Ophthalmic Examination Parameters for the Timing of Corneal Crosslinking Indications in Patients with Keratoconus

Akio Miyakoshi (akio3854@med.u-toyama.ac.jp)
University of Toyama
Atsushi Hayashi
University of Toyama
Toshihiko Oiwake
University of Toyama

Research Article

Keywords: keratoconus, corneal crosslinking, general ophthalmic examination, minimum corneal thickness

Posted Date: August 1st, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1895430/v1

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at International Ophthalmology on November 1st, 2023. See the published version at https://doi.org/10.1007/s10792-023-02881-1.

Abstract

Purpose: To find parameters of a general ophthalmic examination that can detect indications for corneal crosslinking (CXL) (minimum corneal thickness: MCT >400 μm) in patients with keratoconus.

Methods: The cases of the patients referred to Toyama University Hospital for the treatment of keratoconus from August 2011 to May 2021. The percentage of patients with keratoconus who had an MCT <400 μm at their first visit was identified, and we performed a receiver operator characteristic (ROC) analysis to determine the predictive accuracy of general ophthalmic examination parameters and MCT. We calculated the area under the curve (AUC), sensitivity, and specificity of each factor.

Results: The analyses included 66 eyes of 38 Japanese patients aged 25.0±7.1 yrs (range 12–38 yrs) (56 male eyes and 10 female eyes). Thirty percent of the patients had an MCT <400 μm. The AUC for uncorrected distance visual acuity (UCDVA) was 0.85. We set the cut-off value at 1.22 (converted to decimal visual acuity: ≥0.06) and observed 87% sensitivity and 75% specificity. The AUC for corrected distance visual acuity (CDVA) was 0.90. We set the cut-off value at 0.52 (converted to decimal visual acuity: ≥0.3) and observed 89% sensitivity and 75% specificity.

Conclusions: It is advisable to refer patients with keratoconus to a specialized facility for CXL when the following conditions are present: ( ) UCDVA (decimal visual acuity) ≥0.06 and ( ) CDVA (decimal visual acuity) ≥0.3.

1. Introduction

Keratoconus poses a threat to an individual's visual function due to progressive myopia and irregular astigmatism [1]. Corneal crosslinking (CXL), which Wollensak et al. reported in 2003 [2], is the only treatment that stops the progression of keratoconus [3], and the use of CXL is becoming common worldwide. In CXL, the corneal stroma is permeated with riboflavin (Avedro, Waltham, MA, USA) and then irradiated with a 370-nm wavelength ultraviolet A (UVA) beam. In order to prevent UVA-induced damage to corneal endothelial cells, it is recommended that a corneal thickness of ≥ 400 μm be maintained [4].

Among the patients who are first referred to the Toyama University Hospital for the treatment of keratoconus, we frequently encounter patients with a minimum corneal thickness (MCT) < 400 μm. Since there is no clear single index for the early detection of keratoconus, scoring indices that combine several different corneal parameters have been developed [5]. However, there have been no reports from two perspectives: the detection of keratoconus cases by a general ophthalmic examination (that can be performed in ophthalmic clinics without corneal topography or anterior segment optical coherence tomography [AS-OCT]), and the detection of keratoconus cases with indications for CXL. Ophthalmic clinics that regularly see patients with keratoconus may thus worry about or miss the appropriate timing for the patients' referral to a specialized facility.

We conducted the present study to identify general ophthalmic examination parameters that could be used to detect keratoconus cases that are suitable for CXL.

2. Patients And Methods

2.1. Study design and patients

We performed a retrospective study of the patients who were referred to Toyama University Hospital for the treatment of keratoconus the period between August 2011 and May 2021. Exclusion criteria were previous ocular surgery and a history of acute corneal hydrops. The first and last authors take complete responsibility for the integrity of the data and the accuracy of the data analysis.

2.2. Study measurements

The following parameters were analyzed at the time of the patients' initial examination: uncorrected distance visual acuity (UCDVA), corrected distance visual acuity (CDVA), manifest refraction, corneal astigmatism (RT-7000 Auto Ref-Topographer, Tomey, Nagoya, Japan), and AS-OCT (Cornea/Anterior Segment OCT CASIA2, Tomey).

2.3. Study outcomes

We first investigated the percentage of patients with keratoconus who were ineligible for CXL at their first visit. In this study, we defined an MCT < 400 μm as not suitable for CXL. We then divided the patients into two groups based on whether or not the MCT was ≥ 400 μm. We compared the groups' background and laboratory parameters and then obtained the receiver operator characteristic (ROC) curves for general ophthalmic examination parameters that can be measured without corneal topography or AS-OCT plus the MCT. The optimal cut-off value in the ROC curve was calculated to identify an MCT ≥ 400 μm based on the Youden index.

2.4. Statistical analysis

We used the Mann-Whitney U-test to compare the averages of continuous variables (such as age) and Fisher's exact test to compare the proportions of categorical variables (such as sex) between the groups. The threshold for significance was $p < 0.05$. All statistical analyses were conducted using EZR ver. 1.55 [6].

3. Results

We examined 66 eyes of 38 Japanese patients (32 males, 6 females) aged (mean ± standard deviation) 25.0 ± 7.1 years (range 12–38 years): 56 male eyes and 10 female eyes. Thirty percent of the patients already had an MCT < 400 μm at the time of their first visit.

We divided the patients based on whether or not their MCT was ≥ 400 μm and defined the groups as the < 400-μm MCT and ≥ 400-μm MCT groups. Table 1 lists the demographic data of the patients in each

group; there were no significant between-group differences in demographic data.

Table 1
Demographic data of the 38 patients with keratoconus (n = 38)

	MCT < 400 µm	MCT ≥ 400 µm	p-value
No. of eyes	20	46	
Mean age, yrs ± SD	25.5 ± 7.9	24.8 ± 6.7	0.91†
Males/females, n	14 (70%)/6 (30%)	42 (91%)/4 (9%)	0.056‡
Laterality, right, n	9 (45%)	21 (46%)	1.0‡
Atopic dermatitis history, n	5 (25%)	13 (28%)	1.0‡
† Mann-Whitney U-test, ‡ Fischer's exact test.			

Table 2 provides the groups' visual and refractive data. The UCDVA, the CDVA, and the CDVA with a hard contact lens in the < 400-µm MCT group were significantly lower than those in the ≥ 400-µm MCT group. The tomographic data of the two groups are summarized in Table 3; significant deformation of the cornea was observed in the < 400-µm MCT group.

Table 2
Visual and refractive data

	MCT < 400 µm (n = 20)	400 µm ≥ MCT (n = 46)	p-value
UCDVA, logMAR	1.46 ± 0.40	0.80 ± 0.48	< 0.001†
CDVA, logMAR	1.04 ± 0.56	0.19 ± 0.36	< 0.001†
CDVA with HCL, logMAR	0.15 ± 0.23*	−0.05 ± 0.13*	0.001†
Sphere, D	−0.61 ± 5.94	−2.86 ± 4.12	0.082†
Cylinder, D	−2.50 ± 2.92	−3.33 ± 2.61	0.14†
Corneal astigmatism, D	3.81 ± 2.67*	3.84 ± 2.30*	0.88†
* Measurable cases only. † Mann-Whitney U-test. HCL: hard contact lens, CDVA: corrected distance visual acuity, UCDVA: uncorrected distance visual acuity.			

Table 3
Tomographic data

	MCT < 400 µm (n = 20)	MCT ≥ 400 µm (n = 46)	p-value
Kmax	71.7 ± 11.6	53.0 ± 5.9	< 0.001†
MCT, µm	333.3 ± 59.8	475.0 ± 36.7	< 0.001†
Corneal HOA, µm	1.52 ± 1.33	0.88 ± 0.68	0.028†

† Mann-Whitney U-test. HOA: higher-order aberration, Kmax: maximum anterior sagittal curvature, MCT: minimum corneal thickness.

Based on the general ophthalmic examination values (visual acuity and refraction values) listed in Table 2, the ROC curves were drawn and the cut-off value for identifying an MCT ≥ 400 µm was calculated. We observed that the two test items with an area under the curve (AUC) > 0.8 were the UCDVA and the CDVA. The AUC for UCDVA was 0.85. We set the cut-off value at 1.22, and the calculation revealed 87% sensitivity and 75% specificity (Fig. 1). The AUC for CDVA was 0.90. We set the cut-off value at 0.52, and the calculation revealed 89% sensitivity and 75% specificity (Fig. 2).

Discussion

We investigated the percentage and characteristics of patients with keratoconus who were already not indicated for CXL, and we evaluated general ophthalmic examination parameters that could be used to detect patients with keratoconus who were indicated for CXL. We found that at the time of their first visit to our hospital, 30% of the patients were already not indicated for CXL. The results of our analyses demonstrated that the patients with UCDVA (logMAR) <1.22 (converted to decimal visual acuity: ≥0.06) and those with CDVA (logMAR) <0.52 (converted to decimal visual acuity: ≥0.3) had an MCT of ≥400 µm and were likely to be ready for CXL.

A considerable number of studies have investigated the possibility of the early detection of keratoconus [5], and the following parameters have been reported to be useful: the corneal epithelial basal cell density [7], epithelial thickness [8], posterior corneal elevation [9], ratio of the anterior and posterior corneal surface areas [10], corneal light intensity distribution [11], anterior corneal higher-order aberrations [12], and total ocular higher order aberrations [12, 13]. These parameters are calculated from images taken using specialized equipment such as AS-OCT, topography, and Scheimpflug imaging. We have found no published studies of the early detection of keratoconus from two perspectives: the detection of keratoconus patients by a general ophthalmic examination, and the detection of keratoconus patients for whom CXL is indicated. It is significant that our present study identified a threshold value based on general ophthalmic examination parameters that could be used to determine how long an ophthalmic clinic (without corneal topography or AS-OCT) that treats patients with keratoconus should follow the patients.

Of the patients referred to our hospital for treatment of keratoconus, 30% were already not indicated for CXL at the time of their first visit. We defined an MCT <400 μm as not suitable for CXL according to the Dresden protocol [2]. The following modifications to the conventional protocol that has been used to make CXL possible for thin corneas have been reported: hypo-osmolar riboflavin [14], transepithelial CXL [15], iontophoresis-assisted CX [16, 17], a customized epithelial debridement technique [18], lenticule-assisted CXL [19], contact lens-assisted CXL [20], and individualized CXL [21]. However, the evidence regarding the safety and efficacy of these modifications is limited, and long-term follow-ups and large-scale studies are desirable [22]. From the viewpoint of screening to avoid delay, we believe that the criterion of an MCT <400 μm is appropriate at this time.

We propose the UCDVA and CDVA as general ophthalmic examination parameters that can be used to identify keratoconus cases indicated for CXL. It is well known that as the cornea becomes thinner, the visual acuity decreases due to increased irregular astigmatism; however, our present analyses revealed that CDVA with a hard contact lens was not a useful indicator for CXL. This may be because the average visual acuity in our <400-μm MCT group was also good at 0.7 (decimal visual acuity), and there were some cases in which the patient's CDVA with a hard contact lens exceeded 1.0 (decimal visual acuity). If the progress of patients with keratoconus is not monitored closely because they have good vision with correction by a hard contact lens and do not have problems in their daily life, we may miss the time point at which CXL is indicated.

We acknowledge several study limitations. There was a lack of consistency in how and when keratoconus was diagnosed at the referring clinics. However, when dealing with a disease such as keratoconus for which early detection methods are still being debated, it is difficult to exclude the possibility that technological advances such as the introduction of corneal topography and AS-OCT may provide a patient selection bias. In addition, our analyses were of a relatively small number of patients treated at a single institution. There is a possibility of double organ bias. A large-scale multicenter study is needed to further explore general ophthalmic examination parameters that can be used to identify keratoconus cases indicated for CXL.

In summary, it is important not to miss the time point at which CXL is possible by referring patients with keratoconus to a specialized facility for keratoconus when the following conditions is observed: ( ) UCDVA (decimal visual acuity) ≥0.06, and ( ) CDVA (decimal visual acuity) ≥0.3.

Statements And Declarations

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing interests

The authors have no relavant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Toshihiko Oiwake and Akio Miyakoshi. The first draft of the manuscript was written by Akio Miyakoshi and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee, University of Toyama (R2022006).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

References

1. Musch DC, Farjo AA, Meyer RF, Waldo MN, Janz NK (1997) Assessment of health-related quality of life after corneal transplantation. Am J Ophthalmol 124:1–8
2. Wollensak G, Spoerl E, Seiler T (2003) Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. Am J Ophthalmol 135:620–627
3. Meiri Z, Keren S, Rosenblatt A, Sarig T, Shenhav L, Varssano D (2016) Efficacy of corneal collagen cross-linking for the treatment of keratoconus: A systematic review and meta-analysis. Cornea 35:417–428
4. Wollensak G, Spörl E, Reber F, Pillunat L, Richard F (2003) Corneal endothelial cytotoxicity of riboflavin/UVA treatment in vitro. Ophthalmic Res 35:324–328
5. Santodomingo-Rubido J, Carracedo G, Suzaki A, Collar CV, Vincent SJ, Wolffsohn JS (2022) Keratoconus: An updated review. Cont Lens Anterior Eye 101559. doi:10.1016/j.clae.2021.101559
6. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics (2013) Bone Marrow Transplant 48:452–458
7. Xu Z, Jiang J, Yang C, Huang S, Peng M, Li W, et al (2016) Value of corneal epithelial and Bowman's layer vertical thickness profiles generated by UHR-OCT for sub-clinical keratoconus diagnosis. Sci Rep 6: PMC4980663. doi:10.1038/srep31550
8. Abad AM, Piñero DP. New perspectives on the detection and progression of keratoconus (2017) J Cataract Refract Surg 43:1213–1227
9. Belin MW, Khachikian SS (2009) An introduction to understanding elevation-based topography: How elevation data are displayed – A review. Clin Exp Ophthalmol 37:14–29

10. Itoi M, Kitazawa K, Yokota I, Wakimasu K, Cho Y, Nakamura Y, et al (2020) Anterior and posterior ratio of corneal surface areas: A novel index for detecting early stage keratoconus. PLOS ONE 15:e0231074. doi 10.1371/journal.pone.0231074
11. Consejo A, Solarski J, Karnowski K, Rozema J, Wojtkowski M, Iskander DR (2020) Keratoconus detection based on a single Scheimpflug image. Transl Vis Sci Technol 9: PMC7414642. doi:10.1167/tvst.9.7.36
12. Saad A, Gatinel D (2012) Evaluation of total and corneal wavefront high order aberrations for the detection of forme fruste keratoconus. Invest Ophthalmol Vis Sci 53:2978–2992
13. Jafri B, Li X, Yang H, Rabinowitz YS (2007) Higher order wavefront aberrations and topography in early and suspected keratoconus. J Refract Surg 23:774–781
14. Hafezi F, Mrochen M, Iseli HP, Seiler T (2009) Collagen crosslinking with ultraviolet-A and hypoosmolar riboflavin solution in thin corneas. J Cataract Refract Surg 35:621–624
15. Leccisotti A, Islam T (2010) Transepithelial corneal collagen cross-linking in keratoconus. J Refract Surg 26:942–948
16. Bikbova G, Bikbov M (2014) Transepithelial corneal collagen cross-linking by iontophoresis of riboflavin. Acta Ophthalmol 92:e30-34. doi:10.1111/aos.12235
17. Vinciguerra P, Randleman JB, Romano V, Legrottaglie EF, Rosetta P, Camesasca FI, et al (2014) Transepithelial iontophoresis corneal collagen cross-linking for progressive keratoconus: Initial clinical outcomes. J Refract Surg 30:746–753
18. Kymionis GD, Diakonis VF, Coskunseven E, Jankov M, Yoo SH, Pallikaris IG (2009) Customized pachymetric guided epithelial debridement for corneal collagen cross linking. BMC Ophthalmol 9:10
19. Sachdev MS, Gupta D, Sachdev R, Sachdev G, Sachdev R (2015) Tailored stromal expansion with a refractive lenticule for crosslinking the ultrathin cornea. J Cataract Refract Surg 41:918–923
20. Jacob S, Kumar DA, Agarwal A, Basu S, Sinha P, Agarwal A (2014) Contact lens-assisted collagen cross-linking (CACXL): A new technique for cross-linking thin corneas. J Refract Surg 30:366–372
21. Kling S, Hafezi F (2017) An algorithm to predict the biomechanical stiffening effect in corneal cross-linking. J Refract Surg 33:128–136
22. Deshmukh R, Hafezi F, Kymionis GD, Kling S, Shah R, Padmanabhan P, et al (2019) Current concepts in crosslinking thin corneas. Indian J Ophthalmol 67:8–15

Figures

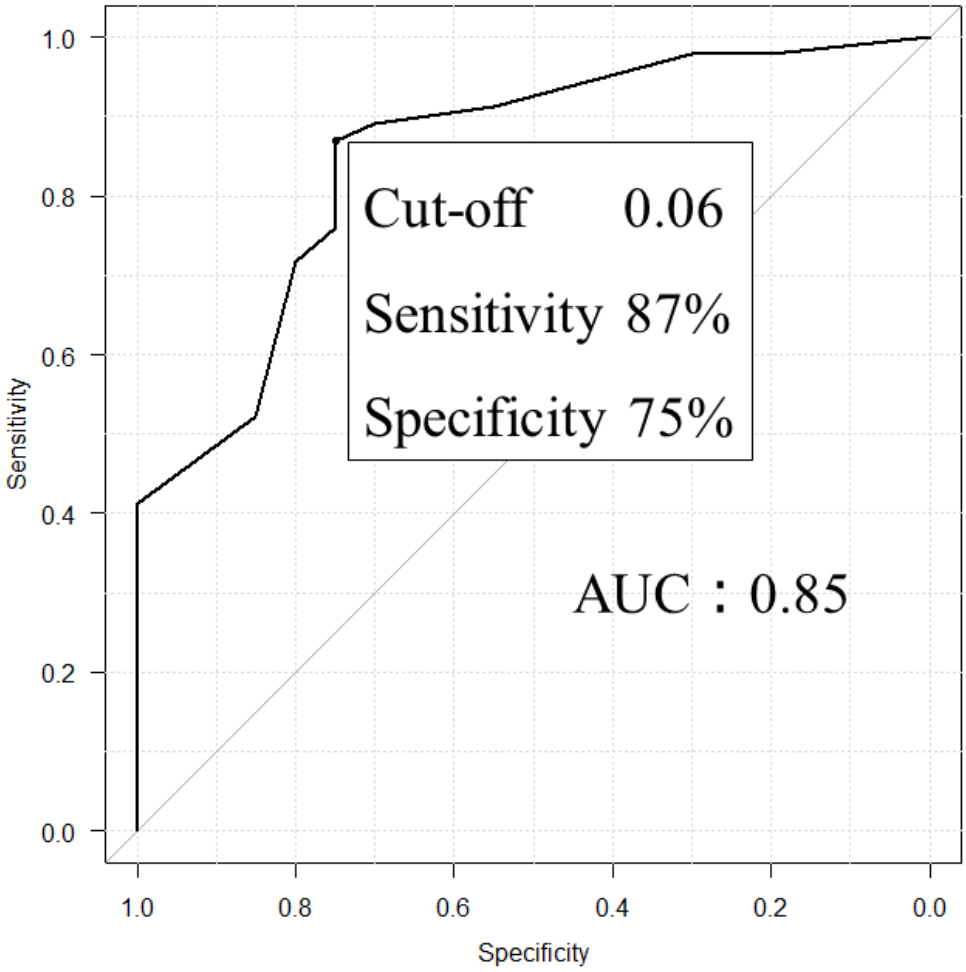

Figure 1

ROC analysis of uncorrected distance visual acuity (UCDVA) (logMAR) between a minimum corneal thickness of <400 μm vs. ≥400 μm. AUC: area under the curve.

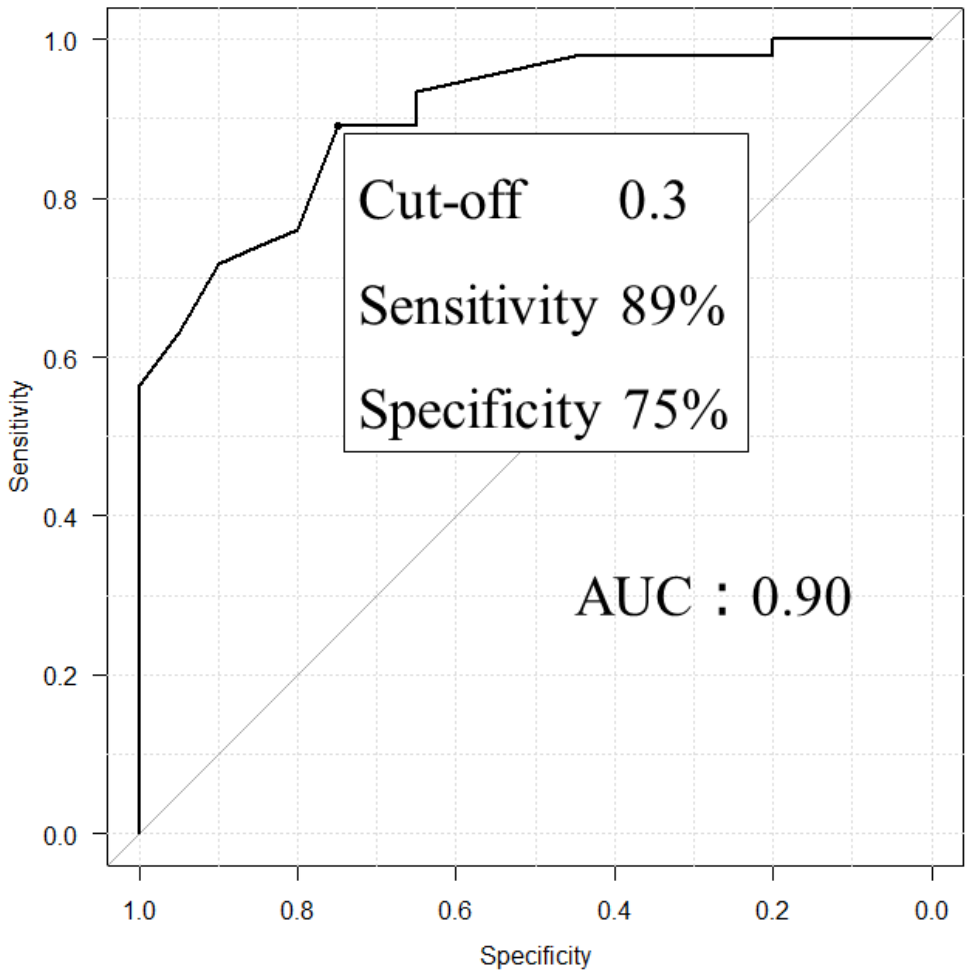

Figure 2

ROC analysis of corrected distance visual acuity (CDVA) (logMAR) between a minimum corneal thickness of 400 μm vs. ≥400 μm.