnisse und chirurgischen Komplikationen der KIR Implantation bei Patienten mit mittelschwerem bis schwerem KK und bestätigter Kontaktlinsenunverträglichkeit zu untersuchen.

Methoden:
In dieser multizentrischen, retrospektiven, konsekutiven Fallserie untersuchten wir die unkorrigierte und brillenkorrigierte Sehschärfe (SC Visus und CC Visus) sowie keratometrische Parameter vor und nach einer medianen Nachbeobachtungszeit von mindestens zwei Monaten nach der KIR-Implantation. Die Behandlungen erfolgten nach einem etablierten Nomogramm und wurden in Zusammenarbeit mit einem Lesezentrum geplant. Zu den Einschlusskriterien gehörten: CC Visus < 0,8; keine zentralen Hornhautnarben; dünnster Hornhautpachymetrie > 350µm und zentraler mittlerer Keratometriewert (meanK) < 55 Dioptrien (D) in der Standardbehandlungsgruppe (SBG). Patienten, die nicht alle strengen Einschlusskriterien erfüllten, aber dennoch nach einer informierten und gemeinsamen Entscheidungsfindung eine Behandlung wünschten, wurden der Nicht-Standard-Behandlungsgruppe (NSG) zugeteilt.

Ergebnisse:
Diese Studie umfasste 118 Personen mit einem Durchschnittsalter von 32 ± 11 Jahren. Durch die KIR-Implantation erhöhte sich der brillenkorrigierte Visus von durchschnittlich 0,4 (Interquartilsbereich: 0,3-0,6) auf 0,7 (Interquartilsbereich: 0,6-1,0) (p <0,0001) nach einer medianen Nachbeobachtungszeit von 161 Tagen (Interquartilsbereich: 111-372 Tage). In unserer Korrelationsanalyse erwies sich ein niedriger präoperativer CC Visus als der stärkste Prädiktor für eine Verbesserung des CC Visus', wobei sich Augen mit einem CC Visus von 0,25 oder niedriger um durchschnittlich 4,3 ± 2,0 Linien. Augen mit einem meanK > 55 D, die somit der NSG zugeordnet wurden, verbesserten sich um 2,86 ± 3,09 Linien im CC Visus und 9,04 ± 4,83 Linien im SC Visus. Dagegen war der postoperative CC Visus dieser Augen postoperativ mit 0,5 deutlich niedriger als der postoperative CC Visus in der STG (p=0,001372). Ein Ringtausch war bei 15 Augen (12,7 %) aufgrund von refraktiven Unter- oder Überkorrekturen erforderlich. Bei 2 Augen (1,7%) traten medizinische Komplikationen auf.

Schlussfolgerung:
Diese Studie bestätigt sowohl die allgemein positive Auswirkung der KIR-Implantation auf den Visus als auch das breite Spektrum an Behandlungsergebnissen. Aufgrund der Reversibilität und der geringen Rate an schwerwiegenden Komplikationen sollte die KIR-Implantation besonders bei Augen mit einem präoperativen CC Visus von 0,25 und einem meanK unter 55 D in Betracht gezogen werden. Die verbleibende Herausforderung liegt in der geringen Vorhersagbarkeit der individuellen Ergebnisse, insbesondere bei Augen mit einer CDVA >0,66.

4. Author Contributions

4.1 Co-authors

Retrospective study of patients diagnosed with KC and undergoing Myoring implantation in one or both eyes in Hamburg, Germany and in KC practices in Wels and Linz, Austria. Diagnosis, surgery and follow up was conducted by the co-authors Daxer, Linke and Steinberg. Original idea to use the visual function questionnaire and to do a retrospective case-series came from Johannes Steinberg and Albert Daxer and was further refined and adapted by myself.
PD Dr. Steinberg prepared the submission for the ethics approval and served as head investigator.
Informed consent of patients was collected by: me in Germany, and Daxer in Austria.
All co-authors reviewed the publication manuscript. Dr Steinberg was particularly critical in the reviewing process. Dr Daxer was in charge of gathering consent for Austrian patients.

Vasyl Druchkiv did the first statistical analysis of the VFQ data without any calculations on visual changes.

4.2 Declaration of Personal Contribution

For all studies, I served as the first author. The draughting and editing of all manuscripts for all publication attempts was done by me, who also served as the corresponding author in all cases. The choice of statistical methods was in vast majority decided by me.
All statistical analyses and figure creation for the publication were my personal work using Python 3.7 and SPSS 28.0.

I also performed all final statistical analyses of the VFQ-data, since some patients had to be excluded from the initial analysis of Vasyl Druchkiv.
The idea to correlate visual improvements with VFQ data and to apply machine learning techniques to the critical question of patient selection was mine as well. All machine learning feature creation was done by me and all algorithm architecture as well.

Informed consent for the interview and pseudonymous analysis of all patients that underwent surgery in Hamburg, was done by me.
I collected and tabulated all the data from the EMR software of patients in Hamburg and organised and tabulated the printouts of patients included in Linz and Wels.

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6. Abbreviations

Abbreviation	Definition
CDVA	Spectacle-Corrected Distance Visual Acuity
CeCo	Centrality Coefficient
CIR	Continuous Intracorneal Ring
CL	Contact Lens
CLI	Contact Lens Intolerance
CXL	Conrela Collagen Crosslinking
Cyl	Refractive Cylinders
D	Dioptres
DALK	Deep Anterior Lamellar Keratoplasty
EF	Ectasia Factor
GC	Glasses Coefficient
ICRS	Intracorneal Ring Segments
KC	Keratoconus
KIR	Kontinuierlicher Intrakornealer Ring
KK	Keratokonus
kMax	Largest Anterior Keratometry Reading
ln (min. pachy)	Natural Logarithm Of Thinnest Pachymetry Reading
meanK	Average Simulated Anterior Keratometry Reading
min. pachy	Thinnest Central Pachymetry Reading
ML	Machine Learning
NPV	Negative Predictive Value
PCA	Primary Component Analysis
PMMA	Polymethylmethacrylate
PPV	Positive Predictive Value
QOL	Quality Of Life
ROC-AUC	Receiver Operator Characteristic Area Under The Curve
SD	Standard Deviation
Sph	Refractive Sphere
topoAsti	Topographical Astigmatism
topoAsti mismatch	Mismatch Between Topographical Astigmatism And CDVA
tPRK	Topography-Guided Photorefractive Keratectomy
UDVA	Uncorrected Distance Visual Acuity
UVA	Ultraviolet A Light
VFQ-39	National Eye Institute 39-Part Visual Function Questionnaire

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8. Curriculum Vitae

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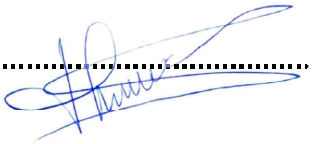

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