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Title: Detection of Post-Laser Vision Correction Ectasia with a new Combined Biomechanical Index

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Running Head: CBI-LVC for the diagnosis of post Laser Vision Correction ectasia.

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Purpose: To validate and evaluate the use of a new biomechanical index, known as the CBI-LVC (Corvis Biomechanical Index-Laser Vision Correction) as a method for separating stable, post-LVC eyes from post-LVC eyes with ectasia.

Setting: Patients were included from 10 clinics/9 countries.

Design: Retrospective, multi-centerre, clinical study.

Methods: The study was designed with two purposes: to develop the CBI-LVC, which combines dynamic corneal response parameters (DCR) provided by a high-speed Scheimpflug camera (CorvVis ST, Oculus, Germany) and then to evaluate its ability to detect post--LVC ectasia. The CBI-LVC includes Integrated Inverse Radius, Applanation 1(A1) Velocity, A1-Deflection Amplitude, Highest Concavity-dArc Length, Deformation Amplitude ratio-2mm, and A1-ArcLength mm. Logistic regression with Wald forward stepwise approach was used to identify the optimal combination of DCRs to create the CBI-LVC, and then separate stable from LVC-induced ectasia. Eighty percent of the database was used for training the software and 20% for validation.

Results: 736 eyes of 736 patients were included (685 stable LVC, and 51 post-LVC ectasia). The ROC curve analysis showed an AUC of 0.991 when applying CBI-LVC in the validation dataset and 0.998 in the training dataset. A cut-off of 0.2 was able to separate stable LVC from ectasia with a sensitivity of 93.3% and a specificity of 97.8%.

Conclusions: The CBI-LVC was highly sensitive and specific in distinguishing stable from ectatic post-LVC eyes. We suggest using CBI-LVC in routine practice, along with topography and tomography, to aid the early diagnosis of post-LVC ectasia and allow intervention prior to visually compromising progression.

INTRODUCTION

Laser vision correction (LVC) surgery with laser-assisted in situ keratomileusis (LASIK), photorefractive keratectomy (PRK), and SMall Incision Lenticule Extraction (SMILE) are widely accepted procedures to correct refractive defects such as myopia, hyperopia, and astigmatism with an excellent safety profile.[1] A rare, but feared complication of LVC (mostly LASIK,[2] but also reported after PRK and SMILE[3]) is iatrogenic ectasia which deforms the cornea and causes significant visual loss.[4]

The ~~frequency~~ incidence of ectasia after LASIK,[5] which is the most commonly seen, is undetermined but has been reported to be between 0.04[6] and 0.2%.[6,7] The prevention/detection of this dramatic complication is a significant concern for refractive surgeons.[8] ~~Particularly~~E~~, e~~arly detection of post-LVC ectasia is critical given the possibility to promptly treat these patients with cross-linking in order to stabilize the cornea.[9]

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Much of the focus on post-laser vision correction ectasia has been on prevention with the identification of many intraoperative risk factors linked to an increase in the likelihood of post-LVC ectasia,[10] including: increased flap thickness, using a microkeratome to create the flap, a high percent of tissue altered (PTA), and low residual stromal bed (RSB), although the sensitivity of the latter factor has been reported to be very low.[11,12] For this reason, many researchers have focused on preoperative characteristics that can increase post-LVC ectasia risk, particularly the need for more careful assessment of topography, tomography and corneal epithelial maps.[13] The evaluation of corneal biomechanical properties is also increasingly used as a key part of the screening process to identify patients who have an increased susceptibility to develop iatrogenic ectasia after LVC.[14] Recent studies have also shown the importance of corneal biomechanics in the diagnosis of keratoconus,[15-16]~~,~~ even in the early stages[17]~~,~~ ~~since~~ as for many~~,~~ it represents the "*primum movens*" in the development of the disease.

These advancements in preoperative assessment have dramatically improved LVC safety record.~~,~~ H~~h~~owever, indices such as the ~~while the~~ Corvis Biomechanical Index (CBI)[16] and the Tomographic Biomechanical Index (TBI),[15] which showed high sensitivity and specificity, ~~they~~ were not created to detect when ectasia develops after refractive surgery.

~~This~~ The aim of this retrospective analysis study ~~aimed to~~ was to develop a new combined biomechanical ~~parameter~~ index (CBI-LVC) based on the Dynamic Corneal Response parameters provided by the Corvis ST (Oculus Optikgeräte GmbH, Wetzlar, Germany) designed ~~aimed~~ to separate ~~between~~ stable corneas post-LVC ~~and~~ from post-LVC ectasia.~~, based on the Dynamic Corneal Response parameters (DCR) provided by the Corvis ST (Oculus Optikgeräte GmbH, Wetzlar, Germany).~~

MATERIALS AND METHODS

Population

Seven hundred and thirty-six eyes of 736 patients were included in this retrospective multi-center~~re~~ study. The patients were included from 10 different clinics to include variability from different continents, as well as to substantially increase the number of patients (particularly with post-LVC ectasia, which is a rare complication) and test the ability of the CBI-LVC in different ethnic groups. The participating centers were:

- Humanitas Clinical Research Centre, Milan, Italy
- ELZA Institute, Dietikon/Zurich, Switzerland
- Center for Refractive Surgery Muenster, Muenster, Germany
- Augenklinik am Neumarkt, Cologne, Germany
- Eye Care, Miami, Florida, USA
- Department of Ophthalmology, the Federal University of the State of Rio de Janeiro (UNIRIO), ~~—~~ Rio de Janeiro, Brazil
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- Eyereum Eye Clinic, Seoul, Korea
- Department of Ophthalmology, Osaka University Graduate School of Medicine, Osaka, Japan
- Department of Cornea & Refractive Surgery, Medical Research Foundation, Chennai, India

The enrolled patients were:

- Group 1: post-LVC eyes that were stable for at least 24 months
- Group 2: eyes with ectasia that developed after laser vision correction after at least ~~one~~ 2 years ~~after the~~post-~~-~~op~~surgery~~

The planned ratio between cases (post-LVC ectasia) and controls (stable post-LVC) was determined to be at least 1:10. That was based on the published value of increasing the control-to-case ratio beyond 5 when P_0 (prevalence of ectasia, in this case) is expected to be less than about 0.15 (ectasia is 0.02%).[18]

Stable post-LVC patients (~~photorefractive keratectomy~~ PRK, ~~laser-assisted in situ keratomileusis~~ LASIK, and ~~Small incision lenticule extraction~~ SMILE were included) had no signs of progression/regression after LVC; stable refraction, typical topography, and tomography as confirmed by a masked examiner (R.V.). All patients in this group had a minimum of 2 year ~~of~~ stable follow-up, which was defined as:

- No increase in posterior elevation of more than 10 µm in differential map
- No increase in anterior curvature in sagittal map of more than 1 D in differential map
- No decrease in pachymetry of more than 20 µm in differential map
- No change in refraction of more than 1.0 D in spherical equivalent (sph. Eq)
- Stability was also confirmed by one masked cornea expert (R.V., P.V. and/or R.A.) who evaluated postoperative maps~~.~~

Post-LVC ectasia was classified based on the evaluation of topography and tomography over time and a history of proven progression over a minimum of 3 months ~~of time~~ and worsening after refractive surgery.

The definition was based on the occurrence of at least two out of four of these parameters based on published definitions of ectasia plus the confirmation of two corneal experts:

- Inferior topographic steepening of 5.0 D over time or more[5]
- Progressive focal steepening of more than 1.5 D in sag~~g~~ittal map[19]
- Decrease in uncorrected distance visual acuity (UDVA) of two or more lines on the Snellen chart~~.~~[5]
- Refractive change of 2D or more of sph. Eq [20]

All cases in this group were confirmed by at least two experts, masked examiners (R.V., P.V. and/or R.A.). All patients had their examinations~~s~~ (including Corvis) before any treatment for ectasia was planned, such as corneal cross-linking (CXL).

Similarly to stable post-LVC cases, all ectasia patients had their Corvis examinations after a minimum of 2 year afterpost--LVC surgery.

Exclusion criteria included any previous ocular surgery (including CXL) or disease, myopia over 10D and any concomitant or previous glaucoma or hypotonic therapies.

Each Institutional Rreview Bboard (IRB) either ruled that approval was not required for this record review study ('exempt' category) or specifically approved the study. The research was conducted according to the ethical standards set in the 1964 Declaration of Helsinki, revised in 2000. Subjects (or parents in case of pediatric subjects) provided written informed consent before using their data in the study. All patients had a thorough ophthalmic examination, comprising of the Corvis ST and Pentacam HR or Pentacam HR/AXL (OCULUS Optikgeräte GmbH; Wetzlar, Germany) examexaminationss.

Corvis ST Measurements

Only Corvis ST and Pentacam examinationss with good quality scores (QS) that enabled calculation of all deformation and tomographic parameters were included in the analysis. All examinationss with the Corvis ST were obtained by experienced technicians and captured by automatic release to ensure the absence of user dependency.

One eye per patient was randomly included in the analysis to exclude the bias of the relationship between bilateral eyes that could influence the result. Randomization was performed using the randomization module in the SPSS software pack.

Dynamic Corneal Response Parameters

The Corvis ST elicits a set of Dynamic Corneal Response parameters (DCRs software version 6.08r22) based on the monitoring of the dynamic corneal response to air pressure. The DCRs that are currently part of the native software of the Corvis were previously described.[16,21,22] The logistic regression analysis (described as follows) selected the following DCRs: Applanation 1 velocity (A1vel), Integrated Inverse Radius (1/R), Applanation 1 Deflection Amplitude (A1Deflamplitude), Highest Concavity and Applanation 1 Arclength (HCArclength and A1Arclength) and Deformation Amplitude Ratio (DAratio).

All parameters used are described in Table 1.

Statistical analysis

The statistical analysis was performed with SPSS version 25 (IBM Corp., in Armonk, NY, USA). Receiver operating characteristic (ROC) curves were used to define the overall predictive accuracy of single DCRs and their combination, which is described as an area under the curve (AUC). The ROC curves were obtained by plotting sensitivity versus specificity and calculated for each value observed. An area of 100% implied that the test perfectly discriminates between groups.

As a first step, all 39 DCRs provided by software version (6.08r22) of the Corvis ST were exported. Logistic regression with a forward stepwise approach was used to identify the optimal combination of parameters. Wald method was used to stepwise include parameters. (This method is based on a test for inclusion based on the significance of the score statistics and on a test for exclusion which is based on Wald statistics.) Out of these 39 parameters, 6 DCRs were used for the creation the CBI-LVC.

Eighty percent of the database was randomly selected and used for training (Database 1), and 20% for validation (Database 2) to check for overfitting. Optimal cut-off points of the CBI-LVC were obtained from the ROC curves as those closest to the perfect classification point.

RESULTS

The mean age of the patients was 32~~3~~.9~~1~~±12~~9~~.3~~2~~ years. It was 33.0±12.1 years in the training dataset and 32.7±12.6 years in the validation dataset. Mean Kmax and mean thinnest point were respectively 54.2±8.0 D and 435.7±45.8 µm for ectasia patients post-LVC and 43.6±1.7 D and 459.7±44.9 µm for stable patients post-LVC. Table 2 shows the number of patients in each group, broken down by type of treatment: SMILE, LASIK and PRK.

There was no statistically significant difference (p>0.05) with regards to baseline characteristics between the training and validation datasets (age, sex, ethnicity).

CBI-LVC

The stepwise logistic regression~~,~~ based on database 1 (training dataset) produced the following formula:

CBI-LVC = EXP (Beta) / (1+ EXP(Beta))

where

Beta = C1 * Integrated Inverse Radius+ C2 * A1velocity + C3 * A1 Defl Amplitude + C4 * HC Arclength+ C5* DA Ratio 2 mm + C6 * A1 Arclength + C7 and C1= 5.2832, C2 = -206.0078; C3= 390.0877, C4 = -105.5705, C5 = 1.8487, C6 = 170.455, C7= -79.899 Values of all constants used in the equation were highly significant (p<0.01).

The ROC analysis of the training dataset (1) showed an AUC of 0.998 (Figure 1). The Sensitivity and Specificity were calculated on two different cut-off values: 0.2 and 0.5, which were chosen as best compromises between sensitivity and specificity.

In dataset 1, a cut-off value of 0.5 provided a sensitivity of 91.7% and a specificity of 99.3%, while a cut-off of 0.2 showed a sensitivity of 100% and a specificity of 97.3%. The validation dataset (2) displayed an AUC of 0.991, and the cut-off value of 0.5 provided a sensitivity of 86.7% and a specificity of 98.5%, while a cut-off of 0.2 showed a sensitivity of 93.3% and a specificity of 97.8% (Figure 1).

DISCUSSION

The diagnosis of post-LVC ectasia (caused by LASIK[8], PRK[23] or SMILE[24]) is a challenging task for refractive and cornea surgeons. Once ectasia is diagnosed, prompt cross-linking should be indicated to stop further progression.[9]

There are many indirect and direct ways to detect ectasia after refractive surgery, such as instability of refractive correction,[25] subsequent regression,[26]~~,~~ progressive steepening and/or thinning.[19]~~.~~ Unfortunately, these well-established indicators are subjective, and they have the disadvantage of requiring proof of the deterioration of refraction, topography/tomography map. In addition, the indicators that are used for preoperative screening are not helpful post-refractive surgery. M~~In fact, m~~ost of these indices are designed for the pre-operative detection of KC and ectasia susceptibility (such as KISA score, BAD-D, CBI, and TBI) and, for this reason, are unable to distinguish between KC and post-refractive surgery~~ and~~ ,~~they~~ commonly appearing abnormal. ~~As a matter of fact,~~ In fact, corneas after LVC are thinner and flatter than normal and ~~they~~ are classified as “abnormal” by these algorithms. ~~Some indices, like Klyce[27] ones, are able to separate KC from post hyperopic-LVC but not post-LVC from ectasia.[27]~~

Due to this lack of an objective method for ~~diagnosing~~ the detection of post-LVC ectasia~~, earlier,~~, ~~frequently~~ diagnosis is frequently done either when the disease is advanced or with the use of differential maps that show thinning, steepening, and increased elevation in a localized area. ~~diagnosis occurs when the disease has advanced, with the regression and change of refraction or signs of thinning on differential maps, along with steepening and increased elevation in a localized area.~~ The drawback of this approach is that the patient ~~has to~~must progress before being diagnosed and indicated for~~the~~ treatment with CXL~~ indicated~~.~~The drawback of this approach is that the patient has to progress~~

~~to the point that vision might be affected before being diagnosed and the treatment with CXL, or in severe cases, deep-anterior lamellar keratoplasty (DALK) may be necessary. Additionally, not all patients that regress or have refractive instability have ectasia.~~

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As with keratoconus, in post-LVC ectasia~~,~~ the changes in corneal biomechanics are believed to take place before any changes to refraction, topography, tomography and epithelial maps are detectable. It is for these reasons that an assessment of corneal biomechanics may help in the early detection of this rare complication. Based~~ing~~ on this, the aim of this multi-center~~re~~ study was to create and validate a biomechanical index with the goal of separating post-LVC ectasia from stable post-LVC with a large dataset.

The database included more than 700 subjects from 10 countries and 4 continents in order to consider possible variability in ethnic groups, as well as to obtain a reasonable number of untreated post-LVC ectasias~~.~~ (d~~D~~ue to the fact that post-LVC ectasia is a relatively rare complication and patients are typically treated promptly with CXL, making these patients ineligible for inclusion). Additionally, the size of the database allowed the validation of the indices and the exclusion of overfitting.

The main outcome of the study was the creation of the CBI-LVC, an index aimed to separate stable post-LVC patients from ectasia regardless of the type of LVC surgery performed. The study was a two-stage process: f~~F~~irst, the optimum combination of parameters for the CBI-LVC was defined. Second, its diagnostic capability was assessed.

The multivariate diagnostic model showed an AUC of more than 0.990 in both the validation and training datasets. We assessed two different cut-off points for the CBI-LVC: 0.2 and 0.5, which were chosen as best compromises between sensitivity and specificity.

In the validation dataset, a cut-off of 0.5 provided a sensitivity of 86.7% and a specificity of 98.5%, while a cut-off of 0.2 showed a sensitivity of 93.3% and a specificity of 97.8%.

To the authors' knowledge, this is the first time that an index has achieveds such a high level of accuracy sensitivity and specificity in separating stable post-LVC from post-LVC ectasia. Even if CBI-LVC sounds similar to the published CBI,[16] this newly created index is not an evolution of the CBI because it aims to diagnose a different disease (CBI-LVC ectasia after LVC and CBI keratoconus).

It is important to note that the CBI-LVC is a purely biomechanical index as it involves only biomechanical parameters and does not include shape nor pachymetry indices (such as, minimum pachymetry, ARTrth, or SimK). This is a significant advantage as CBI-LVC would be less affected if the ectasia is developing in a thin or relatively thick cornea or if the cornea is steep or flat. Nevertheless, more studies are in progress to evaluate whether the implementation of tomography, combined with biomechanics (such as the TBI for KC screening) could improve the accuracy of post-LVC ectasia diagnosis.

In this study, the authors decided to exclude very early or ectasia suspects from the databases to create the CBI-LVC. However, another study is in process, with very promising results, to test the capability of CBI-LVC to diagnose early ectasias.

Presently, there are no validated indices to diagnose post-LVC ectasia in either subclinical or advanced stages. Randleman *et al.* suggested the diagnosis of ectasia as an inferior steepening of > 5D postoperative topographic map, loss of two or more lines of visual acuity, and a change in manifest refraction of 2D of either spherical or cylindrical power.[6] Another report by Twa *et al.* suggested 3 or 4 positive findings out of 9 criteria, which included refractive, pachymetry~~ic~~, and topographic data that could be used to represent the clinical characteristics of post-LASIK.[27] Padmanabhan *et al.* also created a stratification model for the diagnosis of ectasia based on corrected distance visual acuity, refractive spherical equivalent, highest posterior elevation, spherical aberration and anterior corneal surface asphericity.[19] These reports rely on relatively small databases with weak or no validation of the proposed diagnostic criteria.

As ectasia can develop up to nine years after surgery,[28-29] this study does not prove the ability of the CBI-LVC to quantify corneal susceptibility to post-LVC ectasia or predict ectasia over the long term. Long-term studies ~~(more than three years of follow-up, ideally up to six years)~~ are necessary to evaluate whether patients with high CBI-LVC but normal tomography will develop topographical and tomographical signs of ectasia.

~~In addition to the diagnosis of post-LVC ectasia, other promising applications of the CBI-LVC index could include the differential diagnosis between regression after refractive surgery and ectasia. A CBI-LVC inside normal range should confirm that the cornea is not ectatic and a retreatment could be considered. More studies will be needed to evaluate this option.~~

~~External validation is of primary importance when assessing the accuracy of an index created with logistic regression to exclude over-fitting and because a cut-off value in one dataset may not produce the same results in another database.~~

The main strengths of this study are, firstly, the use of a validation dataset which is of primary importance when assessing the accuracy of an index created with logistic regression to exclude over-fitting. Additionally, this study included, the a large number of patients, particularly and in particular with post-LVC ectasia (to the authors' knowledge, it is the largest number of included patients including biomechanical analysis) and the inclusion of subjects with different ethnical origins. The main limitations of the study are the retrospective design and the lack of more years olong-termf follow-up after the refractive surgery in the stable group (minimum two years). With more years of follow-up and the presence of an early biomechanical assessment, it could be evaluated whether the CBI-LVC is able to predict ectasia even when the shape of the cornea is normal. In the current study, only patients with clear ectasia were included. More studies are needed to evaluate this aspect. Presently, the CBI-LVC should not be seen as a tool to predict later development of post-LVC ectasia, but rather as an index to diagnose it. Another possible criticism could be the question of whether an index to diagnose ectasia after LVC is clinically relevant. We believe that, even if ectasia after LVC is a very rare disease and the correct preoperative screening reduces significantly its incidence, an early detection could even improve the excellent LVC safety record via the suggestion of early CXL treatment which would avoid further progression and vision loss.

In conclusion, our study introduces the CBI-LVC for the diagnosis of post-Laser Vision Correction ectasia, which was shown to be highly sensitive and specific to separate stable from ectatic post-LVC patients. The presence of a large external validation dataset confirmed the findings and recommend the use of CBI-LVC in everyday clinical practice, together with topography and tomography, to support the diagnosis of post-LVC ectasia.

WHAT WAS KNOWN:

- Ectasia after Laser Vision Correction is a rare but severe disease which can cause significant visual loss.
- Standard ways to detect ectasia after refractive surgery are instability of refractive correction and subsequent regression, progressive steepening, and thinning.

- Similar toLike keratoconus, in post-LVC ectasia the changes in corneal biomechanics are believed to appear earlier than refractive, topographic, tomographical, and epithelial maps changes are detectable.

WHAT THIS PAPER ADDS:

- We introduced a new combined biomechanical index named CBI-LVC for the diagnosis of post-Laser Vision Correction ectasia which was shown to be highly sensitive and specific to separate stable from ectatic post-LVC patients.

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LEGENDS

Figure 1: Showing the ROC (solid line) and 95 percent Confidence Interval for ROC curve (broken lines) ~~curve~~ of the training dataset and validation datasets of the CBI-LVC applied to separate stable from ectasia post-laser vision correction.

Title: Detection of Post-Laser Vision Correction Ectasia with a new Combined Biomechanical Index

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Running Head: CBI-LVC for the diagnosis of post Laser Vision Correction ectasia.

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Purpose: To validate and evaluate the use of a new biomechanical index known as the CBI-LVC (Corvis Biomechanical Index-Laser Vision Correction) as a method for separating stable post-LVC eyes from post-LVC eyes with ectasia.

Setting: Patients were included from 10 clinics/9 countries.

Design: Retrospective, multi-center, clinical study.

Methods: The study was designed with two purposes: to develop the CBI-LVC, which combines dynamic corneal response parameters (DCR) provided by a high-speed Scheimpflug camera (Corvis ST, Oculus, Germany) and then to evaluate its ability to detect post-LVC ectasia. The CBI-LVC includes Integrated Inverse Radius, Applanation 1(A1) Velocity, A1-Deflection Amplitude, Highest Concavity-dArc Length, Deformation Amplitude ratio-2mm, and A1-ArcLength mm. Logistic regression with Wald forward stepwise approach was used to identify the optimal combination of DCRs to create the CBI-LVC, and then separate stable from LVC-induced ectasia. Eighty percent of the database was used for training the software and 20% for validation.

Results: 736 eyes of 736 patients were included (685 stable LVC, and 51 post-LVC ectasia). The ROC curve analysis showed an AUC of 0.991 when applying CBI-LVC in the validation dataset and 0.998 in the training dataset. A cut-off of 0.2 was able to separate stable LVC from ectasia with a sensitivity of 93.3% and a specificity of 97.8%.

Conclusions: The CBI-LVC was highly sensitive and specific in distinguishing stable from ectatic post-LVC eyes. We suggest using CBI-LVC in routine practice, along with topography and tomography, to aid the early diagnosis of post-LVC ectasia and allow intervention prior to visually compromising progression.

INTRODUCTION

Laser vision correction (LVC) surgery with laser-assisted in situ keratomileusis (LASIK), photorefractive keratectomy (PRK), and SMall Incision Lenticule Extraction (SMILE) are widely accepted procedures to correct refractive defects such as myopia, hyperopia, and astigmatism with an excellent safety profile.[1] A rare, but feared complication of LVC (mostly LASIK,[2] but also reported after PRK and SMILE[3]) is iatrogenic ectasia which deforms the cornea and causes significant visual loss.[4]

The incidence of ectasia after LASIK,[5] which is the most commonly seen, is undetermined but has been reported to be between 0.04 and 0.2%.[6,7] The prevention/detection of this dramatic complication is a significant concern for refractive surgeons.[8] Early detection of post-LVC ectasia is critical given the possibility to promptly treat these patients with cross-linking in order to stabilize the cornea.[9]

Much of the focus on post-laser vision correction ectasia has been on prevention with the identification of many intraoperative risk factors linked to an increase in the likelihood of post-LVC ectasia,[10] including: increased flap thickness, using a microkeratome to create the flap, a high percent of tissue altered (PTA), and low residual stromal bed (RSB), although the sensitivity of the latter factor has been reported to be very low.[11,12] For this reason, many researchers have focused on preoperative characteristics that can increase post-LVC ectasia risk, particularly the need for more careful assessment of topography, tomography and corneal epithelial maps.[13] The evaluation of corneal biomechanical properties is also increasingly used as a key part of the screening process to identify patients who have an increased susceptibility to develop iatrogenic ectasia after LVC.[14] Recent studies have also shown the importance of corneal biomechanics in the diagnosis of keratoconus,[15,16] even in the early stages[17] as for many it represents the "*primum movens"* in the development of the disease.

These advancements in preoperative assessment have dramatically improved LVC safety record. However, indices such as the Corvis Biomechanical Index (CBI)[16] and the Tomographic Biomechanical Index (TBI),[15] which showed high sensitivity and specificity, were not created to detect when ectasia develops after refractive surgery. The aim of this retrospective analysis study was to develop a new combined biomechanical index (CBI-LVC) based on the Dynamic Corneal Response parameters provided by the Corvis ST (Oculus Optikgeräte GmbH, Wetzlar, Germany) designed to separate stable corneas post-LVC from post-LVC ectasia.

MATERIALS AND METHODS

Population

Seven hundred and thirty-six eyes of 736 patients were included in this retrospective multi-center study. The patients were included from 10 different clinics to include variability from different continents, as well as to substantially increase the number of patients (particularly with post-LVC ectasia, which is a rare complication) and test the ability of the CBI-LVC in different ethnic groups. The participating centers were:

- Humanitas Clinical Research Centre, Milan, Italy
- ELZA Institute, Dietikon/Zurich, Switzerland
- Center for Refractive Surgery Muenster, Muenster, Germany

- Augenklinik am Neumarkt, Cologne, Germany
- Eye Care, Miami, Florida, USA
- Department of Ophthalmology, the Federal University of the State of Rio de Janeiro (UNIRIO), Rio de Janeiro, Brazil
- School of Ophthalmology and Optometry, Wenzhou Medical University, Wenzhou, China
- Eyereum Eye Clinic, Seoul, Korea
- Department of Ophthalmology, Osaka University Graduate School of Medicine, Osaka, Japan
- Department of Cornea & Refractive Surgery, Medical Research Foundation, Chennai, India

The enrolled patients were:

- Group 1: post-LVC eyes that were stable for at least 24 months
- Group 2: eyes with ectasia that developed after laser vision correction after at least 2 years post-op

The planned ratio between cases (post-LVC ectasia) and controls (stable post-LVC) was determined to be at least 1:10. That was based on the published value of increasing the control-to-case ratio beyond 5 when P_0 (prevalence of ectasia, in this case) is expected to be less than about 0.15 (ectasia is 0.02%).[18]

Stable post-LVC patients (PRK, LASIK, and SMILE were included) had no signs of progression/regression after LVC; stable refraction, typical topography, and tomography as confirmed by a masked examiner (R.V.). All patients in this group had a minimum of 2 year stable follow-up, which was defined as:

- No increase in posterior elevation of more than 10 µm in differential map

- No increase in anterior curvature in sagittal map of more than 1 D in differential map
- No decrease in pachymetry of more than 20 µm in differential map
- No change in refraction of more than 1.0 D in spherical equivalent (sph. Eq)
- Stability was also confirmed by one masked cornea expert (R.V., P.V. and/or R.A.) who evaluated postoperative maps

Post-LVC ectasia was classified based on the evaluation of topography and tomography over time and a history of proven progression over a minimum of 3 months and worsening after refractive surgery.

The definition was based on the occurrence of at least two out of four of these parameters based on published definitions of ectasia plus the confirmation of two corneal experts:

- Inferior topographic steepening of 5.0 D over time or more[5]
- Progressive focal steepening of more than 1.5 D in sagittal map[19]
- Decrease in uncorrected distance visual acuity (UDVA) of two or more lines on the Snellen chart[5]
- Refractive change of 2D or more of sph. Eq[20]

All cases in this group were confirmed by at least two experts, masked examiners (R.V., P.V. and/or R.A.). All patients had their examinations (including Corvis) before any treatment for ectasia was planned, such as corneal cross-linking (CXL). Similar to stable post-LVC cases, all ectasia patients had their Corvis examinations after a minimum of 2 year post-LVC surgery.

Exclusion criteria included any previous ocular surgery (including CXL) or disease and any concomitant or previous glaucoma or hypotonic therapies.

Each Institutional Review Board (IRB) either ruled that approval was not required for this record review study ('exempt' category) or specifically approved the study. The research was conducted according to the ethical standards set in the 1964 Declaration of Helsinki, revised in 2000. Subjects (or parents in case of pediatric subjects) provided written informed consent before using their data in the study. All patients had a thorough ophthalmic examination, comprising of the Corvis ST and Pentacam HR or Pentacam HR/AXL (OCULUS Optikgeräte GmbH; Wetzlar, Germany) examinations.

Corvis ST Measurements

Only Corvis ST and Pentacam examinations with good quality scores (QS) that enabled calculation of all deformation and tomographic parameters were included in the analysis. All examinations with the Corvis ST were obtained by experienced technicians and captured by automatic release to ensure the absence of user dependency.

One eye per patient was randomly included in the analysis to exclude the bias of the relationship between bilateral eyes that could influence the result. Randomization was performed using the randomization module in the SPSS software pack.

Dynamic Corneal Response Parameters

The Corvis ST elicits a set of Dynamic Corneal Response parameters (DCRs software version 6.08r22) based on the monitoring of the dynamic corneal response to air pressure. The DCRs that are currently part of the native software of the Corvis were previously described.[16,21,22] The logistic regression analysis (described as follows) selected the following DCRs: Applanation 1 velocity (A1vel), Integrated Inverse Radius (1/R), Applanation 1 Deflection Amplitude (A1Deflamplitude), Highest Concavity and Applanation 1 Arclength (HCArclength and A1Arclength) and Deformation Amplitude Ratio (DAratio).

All parameters used are described in Table 1.

Statistical analysis

The statistical analysis was performed with SPSS version 25 (IBM Corp., Armonk, NY, USA). Receiver operating characteristic (ROC) curves were used to define the overall predictive accuracy of single DCRs and their combination, which is described as an area under the curve (AUC). The ROC curves were obtained by plotting sensitivity versus specificity and calculated for each value observed. An area of 100% implied that the test perfectly discriminates between groups.

As a first step, all 39 DCRs provided by software version (6.08r22) of the Corvis ST were exported. Logistic regression with a forward stepwise approach was used to identify the optimal combination of parameters. Wald method was used to stepwise include parameters. (This method is based on a test for inclusion based on the significance of the score statistics and on a test for exclusion which is based on Wald statistics.) Out of these 39 parameters, 6 DCRs were used for the creation the CBI-LVC.

Eighty percent of the database was randomly selected and used for training (Database 1), and 20% for validation (Database 2) to check for overfitting.

Optimal cut-off points of the CBI-LVC were obtained from the ROC curves as those closest to the perfect classification point.

RESULTS

The mean age of the patients was 32.9±12.3 years. It was 33.0±12.1 years in the training dataset and 32.7±12.6 years in the validation dataset. Mean Kmax and mean thinnest point were respectively 54.2±8.0 D and 435.7±45.8 µm for ectasia patients post-LVC and 43.6±1.7 D and 459.7±44.9 µm for stable patients post-LVC. Table 2 shows the number of patients in each group, broken down by type of treatment: SMILE, LASIK and PRK.

There was no statistically significant difference (p>0.05) with regards to baseline characteristics between the training and validation datasets (age, sex, ethnicity).

CBI-LVC

The stepwise logistic regression based on database 1 (training dataset) produced the following formula:

CBI-LVC = EXP (Beta) / (1+ EXP(Beta))

where

Beta = C1 * Integrated Inverse Radius+ C2 * A1velocity + C3 * A1 Defl Amplitude + C4 * HC Arclength+ C5* DA Ratio 2 mm + C6 * A1 Arclength + C7

and C1= 5.2832, C2 = -206.0078; C3= 390.0877, C4 = -105.5705, C5 = 1.8487, C6 = 170.455, C7= -79.899 Values of all constants used in the equation were highly significant (p<0.01).

The ROC analysis of the training dataset (1) showed an AUC of 0.998 (Figure 1). The Sensitivity and Specificity were calculated on two different cut-off values: 0.2

and 0.5, which were chosen as best compromises between sensitivity and specificity.

In dataset 1, a cut-off value of 0.5 provided a sensitivity of 91.7% and a specificity of 99.3%, while a cut-off of 0.2 showed a sensitivity of 100% and a specificity of 97.3%. The validation dataset (2) displayed an AUC of 0.991, and the cut-off value of 0.5 provided a sensitivity of 86.7% and a specificity of 98.5%, while a cut-off of 0.2 showed a sensitivity of 93.3% and a specificity of 97.8% (Figure 1).

DISCUSSION

The diagnosis of post-LVC ectasia (caused by LASIK[8], PRK[23] or SMILE[24]) is a challenging task for refractive and cornea surgeons. Once ectasia is diagnosed, prompt cross-linking should be indicated to stop further progression.[9]

There are many indirect and direct ways to detect ectasia after refractive surgery, such as instability of refractive correction,[25] subsequent regression,[26] progressive steepening and/or thinning.[19] Unfortunately, these well-established indicators are subjective, and they have the disadvantage of requiring proof of the deterioration of refraction, topography/tomography map. In addition, the indicators that are used for preoperative screening are not helpful post-refractive surgery. Most of these indices are designed for the pre-operative detection of KC and ectasia susceptibility (such as KISA score, BAD-D, CBI, and TBI) and, for this reason, are unable to distinguish between KC and post-refractive surgery, commonly appearing abnormal. In fact, corneas after LVC are thinner and flatter than normal and are classified as "abnormal" by these algorithms.

Due to this lack of an objective method for the detection of post-LVC ectasia, diagnosis is frequently done either when the disease is advanced or with the use of differential maps that show thinning, steepening, and increased elevation in a localized area. The drawback of this approach is that the patient must progress before being diagnosed and indicated for treatment with CXL.

As with keratoconus, in post-LVC ectasia the changes in corneal biomechanics are believed to take place before any changes to refraction, topography, tomography and epithelial maps are detectable. It is for these reasons that an assessment of corneal biomechanics may help in the early detection of this rare complication. Based on this, the aim of this multi-center study was to create and validate a biomechanical index with the goal of separating post-LVC ectasia from stable post-LVC with a large dataset.

The database included more than 700 subjects from 10 countries and 4 continents in order to consider possible variability in ethnic groups, as well as to obtain a reasonable number of untreated post-LVC ectasias (due to the fact that post-LVC ectasia is a relatively rare complication and patients are typically treated promptly with CXL, making these patients ineligible for inclusion). Additionally, the size of the database allowed the validation of the indices and the exclusion of overfitting.

The main outcome of the study was the creation of the CBI-LVC, an index aimed to separate stable post-LVC patients from ectasia regardless of the type of LVC surgery performed. The study was a two-stage process: first, the optimum combination of parameters for the CBI-LVC was defined. Second, its diagnostic capability was assessed.

The multivariate diagnostic model showed an AUC of more than 0.990 in both the validation and training datasets. We assessed two different cut-off points for the CBI-LVC: 0.2 and 0.5, which were chosen as best compromises between sensitivity and specificity.

In the validation dataset, a cut-off of 0.5 provided a sensitivity of 86.7% and a specificity of 98.5%, while a cut-off of 0.2 showed a sensitivity of 93.3% and a specificity of 97.8%.

To the authors' knowledge, this is the first time that an index has achieved such a high level of sensitivity and specificity in separating stable post-LVC from post-LVC ectasia. Even if CBI-LVC sounds similar to the published CBI,[16] this newly created index is not an evolution of the CBI because it aims to diagnose a different disease (CBI-LVC ectasia after LVC and CBI keratoconus).

It is important to note that the CBI-LVC is a purely biomechanical index as it involves only biomechanical parameters and does not include shape nor pachymetry indices (such as, minimum pachymetry, ARTh, or SimK). This is a significant advantage as CBI-LVC would be less affected if the ectasia is developing in a thin or relatively thick cornea or if the cornea is steep or flat.

Presently, there are no validated indices to diagnose post-LVC ectasia in either subclinical or advanced stages. Randleman *et al.* suggested the diagnosis of ectasia as an inferior steepening of > 5D postoperative topographic map, loss of two or more lines of visual acuity, and a change in manifest refraction of 2D of either spherical or cylindrical power.[6] Another report by Twa *et al.* suggested 3 or 4 positive findings out of 9 criteria, which included refractive, pachymetry, and topographic data that could be used to represent the clinical characteristics of post-LASIK.[27] Padmanabhan *et al.* also created a stratification model for the diagnosis of ectasia based on corrected distance visual acuity, refractive spherical equivalent, highest posterior elevation, spherical aberration and anterior corneal surface asphericity.[19] These reports rely on relatively small databases with weak or no validation of the proposed diagnostic criteria.

As ectasia can develop up to nine years after surgery,[28,29] this study does not prove the ability of the CBI-LVC to quantify corneal susceptibility to post-LVC ectasia or predict ectasia over the long term. Long-term studies are necessary to evaluate whether patients with high CBI-LVC but normal tomography will develop topographical and tomographical signs of ectasia.

The main strengths of this study are, firstly, the use of a validation dataset which is of primary importance when assessing the accuracy of an index created with logistic regression to exclude overfitting. Additionally, this study included a large number of patients, particularly with post-LVC ectasia (to the authors' knowledge, it is the largest number of included patients including biomechanical analysis). The main limitations of the study are the retrospective design and the lack of long-term follow-up after the refractive surgery in the stable group (minimum two years). With more years of follow-up and the presence of an early biomechanical assessment, it could be evaluated whether the CBI-LVC is able to predict ectasia even when the shape of the cornea is normal. In the current study, only patients with clear ectasia were included. Presently, the CBI-LVC should not be seen as a tool to predict later development of post-LVC ectasia, but rather as an index to diagnose it.

In conclusion, our study introduces the CBI-LVC for the diagnosis of post-Laser Vision Correction ectasia, which was shown to be highly sensitive and specific to separate stable from ectatic post-LVC patients. The presence of a large external validation dataset confirmed the findings and recommend the use of CBI-LVC in everyday clinical practice, together with topography and tomography, to support the diagnosis of post-LVC ectasia.

WHAT WAS KNOWN:

- Ectasia after Laser Vision Correction is a rare but severe disease which can cause significant visual loss.
- Standard ways to detect ectasia after refractive surgery are instability of refractive correction and subsequent regression, progressive steepening, and thinning.
- Like keratoconus, in post-LVC ectasia the changes in corneal biomechanics are believed to appear earlier than refractive, topographic, tomographical, and epithelial maps changes are detectable.

WHAT THIS PAPER ADDS:

- We introduced a new combined biomechanical index named CBI-LVC for the diagnosis of post-Laser Vision Correction ectasia which was shown to be highly sensitive and specific to separate stable from ectatic post-LVC patients.

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LEGENDS

Figure 1: Showing the ROC (solid line) and 95 percent Confidence Interval for ROC curve (broken lines) of the training dataset and validation datasets of the CBI-LVC applied to separate stable from ectasia post-laser vision correction.

SYNOPSIS

Corneal Biomechanics evaluation post Laser Vision Correction (LVC) is able to accurately separate stable patients from ectasia after LVC.

Figure 1

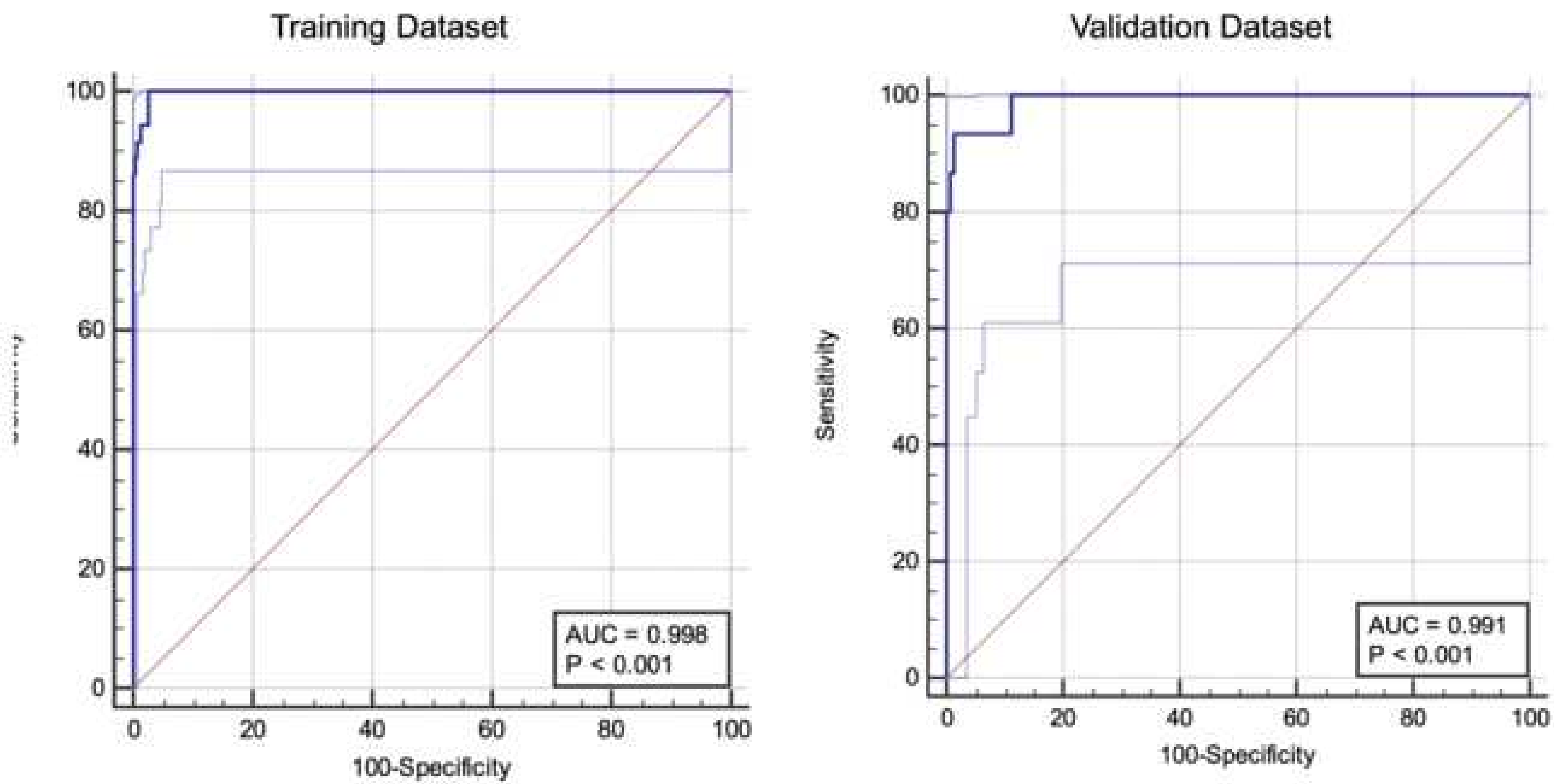
Training Dataset
100
80
60
40
20
0
0
20
40
60
80
100
100-Specificity
AUC = 0.998
P < 0.001
Validation Dataset
Sensitivity
100
80
60
40
20
0
0
20
40
60
80
100
100-Specificity
AUC = 0.991
P < 0.001

Table 1 showing details of the Dynamic Corneal Response Parameters of Corvis ST which were included for the creation of the CBI-LVC

CORVIS ST – PARAMETERS	
Applanation Velocity 1	Velocity of the Cornea at the moment of first applanation (in meters per seconds [m/s]).
Integrated Inverse Radius	This parameter is calculated based on the inverse concave radius curve. The Inverse Concave Radius (1/R) is plotted over the duration of the air pulse and the integrated sum (integrated Inverse radius) is calculated between the first and second applanation events.
Applanation 1 Deflection Amplitude	Largest displacement of corneal apex in the anterior-posterior direction at the moment of 1st applanation.
Highest Concavity Arclength	Measurement (in millimeters) of the arclenght at the moment of highest concavity
Applanation 1 Arclength	Measurement (in millimeters) of the arclenght at the moment of applanation 1.
Deformation Amplitude Ratio	Describe the ratio between the deformation amplitude at the apex and the average deformation amplitude measured at 1 from the center

Table 2

	Post-LVC Stable	Post-LVC Ectasia
No. of eyes	685	51
LASIK	145	50
SMILE	357	0
PRK	183	1

Table 1: Shows details of each subgroup with details of how many stable and ectasia post Laser Vision Correction (LVC) patients were previously treated with LASIK, SMILE or PRK.

Author Photograph

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Article Title: Detection of Post-Laser Vision Correction Ectasia with a new Combined Biomechanical Index

I have made substantive intellectual contributions to the content of this manuscript in the following areas:

Author Name	Concept and design	Data acquisition	Data analysis / interpretation	Drafting manuscript	Critical revision of manuscript	Statistical analysis	Securing funding	Admin, technical or material support	Supervision	Final approval
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PAOLO VINCIGUERRA	X	X			X				X	X
OMID KERMANI		X			X					X
SUPHI TANERI		X			X					X
CYNTHIA J ROBERTS		X	X		X					X
RENATO AMBROSIO	X	X			X					X
SHIZUKA KOH		X			X					X
AHMED ELSHEIKH		X			X	X				X
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Article Title: Detection of Post-Laser Vision Correction Ectasia with a new Combined Biomechanical Index

I have made substantive intellectual contributions to the content of this manuscript in the following areas:

Author Name	Concept and design	Data acquisition	Data analysis / interpretation	Drafting manuscript	Critical revision of manuscript	Statistical analysis	Securing funding	Admin, technical or material support	Supervision	Final approval
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Bernardo Lopes		X			X					X
Anika Rost		X			X					X
Pietro Rosetta		X			X					X
Ashkan Eliasy		X			X					X
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