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Predictive Factors of the Standard Corneal Collagen Cross-Linking Outcomes among Keratoconus Patients in Palestine.

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Thesis Approval

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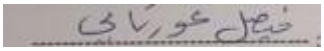
Faisal Awartani, PhD (Internal Evaluator)	

Declaration

I certify that, this thesis content has not been submitted to fulfil the requirement for academic degree, it also includes no previously published material except where due reference is made.

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Dedication

This thesis dedicated to the people who have supported me throughout my education.

Thanks for making me see this adventure through to the end.

Acknowledgement

First and foremost, praises and thanks to Allah, the Almighty, for blessings throughout my study work to complete the study successfully.

I would like to express my profound and sincere gratitude to my study supervisor, **Dr. Liana Al Labadi** and **DR. Hamzeh Al Zabadi** for invaluable guidance thought my study that was great honor to study and work under her supervision.

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List of Acronyms and Abbreviations

KC	Keratoconus
CXL	Collagen cross – linking
BCVA	Best corrected visual acuity
UCVA	Uncorrected visual acuity
K max	Maximum keratometry
CCT	Central corneal thickness
D	Diopter
Log MAR	Logarithm of the Minimum Angle of Resolution
IOP	Intraocular pressure
SEMR	Spherical equivalent manifest refraction
OD	Right eye
OS	Left eye
OU	Both eyes

Abstract

Background: Corneal cross-linking is the first line treatment for slowing the progression of Keratoconus, a progressive corneal ectatic disorder. Limited standardized guidelines are available on the impact of preoperative factors on the clinical outcomes of corneal CXL.

Purpose: To determine the effects of pre-operative presumed predictive factors on clinical and topographic outcomes in adults with keratoconus1 year following standard corneal cross-linking treatment.

Methods: A retrospective chart review study included 30 keratoconus patients (46 eyes) who underwent standard corneal collagen cross-linking treatment in an ophthalmology tertiary center in the city of Nablus, West Bank during the period from August 2019 until August 2021. Post-treatment best-corrected visual acuity and maximum keratometry were considered to be the predictive variables. Univariable analyses were performed to determine correlations between baseline parameters and follow-up measurements. Correlating factors ($P \leq .20$) were then entered into a multivariable linear regression analysis. finally a subgroup analyses were performed according to the age (≥25years and < 25 years), gender (Male and Female), family history of KC (positive and negative), smoking history (positive and negative), atopic constitution history (positive and negative), pre-operative K max (≥54 D and <54 D), pre-operative BCVA (<0.2 and ≥0.2

Log MAR), pre-operative UCVA (<0.6 and ≥0.6 Log MAR) pre-operative corneal thickness (<446 μ and ≥446 μ), pre-operative corneal apex thickness (<461 μ and ≥461 μ), pre-operative SEMR (≥-2.6 D and < -2.60 D) and the cone locations (central or eccentric) determine the associations between preoperative patient characteristics and outcomes (changes in visual acuity and maximum keratometry) of CXL treatment.

Results: multivariate analysis identified negative family history of keratoconus as a significant factor for predicting of post-operative best-corrected visual acuity (ß coefficient = 0.343 P =0.040), while Posttreatment maximum keratometry could be predicted based on pretreatment apical pachymetry (ß coefficient = 0.939, P =0.036).

Conclusions: Results of this study found that in patients with progressive keratoconus, family history, pre-operative best-corrected visual acuity, pre-operative corneal thickness, and smoking history appear to affect the success of the corneal cross-linking treatment.

Keywords

Keratoconus, visual acuity, retrospective study, Middle-East, Multivariate analysis, West Bank, Univariate analysis.

Chapter 1:

Introduction

1.1. Background

Keratoconus (KC), derived from the Greek word "cornea" and "cone," is a bilateral, asymmetric, progressive disorder that primarily affects people of working age. It is characterized by localized thinning of the corneal stroma with secondary ectasia, in which the central part of the cornea becomes progressively thin and bulges forward in a cone-shaped way. This results in myopia and irregular astigmatism in the affected cornea(Mas Tur et al., 2017).

Globally, the reported prevalence of keratoconus differs broadly depending on the geographical area and the diagnostic standards used. The prevalence documented in literature can range from 0.3 per 100,000 in Russia to 2300 per 100,000 in Central India (0.0003%-2.3%). In 2015, a cross-sectional study conducted on a sub-population of Palestinian students found the prevalence of keratoconus to be 1.5%(Shehadeh et al., 2015).

Over the past century, several treatment options for patients with progressive KC have been developed, including the use of glasses and different types of contact lenses. In severe progressive cases, contact lenses would no longer be an option due to poor tolerance and poor vision(Severinsky and Millodot, 2010). In advanced stages, corneal transplantation such as penetrating keratoplasty or deep anterior lamellar keratoplasty may be the only and final treatment option. Unfortunately, none of the mentioned traditional treatment modalities can affect the natural course of progression of KC. As recently as the late twentieth century, collagen cross-linking (CXL) was reported to be of great value for stiffening the corneal tissue(Mohammadpour et al., 2017). Corneal CXL

has now become a preferred surgical treatment option and the first line of treatment for progressive keratoconus and other corneal ecstatic disorders offering new promise for slowing down or stopping KC progression(Sorkin and Varssano, 2014).

The standard corneal collagen cross-linking isa minimally invasive surgery that is used to slow or halt the progression of corneal ectasias such as keratoconus, first reported by Wollensak and colleagues(Wollensak et al., 2003).

Corneal CXL is indicated specifically for cases that prove to be progressive. Several studies define the progression of KC as an increase of 1.00 Diopter or more in the maximum keratometry (K max) , an increase of 1.00 Diopter or more in the refraction cylinder, an increase of >0.50 D in manifest refraction spherical equivalent (MRSE)over a period of one year, in addition to the reduction of central corneal thickness ≥ 5% in three consecutive tomography scans over a period of six months(Hirji et al., 2015; Mohammadpour et al., 2018).

1.2. Context Regarding Corneal CXL Outcomes

The success of corneal CXL treatment depends on a number of clinical outcomes, such as post-operative visual acuity, post-operative maximum keratometry, and the lack of side effects. The clinical outcome is generally positive and shows promising results, although loss of visual acuity and further KC progression has been documented in some cases(Olivo-Payne et al., 2019). Predictors of corneal CXL outcome have been previously explored worldwide. Several factors have been reported to be positive predictors for standard corneal CXL outcomes including younger age, pre-operative best corrected visual acuity (BCVA) of> 0.3 Log MAR, higher pre-operative maximum keratometry (

K max) (≥54 D), a more central cone, and central corneal pachymetry less than 450 µm (Greenstein and Hersh, 2013; Wisse et al., 2019).

1.3. Study Significance

In Palestine, although KC is highly prevalent and the number of corneal CXL procedures is on the rise, limited studies evaluated the predictive factors for corneal CXL outcomes. This is concerning, especially since there are a few standardized guidelines on the impact of preoperative factors on the clinical outcomes of corneal CXL (Shehadeh et al., 2015). The aim of this study is to identify predictive clinical parameters associated with the overall outcome of corneal CXL 1-year-post-operatively. Standard corneal CXL remains the most commonly performed corneal CXL procedure in the country, and results of this study can be utilized to provide clinicians with evidence-based guidelines that will assist in predicting post-operative outcomes following corneal CXL in an effort to improve clinical outcomes and patient satisfaction.

1.4. Study Aim

The aim of the study is to identify predictive factors associated with the overall outcome of corneal CXL 1-year post-operative.

1.5. Study Objectives

- To provide demographical, medical and clinical characteristics of KC patients undergoing standard corneal CXL among a Palestinian sub-population.
- To evaluate the change in BCVA, UCVA, K Max, MRSE, and corneal pachymetry one year after standard corneal CXL was performed.

- Determine correlation between post-operative predictive factors and demographical, medical and clinical characteristics.

1.6. Expected Outcomes

It is expected that positive post-corneal CXL outcomes would be associated with worsening best corrected visual acuity, steeper maximum keratometry reading, thinner cornea, and central location of the cone.

Chapter 2:

Literature Review

2.1. Introduction

PubMed, MEDLINE, and Google Scholar were utilized to search for English-published articles on the predictive factors of corneal CXL. Keyword combinations of "keratoconus," "corneal collagen crosslinking," "predictive factors," "outcomes," and "cornea" were used. A total of 76 articles were retrieved.

2.2. Africa

Predictors for topographic and clinical results in adult keratoconus patients one year after conventional corneal CXL were evaluated in a retrospective cohort study in Egypt in 2017(Badawi et al., 2017). Both univariate and multivariate analysis were used to analyze the data collected, which also added another point of strength to the study besides the relatively large sample size. According to the results, a lower preoperative BCVA (>0.3 Log MAR), a steeper preoperative K max (>54D), and a thinner preoperative pachymetry (450 at the thinnest point) were all significantly predictive of a higher post-corneal CXL BCVA improvement and better outcomes. For both postoperative CXL outcomes, neither gender nor family history had an effect on the improvement of BCVA or the reduction of K max. The postoperative BCVA was not significantly affected by cone location. The central cone and worse preoperative BCVA (>0.3 Log MAR) appeared to be significant predictors of the postoperative decrease in K max for postoperative corneal flattening(Badawi et al., 2017).

2.3. Europe

Netherlands

A prospective cohort study was conducted in the Netherlands in 2013 at the University of Utrecht's ophthalmology department to investigate the presumed predictive factors, including atopic constitution, family history, and smoking history, on visual acuity and keratometry value outcomes for successively treated keratoconus patients (102 eyes) with minimal 1-year follow-up after CXL. Atopic constitution was associated with poor BCVA outcomes one-year post-CXL (P =.03). Treatment results were inconclusive. altered treatment results. Multivariable analysis findings showed that with respect to visual acuity at the 1-year follow-up. Pre-operative Log MAR BCVA was the sole independent predictor. Cone eccentricity was found as the single predictor for keratometry results 1 year after corneal CXL with a ß value of 0.709, which suggests that the more eccentric the cone at the beginning point, the steeper K max 1 year after CXL treatment, which is a negative post-CXL outcome. The study's key strength is standardized data collection by one qualified optometrist. The study's low dropout rate means the results are unlikely to be impacted by dropout bias(Wisse et al., 2014).

Switzerland

A prospective study was conducted to evaluate the complication risk of CXL for primary keratectasia and keratoconus to generate suggestions for preventing problems (Koller et al., 2009). BCVA, intraocular pressure, corneal topography imaging, and slit lamp evaluation for anterior and posterior eye segments before and post-surgery. A cohort of 117 eyes of 99 individuals were analyzed. ANOVA and the Mann-Whitney U test were used to detect complications and risk variables. Sterile infiltrates and central stromal

scarring occurred in 7.6% and 2.8% of participants aged 35 and older with a preoperative CDVA of 20/25 or greater. However, the sample size in this trial was too small to make generalizations regarding the genuine efficacy and safety of corneal CXL (Koller et al., 2009).

Italy

A non-randomized, open experiment was conducted at Santa Maria delle Scotte Hospital (Siena University, Siena, Italy) and the Department of Ophthalmology at Agostino Gemelli Hospital (Rome Catholic University, Rome, Italy). The study's purpose was to describe the long-term outcomes of 363 keratoconus eyes treated with standard corneal CXL. Forty-four eyes out of the total eyes with a minimum follow-up of 48 months had a minimum corneal thickness of 400 m at the thinnest point evaluated by OrbscanIIz, a topographic mean K value of less than 55 diopters (D), and a clear cornea by slit-lamp examination. The Mann–Whitney U test was used for nonparametric data (uncorrected visual acuity and best corrected visual acuity [BCVA]) and the paired t test for parametric data (refraction, mean curvature power, central corneal thickness, and intraocular pressure [IOP]. According to the findings of the Siena Eye Cross Study, the mean K value was lowered by 2 diopters, and coma aberration diminution with corneal symmetry improvement was detected in more than 85 percent of patients. The UCVA and BCVA gradually improve 2.7 Snellen lines, 1.9 Snellen lines respectively(Caporossi et al., 2010).

Germany

Retrospective interventional case series study conducted in 2015 to analyze the 10-year results of corneal collagen crosslinking (CXL) for keratoconus at the Department of

Ophthalmology, University Hospital, Dresden, Germany. The study included 34 eyes treated for progressive keratoconus from 2000 to 2004.Both BCVA and K max improved significantly after 10 years of standard CXL. The limitations of the study include the design (retrospective, nonrandomized, and without a control group) and small sample size. In addition, results are analyzed by eyes rather than patients(Raiskup et al., 2015).

2.4. North America

In a retrospective randomized controlled clinical trial conducted at the Cornea and Laser Eye Institute-Hersh Vision Group USA in 2012, 99 eyes (66 keratoconus, 33 ectasia) from 76 patients who received CXL were included to examine preoperative topographic cone location on 1-year results of standard epi-off corneal CXL Participants with maximum K within the middle 3-mm, 3-to-5-mm, and outside the 5-mm optical zones were separated into three groups. K max, UCVA significantly improved by -1.60±3.40diopters (D) (P<.001), -0.08±0.25 Log MAR(P=.001), and -0.10±0.18 Log MAR (P<.001), respectively, among the three groups. In the central cone group, maximum K fell by 2.604.50 D (P.001), 1.102.50 D (P=.02), and 0.401.20 D (P=.08). Centrally positioned cones flatten more than peripherally located cones. Although the combination of KC patients and corneal ectasia post LASIK in the study analysis, the relatively large sample size and study design add a strength point in this study(Greenstein et al., 2012).

1.5. ASIA

India

A retrospective case control study was conducted in India in 2020 with the goal of examining the clinical and topographical characteristics of eyes that displayed more than

5D of corneal flattening following corneal CXL for progressive keratoconus, in addition to determining the preoperative characteristics that are significant predictors of corneal CXL(Padmanabhan et al., 2021). The research looked at data from a total of 548 eyes. Participants were divided into two groups; patients who developed ≥5 D corneal flatting n = 43 were compared with the second group, which included the remaining participants. High pre-operative K max and the period of time post-CXL were significant predictors of this response, which was accompanied by significant corneal thinning. In addition to the reasonably large sample size, the data collected was subjected to univariate and multivariate analysis. (Padmanabhan et al., 2021).

Turkey

A retrospective study in Turkey was conducted to examine the influence of preoperative patient characteristics on the results of standard (CXL) treatment in patients with progressive keratoconus. A total of 96 eyes from 96 individuals with progressive keratoconus who had undergone unilateral CXL surgery were included in the study. Preoperative patient characteristics were examined to see if there were any associations between baseline characteristics and postoperative outcomes (changes in BCVA and change in K max). The mean BCVA significantly improved from 0.39±0.29 Log MAR to 0.28±0.22 Log MAR (P = 0.001) and the K max significantly improved from 54.54±5.50 D to 53.52±5.18 D 1 year after CXL treatment (P = 0.001). Participants with a worse preoperative BCVA of more than 0.3 Log MAR improved more visually after CXL treatment (P = 0.001). However, being older than 30 years old and having a baseline thinnest corneal point greater than 450 µ were both associated with greater improvement in K max (P = 0.024 and P = 0.005, respectively)(Toprak et al., 2014).

2.6. Palestinian Situation

A prospective cohort study was conducted at An-Najah National University hospital in Nablus to compare the 36-month visual acuity, refraction, corneal topography, and corneal pachymetry outcomes after standard and accelerated corneal collagen crosslinking in progressive keratoconus eyes(Shalabi et al., 2021). The study included a total of 191 eyes from 76 participants. For participants who underwent standard corneal CXL, UCDVA, and CCT all improved a lot, but no improvement in BCVA, K max, and SEMR was reported. The study's strongest aspect was a large sample size with a three-year postoperative follow-up period, it is focused mainly on the comparison between standard and accelerated CXL in respect to their result 36 months post treatment, while our study focused only for prediction standard CXL outcomes(Shalabi et al., 2021).

2.7. Comparison of Different Studies

Table 1**:** Outcomes from some clinical study using the standard CXL procedure.

Study name	Sample size (of eye)	Mean age (years)	Study period (year)	Mean K max change (D)	Mean BCVA Change
Toprak et al., 2014	96	29.42	1	1.2	-0.11 Log MAR
Badawi et al., 2017	136	24.6	1	2.01	-0.14 Log MAR
Greenstein et al., 2012	104	-	1	1.6	-0.10 Log MAR
Wisse et al., 2014	102	23	1	1.3	-0.13LogMAR
Caporossi et al., 2010.	44	10-50	4	2	1.9 lines
Raiskup et al., 2015	34	28.4	10	6.2	0.14LogMAR

Log MAR: - Logarithm of the Minimum Angle of Resolution: - Diopter

2.8. Summary

Based on the currently available data, we can therefore claim that CXL is a safe surgery that successfully slow the keratoconus progressions. In addition to corneal stabilization, previous studies reported that there is an improvement in both visual and topographic outcomes post standard CXL.

Chapter 3

Study Methodology

3.1. Study Design

A retrospective cohort study based on medical records review was conducted to identify predictive factors associated with the overall outcome of corneal CXL 1-year post-operatively.

3.2. Study Setting

The study was conducted at a tertiary eye care center in the city of Nablus, in the northern West Bank. Nablus is considered to be the second largest Palestinian city in the West Bank, and the largest governate in the north, located 70 km north of Jerusalem, and lies 550 meters above sea level. According to the 2017 census results, the population of Nablus was 387,240, with 50.7% males and 49.3% females, Representing 8.2% of all Palestinian population and 13.6 % of the West Bank population. Nablus is considered to be the main hub for medical services for more than one million people(PCBS, 2018, Najah National Hospital, 2022).

3.3. Study Population

The study population included all adult KC patients who underwent standard CXL treatment at the ophthalmology department during the period from August 2019 until August 2021. All Palestinian adults, 18 years old and above, diagnosed with a progressive KC, and undergoing standard epithelial-off corneal CXL and assessed with corneal tomography before and after corneal CXL were included in the study. Patients who had

incomplete medical records and missing at least 1 tomography image were excluded from the study.

3.4. Study Sampling and Sample Size

Using convenience sample, 46 eyes of 30 keratoconus patients who underwent corneal CXL between August 2019 until August 2021, and who met the inclusion criteria, and whose records were complete were included in the study.

3.5. Data Collection Tools

The data was collected by the main optometrist researcher and one full-time optometrist working in the tertiary eye center with experience of more than two years working with patients and medical records. BCVA and UCVA was measured using Snellen visual acuity charts (NIDEK CP-690 auto chart projector), K max, corneal thickness, and cone location was assessed using Pentacam corneal tomography (Oculus Pentacam V.6.09r39). SEMR was assessed using trial frame subjective refraction conducted full-time optometrists employed at the tertiary eye center during the study period.

A data collection form was developed by research team, as seen in ***appendix 2*.**The data retrieved from medical records and recorded in the data collection form included demographical data (age, gender), medical and ocular history (Family history of KC, smoking history, and atopic constitution history), laterality (OD, OS, OU), in addition to clinical parameters obtained pre and post operation (UDVA, BCVA, K max, MRSE, CT, Cone location).

3.6. Data Analysis

The SPSS software version 25 was used for statistical analysis. Data processing and cleaning were conducted through fixing structural error, processing missing data and finally validation of the remained data. For continuous data, descriptive statistical analysis was displayed as mean ± standard deviation (SD) and for categorical data as a number with a percentage. The main study outcomes were changes in BCVA and changes in K max one-year post-CXL follow-up. The paired sample *t*-test was used to compare the baseline and one-year changes in both K max and BCVA. The independent sample *t*-test was used to compare between the subgroups according to baseline data, The Mann–Whitney U test and Wilcoxon signed ranks test was used to analyze the nonparametric data.

At the 95 % confidence interval, a *p* value of < 0.05 was considered statistically significant. All predictive variables were then determined using univariate linear regression to assess the relationship between the clinical outcomes and the predictors. Histograms were used to check the normality of the variables. The B coefficients between the primary predictive factors and the predictive variables were determined using univariate analysis. A multivariate linear regression was then used to establish the independent predictive factors. Predictive variables with a *p* value less than 0.20 in the univariate analytic model were included again in the multivariate model.

3.7. Ethical Considerations

Ethical approval was obtained from Helsinki Committee (Palestinian health research council) in Gaza with code number (PHRC/HC/873/21), as seen in ***appendix 1***. Additional permissions to conduct the study and to review patient medical records were

obtained from the Arab American University (appendix 3) and An-Najah National University Hospital (verbal permission). No identifiers or personal information were collected or stored including participants' name, identification number or any other information to protect the patient's privacy and maintain research confidentiality. All information collected was treated as confidential and will not be released to a third party unless required to do so by law and will not be used for any purpose other than the scope of this research. Legal and ethical principles were maintained at all times during the writing process of this thesis.

This research was based purely on medical records review. No participants were subjected to any harm. The authors of the studies and material used in the literature review were given full credit, and referenced accordingly. Plagiarism was avoided, and copyrighted work was respected and not used in a bad manner.

Chapter 4:

Results

4.1. Data Preparation and Cleaning

Prior to analyzing the data, the data was inserted into an excel sheet and then imported to SPSS version 25.0 where coding was prepared. Each item was given a unique variable name. Data cleaning was performed for data entry errors, outliers, and missing values. Demographical data had no missing items.

4.2. Demographical Characteristics

Forty-six eyes (n= 46) of thirty patients who had standard corneal CXL treatment for progressive keratoconus and met the eligibility criteria were included in this retrospective study. Among study participants, as shown in Table 2, 46.7% (n=14) were females and 53.3% (n=16) were males with a mean (SD) age of 22.60±4.24years, and67.4% (n=20 patients) underwent bilateral standard corneal CXL.50.0 %(n=15patients) of all participants had a positive family history of keratoconus, 60.0 %(n=18patients)had a positive smoking history, and 53.4 % (n=16 patients) had a positive atopic constitutions history.

Table 2: Baseline demographical and medical Characteristics of 46 Eyes of 30 Keratoconus Patients

Demographical & Medical Characteristics	**N (%)**
Gender	
Male	16 (53.3)
Female	14(46.7)

Age (years) mean	Mean (range)= 22.5 (18-32)
Laterality Unilateral Bilateral	 15(32.6) 31(67.4)
Family history of KC Positive Negative	 15(50.0) 15(50.0)
Smoking history Negative Positive	 12(40.0) 18(60.0)
Atopic constitution Negative Positive	 14(46.6) 16(53.4)

As shown in Table 3, 39.1% (n=18 eyes) had a central cone location, the mean BCVA at the baseline was 0.27 Log MAR, while Kmax mean was 55.56 D pre-operative , thinnest pachymetry and apical pachymetry had a baseline mean of (432.6 µ, 450.48 respectively).

Table3 - The baseline clinical characteristics of 46 Eyes of 30 Keratoconus Patients.

Baseline Clinical Parameters	**Mean (range)**
Best corrected visual acuity	0.27(0.00 - 1.30) Log MAR
Uncorrected visual acuity	0.83 (0.00 - 1.30) Log MAR
Maximum keratometry	55.56 (45.6 - 71.5) D
thinnest pachymetry	432.6(360 – 499) µ
Apical pachymetry	450.48(378 – 511) µ
Spherical equivalent manifest refraction	-4.64(-24.00 - +1.00) DS
Cone location	N (%)18(39.1) Central cones N (%) 28(60.9) eccentric cone

Log MAR; -Logarithm of the Minimum Angle of Resolution, D: -diopter, DS: -diopter sphere.

4.3. Overall Outcomes at One Year

The mean change in UCVA (Log MAR) pre and post treatment showed a significant improvement (p=0.000) post-operative, while the BCVA change (Log MAR) did not show any statistically significant improvement (p=0.696). The K max change showed stabilization and maintained baseline values in 1 eye (2.2 %), and improved (flattened) by (0.3–5.5 D) compared to baseline values in 30 eyes (65.2 %). Worsening and progression of KC was documented in 15 eyes (32.6%) based on K-Max results. Table 4 shows the changes seen in clinical parameters between baseline and one-year post-corneal CXL.

Table 4: Mean changes among clinical parameters between baseline and one-year post-corneal CXL and their perspective P values among a total of 46 eyes.

Clinical Parameters	**Baseline mean ± SD**	**One-year mean ± SD**	***P* value**
UCVA	0.68±0.44LogMAR	0.47±0.4LogMAR	**0.000***
BCVA	0.19±0.29LogMAR	0.19±0.3LogMAR	0.696
K max	54.7±6.6D	53.9±6.5D	0.006*
Apical pachymetry	461.3±39µ	442.9±50.5µ	**0.001***
Thinnest pachymetry	446.3±41.6µ	412.8±93.1µ	**0.000***
Manifest refraction	-3.4±4.6D	-2.9±4.3D	0.082

UCVA: uncorrected visual acuity; **BCVA**: best-corrected visual acuity; **Log MAR:** logarithm of the minimum angle of resolution; **K max:** maximum K reading; ***P significant** at the value <0.05.

4.5. Univariate Analysis

Univariate analysis was performed on all dependent predictive variables to assess their relationship with the change in mean BCVA and mean K max post-corneal CXL, as shown in table 6. Only positive family history for KC was a prominent predictor of the BCVA change (ß coefficient: -0.369, CI95% -0.24-0.032 P= .01). A positive history for

smoking and apical pachymetry were statistically significantly in respect to the mean K max value change (ß coefficient: -0.292, CI95% -2.16 – 0.003, *P*= .04) (ß coefficient: 0.014, CI95% 0.00 – 0.028, *P*=0.03) respectively.

Table 5: Univariate linear regression of the baseline predictive factors and its significance on the treatment outcomes

	BCVA change			**K max change**		
Baseline predictive factors	**B coefficient**	**95% CI of the difference**	***P* value**	**B coefficient**	**95% CI of the difference**	*P* value
Age	0.003	-0.010 – 0.017	0.603	-0.108	-0.210 – 0.048	0.214
Family history	-0.369	-0.24 – 0.032	**0.012***	-0.042	-1.267 – 0.957	0.780
Atopic constitution	-0.075	-0.140 – 0.084	0.621	-0.035	-1.244 – 0.988	0.819
Smoking	-0.025	-0.123 - 0.104	0.869	0.292	-2.16 – -0.003	**0.040***
SEMR(D)	0.089	-0.008 – 0.015	0.585	-0.169	-0.185 – 0.051	0.261
UCVA (Log MAR)	-0.25	-0.151 – 0.101	0.689	0.170	-0.53 – 1.94	0.257
BCVA (Log MAR)	-0.255	-0.348 – 0.024	0.050	0.053	-1.57 – 2.24	0.727
thinnest pachymetry(µ)	0.033	-0.001 – 0.002	0.825	0.195	-0.005 -0.022	0.195
Apical pachymetry (µ)	0.012	-0.001 – 0.002	0.937	0.014	0.02 -0.028	**0.030 ***
Cone location	0.07	-0.088 - 0.141	0.644	0.065	-0.892 – 1.383	0.655
K max(D)	0.036	-0.007 – 0.010	0.810	-0.179	-0.133 – 0.034	0.235
Gender	-0.162	-0.173 – 0.05	0.281	-0.092	-1.46 – 0.78	0.543

SEMR: spherical equivalent manifest refraction; BCVA: best-corrected visual acuity; UCVA: uncorrected visual acuity; Log MAR: logarithm of minimal angle of resolution; K max: maximum keratometry; D: diopter; CI; confidence interval; B coefficient: the value which indicates how the dependent variable will differ per unit change in the predictive variable Significant at the value <0.05.

4.6. Multivariate Analysis: -

Multivariate analysis was conducted as shown in Table 6. With respect to BCVA outcome, only positive family history for keratoconus was an independent factor (ß coefficient: -0.343, CI95% -0.252 – 0.104, P value 0.048), which means that a positive family history could be associated with more improvement in BCVA. With regards to the post-corneal CXL corneal flattening (k max), only the apical pachymetry was the sole predictor (B coefficient 0.939, and 95% CI -0.004 –0.093, P value 0.05), which means that the thicker apical pachymetry pre-operative, the more the improvement will be in the

mean K max (more flattening). All other parameters that were assessed in this multivariable analysis did not appear to have an individual effect on treatment outcome.

Table 6. Multivariate linear regression of the baseline predictive factors and its significance on the treatment outcomes.

	BCVA change			**K max change**		
Baseline predictive variables	B	95% CI of the difference	*P* value	B	95% CI of the difference	*P* value
Family history	-0.343	-0.252 – -0.001	**0.040***	-	-	-
Smoking	-	-	-	-0.192	-2.004 – 0.578	0.270
BCVA	-0.411	-0.610 – 0.089	0.139	-	-	-
Thinnest pachymetry	-	-	-	-.675	-0.074 -0.014	0.176
Apical pachymetry	-	-		0.939	-0.004 -0.093	**0.036***

BCVA: best-corrected visual acuity; Log MAR: logarithm of minimal angle of resolution; CI; confidence interval; B coefficient: the value which indicates how the dependent variable will vary per unit change in the predictive variable; test used: multivariate linear regression test; ∗P significant at the value <0.05.

4.4. Subgroup Comparative Analysis

As shown in Table 5 The study participants were divided into subgroups with cutoff values in accordance with age (≥25years and < 25 years), gender (Male and Female), family history of KC (positive and negative), smoking history (positive and negative), and atopic constitution history (positive and negative). Clinical parameters of participants were also categorized into subgroups according to the mean value obtained in the study with pre-operative K max (≥54 D and <54 D), pre-operative BCVA (<0.2 and ≥0.2 Log MAR), pre-operative UCVA (<0.6 and ≥0.6 Log MAR) pre-operative corneal thickness (<446 μ and ≥446 μ), pre-operative corneal apex thickness (<461 μ and ≥461 μ), pre-operative SEMR (≥-2.6 D and < -2.60 D) and the cone locations (central or eccentric).

4.4.1. Age

Participants were classified into two groups according to age. For those whose age < 25 years (n = 9 patients,30.0%), the mean K max significantly improved from (54.3±6.09 to

53.6 ± 6.4) at 1-year post-corneal CXL treatment (*P*=0.041), whereas improvement in BCVA from (0.23 ±0.3 Log MAR to 0.20 ±0.32 Log MAR) was not statistically significant (*P* = 0.335). For those participants whose age ≥ 25 years (n= 21 patients,70.0 %), the improvement in mean BCVA (0.1±0.1 Log MAR to 0.17±0.27 Log MAR) was not statistically significant (*P* = 0.358) between baseline and 1 year post-operative , whereas the decrease in K max (55.3±7.02 D to 54.5±7.02 D) post-corneal CXL treatment was not statistically significant (*P*=0.075).Overall, when looking at age, there was no statistically significant difference between the two age groups when comparing post-operative changes in BCVA (*P*=0.154) and K max (*P*=0.79).

4.4.2. Gender

Among female participants (n = 14patients 46.7%), there was no improvement in mean BCVA (0.21±0.33 Log MAR to 0.23±0.3 Log MAR) (*P* = 0.545), whereas K max improved post-corneal CXL treatment (54.2±7.5 D to 53.6±7.4 D), with no statistical significance (*P*=0.103). Among male participants (n=16 patients 53.3%), the mean BCVA improved (0.166±0.22 Log MAR, to 0.13 ±0.15 Log MAR) with no statistical significance (*P* = 0.306), while K max statically improved (55.3±5.2 D to 54.3±5.1 D) (*P* = 0.021) between baseline and 1-yearpost-corneal CXL treatment.

Overall, when looking at gender, there was no statistically significant difference between the two groups when comparing post-operative changes in BCVA (*P*=0.281) and K max (0.543).

4.4.3. Pre-operative UCVA

Among participants whose UCVA is ≥0.6 Log MAR (n= 22 eyes, 47.8%), both the mean BCVA and K max was not statistically significant (0.32 ±0.37 Log MAR to 0.30 ± 0.40

Log MAR (*P* = 0.678), (54.32±7.19 D to 53.78 ±7.36 D) (*P*= 0.195) respectively. Among participants whose UCVA is < 0.6 Log MAR (n=24 eyes, 52.2%), the mean BCVA was not statistically significant (*P* = 0.336) (0.07 ±0.08 Log MAR to 0.09 ±0.10 Log MAR), whereas the K max was statistically significant improved (*P* =0.013) (55.07 ±5.89 D to 54.07 ±5.89 D).

Overall, when looking at pre-operative UCVA, there was no statistically significant difference between the two groups when comparing post-operative changes in BCVA (*P*=0.452) and K max (0.402).

4.4.4. Pre-operative BCVA

Among participants whose BCVA is≥ 0.2 Log MAR (n=17 eyes, 36.9%), the mean BCVA was not statistically significant (*P* = 0.732) (0.42±0.37 Log MAR to 0.40±0.41 Log MAR) similar to the post-operative improvement in K max (57.07±7.08 D to 56.39±7.61 D) which was also non-statistically significant (*P* = 0.234).

among participants whose BCVA is<0.2 Log MAR (n = 29 patients, 63.1%), the mean BCVA was not statistically significant (*P*=0.471) (0.05±0.06LogMARto 0.060±0.09 Log MAR), whereas the K max change statistically significant improved post-operative (*P* = 0.009) (53.33±6.05 D to 52.49±5050 D). Overall, when looking at pre-operative BCVA, there was no statistically significant difference between the two groups when comparing post-operative changes in BCVA (*P*=0.609) and K max (*P*=0.766).

4.4.5. Pre-operative K max

Among participants whose K maxis ≥54 D (n = 26 patients, 56.5%), the baseline BCVA was not statistically significant (*P* = 0.5) (0.22±0.29 Log MAR to 0.25±0.31 Log MAR),

whereas K max was statistically significant improved (*P* = 0.045) (59.00±5.50 D to 58.20 ±5.40 D) post-operative. Among participants whose K max is < 54 D (n = 20 patients 43.5%), the mean BCVA improved from (0.15±0.29 Log MAR to 0.11±0.28 Log MAR, *P* = 0.213) with the change being statistically non-significant. Whereas the K max improved (49.09±2.3 D to 48.38±2.32 D, *P* = 0.072) with the change being statistically non-significant, Comparison of the postoperative changes in BCVA and K max between subgroups indicates that here were no significant differences between two groups in terms of change in BCVA and K max post-corneal CXL treatment (*P* = 0.227, *P* = 0.829, respectively).

4.4.6. Preoperative Thinnest Pachymetry

Among participants who's thinnest pachymetry is ≥ 446 μ (n =22 patients, 47.8 %), the improvement in the baseline mean BCVA was insignificant (0.14±0.2 Log MAR to 0.12±0.20 Log MAR, *P* =0. 623), similar to the post-corneal CXL improvement in K max (51.20±3.90 D to 50.70±4.01 D, *P*= 0.079), which was also non-statistically significant.

Among participants who's thinnest pachymetry is <446 mm (n = 24 patients, 52.2 %), the mean reduction in BCVA was not statistically significant (0.24±0.30 Log MAR to 0.25±0.3 Log MAR, *P* = 0.810), whereas the mean K max improvement (57.90±7.06 D to 56.8±7.10 D, *P*= 0.036) was statistically significant. Overall, there was no significant difference between the subgroups with respect to improvement in BCVA and K max (*P* = 0.656 and *P* = 0.393 respectively) when comparing the postoperative changes in BCVA and K max between thinnest pachymetry subgroups.

4.4.7. Preoperative Corneal Apex Pachymetry

Among participants whose apex pachymetry is ≥ 461μ (n =26 patients, 56.5 %), the baseline means BCVA remained the same (0.19±0.3 Log MAR to 0.19±0.30 Log MAR, P =0. 953), while the improvement in the mean K max (from 52.00±5.3 D to 51.80±5.9 D) post-corneal CXL treatment was statistically non-significant (P=0.396). As for participants whose apex pachymetry is <461 μ (n = 20 patients, 43.6 %), the mean BCVA remained the same (0.19±0.20 Log MAR to 0.19±0.0.2 Log MAR, P = 0.989), whereas the post-corneal CXL improvement in the mean K max (58.10±6.60 D to 56.0±6.40 D) was statistically significant (P= 0.005). Overall, comparison of the postoperative changes in BCVA and K max between subgroups showed that apex pachymetry less than 461 μ was a good predictor for postoperative K max improvement (P= 0.027), while it had negligible effect on the changes in BCVA (P= 0.966).

4.4.8. Cone Location

Among participants who have a central cone (n =18 eyes, 39.1%), There was non-statistically

significant improvement in the mean BCVA (0.21±0.35 Log MAR to 0.19±0.31 Log MAR, P= 0.66), while the improvement in the mean K max (53.20±6.40 D to 52.20±5.80 D) 1-yearpost-operative was statistically significant (P= 0.05). Among participants who have eccentric cones (n =28 eyes, 60.9%), there were no statistically significant improvements in either the mean BCVA (0.21±0.35 Log MAR, to 0.19±0.31 Log MAR, P = 0.803), nor the mean K max improved from (55.60±6.60 D to 55.00±6.80 D, P = 0.55) at 1-year post-corneal CXL. Comparison of the postoperative changes in BCVA and K max between the two subgroups indicated that the changes in mean BCVA and K

max post-corneal CXL treatment did not show any statistically significant differences between the two groups (P = 0.64, P = 0.66, respectively).

4.4.9. Spherical Equivalent Manifest Refraction (SEMR)

Among participants whose SEMR is ≥ -2.60DS (n = 25 eyes, 54.3%), there was a non-statistically significant worsening of the mean BCVA (0.11± 0.10 Log MAR to 0.14 ± 0.22 Log MAR, *P* = 0.417), and a statistically significant improvement in the K max (54.30 ± 5.68 D to 53.41 ± 5.24 D, *P* = 0.01) 1-yearpost-corneal CXL treatment. Among participants whose SEMR is< -2.60 DS (n= 21 eyes, 45.7%), there was mild non-statistically significant improvement in both the mean BCVA and the mean Kmax one-year post-corneal CXL treatment (*P*=0.31 and 0.18, respectively). Overall, comparison of the postoperative changes in BCVA and K max between the two subgroups indicated that the changes in mean BCVA and mean K max post-corneal CXL treatment did not show any statistically significant differences (*P*= 0.20 and *P*=0.63 respectively).

4.4.10. Family History

Among participants who have positive family history (n =15patients,50.0%), the improvement in the mean BCVA and the mean Kmax was not statistically significant (P= 0.13 and 0.13 respectively), while those with negative family history of KC (n=15patients,50.0%), had a statistically significant improvement in the mean BCVA and the mean K max (*P*= 0.026 and 0.009 respectively). Comparison of the postoperative changes in BCVA and K max between subgroups showed that negative family history of KC was a good predictor for postoperative BCVA improvement only, and have non-statistical effect on Kmax (*P* values were 0.011 and 0.073, respectively).

4.4.11. Smoking History and Atopic Constitutions

Among participants who have positive history for smoking, there was a statistically significant improvement in the mean K max one-year post-operative (*P*=0.003), while there was no statistically significant change in BCVA (*P* = 0.88). As for participants with a negative history of smoking, there was no statistically significant improvement in both the mean BCVA and the mean K max (*P* = 0.88 and 0.68 respectively). Comparison of the postoperative changes in BCVA and K max between subgroups showed that appositive history for smoking was a good predictor for postoperative K max flatting while it was not statistically significant in respect to the changes of BCVA (*P* values were 0.049 and 0.869, respectively).

Among participants who have a negative history of atopic constitutions, there was a statistically significant improvement in the mean K max one-year post-corneal CXL (*P*= 0.041), while there was a non-statistically significant improvement in the mean BCVA (*P*= 0.49). As for participants with a negative history of atopy, there was a statistically non-significant worsening in the mean BCVA (*P*= 0.80), and a statistically non-significant improvement (flattening) in the mean K max (*P*= 0.07). Overall, the changes in mean BCVA and mean K max post-operative did not show significant differences between two groups (*P* = 0.62.*P* = 0.81, respectively).

Table 7: The changes in BCVA and K max one-year post-corneal CXL among the defined subgroups

BCVA changes				**K max changes**		
The defined subgroup	Mean (median) difference	95% CI of the difference	*P* value	Mean difference	95% CI of the difference	*P* value
Age ≥25 <25	0.083	-0.03 – 0.2	0.154	-0.15	-1.3 – 1.03	0.79
Gender Female Male	0.06	-0.05 – 0.17	0.281	0.34	-0.78 – 1.4	0.543
Pre-operative BCVA ≥0.2 < 0.2	-0.036	-0.18 – 0.112	0.609	0.170	-0.980 – 1.321	0.76
Preoperative UCVA ≥0.6 < 0.6	-0.041	-0.153 - 0.069	0.451	0.463	-0.640 - 1.560	0.402
Preoperative K max ≥54 D <54 D	0.06	-0.04 – 0.17	0.227	-0.12	-1.2 – 1.00	0.829
Thinnest pachymetry ≥446 µ <446 µ	-0.02	-0.13 – 0.08	0.656	0.47	-0.36 – 1.57	0.393
Apex pachymetry ≥461 µ <461 µ	-0.002	-0.11 – 0.11	0.966	0.52	0.14 – 2.2	**0.027***
Cone location Central Eccentric	-0.02	-0.14 – 0.08	0.64	-0.24	-1.38 – 0.89	0.66
SEMR **≥ -2.6 D** **< -2.6 D**	0.07	-0.03 - .18	0.2	-0.26	-1.03 – 0.84	0.6
Family history Negative Positive	0.13	0.13 – 0.05	**0.011***	0.15	-0.95 - 1.26	0.073
Smoking history Negative Positive	0.009	-0.10 - 0.12	0.869	1.083	0.003 - 2.16	**0.040***
Atopic constitutions Negative Positive	0.027	-0.08 - 0.13	0.62	0.127	-0.988 - 1.243	0.81

CI: confidence interval; , BCVA : best corrected visual acuity , UCVA : uncorrected visual acuity , K max :maximum keratometry , SEMR: spherical equivalent manifest refraction, test used: independent t-test*Mann-Whitney U test**,∗P significant at the value < 0.05.

Chapter 5:

Discussion and Conclusion

5.1Mainstudy Finding

The aim of the present study was to evaluate predictive variables associated with overall outcomes for standard corneal CXL. With respect to visual acuity at the 1-year follow-up, the only independent predictor identified was the negative family history of KC with a ß coefficient of -0.343 (CI95% -0.252--0.001, P = .040). This suggests that a negative family history of KC leads to improved BCVA post-operative. Univariate analysis indicated that worse pre-operative BCVA> 0.2 Log MAR was also associated with improvement in BCVA one-year post-corneal CXL, that's will conclude by that worse BCVA pretreatment usually have a central cone location and receiving more centered treatment effect. However, multivariate analysis revealed that this effect was not significant. No previous studies documented any significant correlation between postoperative BCVA and a negative family history of KC. These results were inconsistent with (Wisse et al,2014), which reported an insignificant correlation with BCVA outcomes. Previous studies evaluating the correlation between positive keratoconus family history and disease severity which is far from being fully clarified, suggest that KC is also associated with several diseases, especially those belonging to the atopic diathesis. in the other hand, Genome-wide association studies identify more than 60 genes/loci related to KC Among them are the genes LOX (a lysyl oxidase whose copper-dependent amine oxidase activity functions in the crosslinking of collagens and plays a significant role in collagen chain trimerization).

found that patients with a positive family history of KC are more likely to develop a severe picture of KC and were subsequently associated with a higher risk for progression post CXL(Naderan et al., 2016; Wisse et al., 2014).

With respect to post-operative Kmax, thicker apical pachymetry was the sole predictor of keratometry outcomes at the 1-year follow-up, with a ß coefficient of 0.939 (CI95% -0.004- 0.093, P = .05). This suggests that Kmax is more likely to improve with thicker apical pachymetry values. The univariate analysis in this study revealed that positive smoking history is associated with more K max flatting (improvement) one-year post treatment. No other factors remained significantly associated with either BCVA or K max in our univariate or multivariate analysis, these results are compatible with the prior studies in points and contrasted with them in other points. Therefore, there is a necessity for more studies to confirm what we have concluded. The role for apical pachymetry was documented only by (Greenstein et al ,2012) who found that there was no relationship between apical pachymetry and both BCVA and K max post-corneal CXL. The results of our study can be explained by the fact that during the CXL procedure a flat, perpendicular emission plane was used for transporting the UV light. And due to the oblique incident angle of UV light rays, the peripheral cornea is exposed to less intense UV light compared to the central part, that's mean the corneal apex (center) receives more focused treatment than non-apical corneal areas. The role for smoking history was suggested previously (Hafezi et al,2007 and Spoerl et al,2009) , who reported that smoking may cause the cornea to stabilize, which would likely improve the outcome of CXL treatment. This is because tobacco cigarettes contain toxic chemicals like carbon monoxide, which change both corneal rigidity parameters Corneal Resistance Factor and corneal hysteresis and make free radicals and reactive oxygen species, which are important in the polymerization

process. Despite this, smoking should not be promoted among keratoconus patients as it has other evidence-based health implications.(Greenstein et al., 2012). (Hafezi, 2009; Spoerl et al., 2007).

5.2. Overall Outcomes

In the current study, both the mean BCVA (log MAR) and the mean K max improved after one year of CXL with no statistical significance reported. It should be noted that post-operative BCVA in our study was conducted using best-corrected glasses, and that if it was measured using best-corrected specialty contact lenses, our results may have been different. These results were inconsistent with (Badawi et al ,2017) where statistically significant improvement in the mean Kmax was reported. Our results were consistent with(Shalabi et al ,2021), which was also conducted at An-Najah National University Hospital(Badawi et al., 2017; Shalabi et al., 2021).

5.3. Subgroups Comparison

Regarding the patients' age, the most significant improvements have been seen in patients younger than 25 years. Similarly, (Badawi et al ,2017) found that younger patients had better K max outcomes post-corneal CXL. These results are consistent with the fact that younger patients(< 25 years) have more advanced and aggressive KS, and usually they have more central cone than older patients(Mukhtar and Ambati, 2018). In addition, the mean participant age in our study was younger than in other studies(Badawi et al., 2017). In agreement with our results (Koller et al, 2009and Wisse et al, 2014) reported that older patients had worse outcomes and were more likely to experience complications. In our study, the majority of participants were in their second decade of life, who usually have

a more accelerated progression of KC , and that's make them motivated to receive the treatment (Koller et al., 2009; Wisse et al., 2014).

With respect to preoperative UCVA, better preoperative UCVA levels<0.6 Log MAR were associated with more corneal flatting after the intervention. These findings were in line with those of (Badawi et al , Vinciguerra et al., 2009 and Shalabi et al.), who reported statistically significant improvement in corneal flatting secondary to a decrease in SEMR, particularly in patients with higher SEMR(Badawi et al., 2017; Vinciguerra et al., 2009; Shalabi et al., 2021).

Concerning the cone location, our results found a difference in response between the central and eccentric cones. The more centrally located cones had a significant improvement in the mean Kmax post-corneal CXL. (Greenstein et al. and Wisse et al) reported that patients with centrally located cones are more likely, rather than eccentrically located cons, to benefit with respect to corneal flatting. This result can be interpreted by the fact that the incidence angle of a ray with the corneal surface declines towards the peripheral cornea. This leads to a less powerful and inconsistent beam in peripherally located cones(Greenstein et al., 2012; Wisse et al., 2014).

Despite these differences in K max improvement following CXL, the preoperative location of the cone did not appear to statistically significantly affect BCVA outcomes. However, even with an insignificant difference between the two cone locations regarding BCVA improvement, we found that the central cone subgroup showed better improvement in BCVA than in the peripheral cones. This finding could be explained by the relationship between the visual acuity and the cone location. Whereas, the worst preoperative BCVA appeared to be closely related to the central cones (Vinciguerra et al., 2009).

Concerning atopic constitution, a negative history of atopic constitution significantly improved K max one year after CXL, which is consistent with the findings of (Pour Azizi et al.), who reported a significant association between positive atopic constitutions and corneal flatting after CXL. Furthermore, positive atopic constitutions are associated with predominant eye rubbing secondary to severe ocular itching, which may cause an increase in protease, an inflammatory mediator, and protease activity. This may then lead to the KC getting worse and, as a result, to worse CXL results(Peyman et al., 2020).

5.4. Study Strengths and Limitations

Although this study is the first study of its kind in Palestine, it has some limitations. First, it was not easy for us to get permission for data collection. This was in addition to the difficulties that we faced during the data collection period due to the general health conditions and COVID-19. Second, the relatively small sample size was a limitation.

A retrospective chart review design has many limitations that have been faced, including incomplete, inaccurate, some missing or incomplete data, and poor quality of information in patient files. So, this study needs to be confirmed in future prospective research before it can be used in clinical practice.

This study has several strengths. First, the study evaluated multiple demographic and clinical parameters. In addition to that, our study included only keratoconus patients rather than including both KC and post-ectasia patients as reported by(Caporossi et al., 2010; Greenstein et al., 2012; Wisse et al., 2014) in Italy, USA and Netherlands respectively.

In Palestine, limited studies were performed. Our study was the first one in which we evaluate the predictive factor for corneal CXL outcomes.

5.5. Implications for Public Health, Research, and Health Informatics

The results of our study have provided more information on the demographics and treatment outcomes of KC patients undergoing corneal CXL in the Palestinian area, allowing ocular health care providers to appropriately choose patients who are predicted to be good candidates for the surgery. Additionally, this could help KC patients to maintain their quality of life and avoid any difficulties related to expensive donor keratoplasty surgery.

Because early detection of keratoconus (asymptomatic keratoconus) can prevent disease progression, a collaborative effort should be directed toward more frequent screening and careful monitoring of disease progression in order to identify and treat affected patients as early as possible and avoid them developing desired outcomes.

Even though there have been several studies done in developed countries that show how important it is to screen for and diagnose KC early, there isn't enough evidence in developed countries and locally to help make a clinical decision.

5.6. Summary

In respect to the BCVA, univariate analysis reported that the worse BCVA and negative family history of KC were relatively good predictors of improvement, while multivariate analysis revealed a interrelation with only negative family history. Concerning the flattening of the cornea after surgery, univariate analysis found that a history of smoking and a thinner Apical Pachymetry were the most important predictors, while multivariate analysis only looked at the effect of the Apical Pachymetry.

These results are well-matched with the previous studies in some ways and contrasted with them in others. Additional research is required to corroborate our findings.

5.7. Conclusions

Corneal CXL actually helps Palestinian patients suffering from progressive keratoconus. Patients with a negative family history of KC and worse pre-operative BCVA are more likely to benefit from CXL (in terms of visual acuity). In regards to corneal flattening, smoker patients and participant with a thinner apical pachymetry will benefit more (in term of K max).

5.8. Recommendations

- Ongoing prospective research should be conducted in different population with a larger sample size and longer follow-up period.
- Develop and implementations of health information system and database in ophthalmology department.
- Enhance ocular health care provider education regarding the important of early detection and treatment.
- Awareness program of the KC main risk factors, sign and symptoms for people can lead to an earlier detection and treatment of KC.

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Appendices

Appendix 1: Helsinki Committee Ethical approval for Data collection

المجلس الفلسطيني للبحث الصحي
Palestinian Health Research Council

تعزيز النظام الصحي الفلسطيني من خلال مأسسة استخدام المعلومات البحثية في صنع القرار
Developing the Palestinian health system through institutionalizing the use of information in decision making

Helsinki Committee
For Ethical Approval

Date: 05\04\2021 **Number:** PHRC/HC/873/21

Name: Yousef Mohammad Mohammad awlad Mohammad الاسم:

We would like to inform you that the committee had discussed the proposal of your study about: نفيدكم علماً بأن اللجنة قد ناقشت مقترح دراستكم حول:

Predictive Factors of the Cross-Linking Outcomes among Keratoconus Patients in Palestine

The committee has decided to approve the above mentioned research. Approval number PHRC/HC/873/21 in its meeting on 05\04\2021 و قد قررت الموافقة على البحث المذكور عاليه بالرقم والتاريخ المذكوران عاليه

Signature

Member Dr. Khamis Elessi

Member Dr. Yehia Abed

For **Chairman**

Genral Conditions:-
1. Valid for 2 years from the date of approval.
2. It is necessary to notify the committee of any change in the approved study protocol.
3. The committee appreciates receiving a copy of your final research when completed.

Specific Conditions:-

E-Mail:pal.phrc@gmail.com

Gaza - Palestine غزة - فلسطين
شارع النصر - مفترق العيون

Appendix 2: Data Collection sheet

Arab American University

Faculty of graduate studies

الجامعة العربية الأمريكية

كلية الدراسات العليا

Study Title:			
Section 1: Demographic characteristics of study sample			
File Code			
Gender	☐ Male	☐ Female	
Age	☐ 19-40	☐ 41-60	
	☐ 61-80	☐ above 80	
	☐ Missing		
Place of living	☐ city	☐ town	
	☐ village	☐ refugee camp	
	☐ Missing		
Family History of Keratoconus	☐ Yes	☐ No	
	☐ Missing		
Smoking History	☐ Current smoker	☐ Previous smoker	☐ No smoking history
	☐ Missing		
Atopic Constitution	☐Positive	☐Negative	☐ Missing
Laterality	☐OD	☐OS	☐OU
	☐ Missing		
Section 2: Pre-Operative Assessment			
Eye Undergoing CXL	☐OD	☐OS	
Kmax	(Diopters)		
Uncorrected DVA (UDVA)		☐ Missing	
Corrected DVA (CDVA)		☐ Missing	
Manifest Refraction SEQ (MRSE)	(Diopters)	☐ Missing	
Cone Eccentricity	Central Cone	Eccentric Cone	
IOP	(mmHg)	☐ Missing	
Corneal Thickness	Apex (um)	Thinnest Point (um)	
	Pupil Center (um)		
Section 3: Post-Operative Assessment			
Date of Post-operative Assessment			
Kmax	(Diopters)		
Uncorrected DVA (UDVA)		☐ Missing	
Corrected DVA (CDVA)		☐ Missing	
Manifest Refraction SEQ (MRSE)	(Diopters)	☐ Missing	
IOP			
Corneal Thickness	Apex (um)	Thinnest Point (um)	
	Pupil Center (um)		

الملخص

مقدمة:- عملية تثبيت القرنية، هو إجراء يستخدم لتقوية القرنية، ويطلق عليه أيضاً تثبيت القرنية المخروطية لأن هذا الإجراء يتم للقرنية المخروطية، إذ تكون القرنية في هذه الحالة ضعيفة، ورقيقة، وغير منتظمة الشكل. اليوجد في فلسطين بيانات أو سجل واضح حول نتائج عملية تثبيت القرنية و تأثير العوامل االمختلفة على نتاجها على المدى القريب و كذلك البعيد .

منهجية الدراسة: تم إجراء مراجعة رجعية غير تدخلية لدراسة السجالت الطبية لملف المريض من أب 2019 الى أب 2021 في مستشفى النجاح التعليمي . شملت المجموعة المستهدفة أألشخاص الذين تبلغ أعمارهم 18 عاًما فأكثر و يعيشون في الضفة الغربية و يعاونون من مرض القرنية المخروطية و تم عمل تثبيت للقرنية لهم في الفترة المعتمدة للدراسة .

النتائج: غياب التاريخ العائلي للقرنية المخروطية من اهم العوامل لتوقع حدة الابصار بعد عملية تثبيت القرنية المخروطية , بالاضافة الى ان كلما زادت سماكة القرنية في المنطقة الرئيسية كانت قراءات القرنية افضل بعد اجراء عملية تثبيت القرنية .

الخلاصة: اشارت هذه الدراسة الى ان المرضى الذين يعانون من القرنية المخروطية , و يملكون تاريخ عائلي سلبي للمرض , و يعانون من ضعف في حدة الرؤية , بالاضافة لكونهم مدخنين يحصلون على نتائج افضل بعد اجراء عملية تثبيت القرنية .