

Journal of Cataract and Refractive Surgery Publish Ahead of Print DOI: 10.1097/j.jcrs.000000000001079

Postoperative vault prediction for phakic implantable collamer lens surgery: the LASSO formulae

Running title:

LASSO ICL sizing formulae

Authors

Leandro Rocamora MSc,¹ José I. Orlando PhD,^{1,2} Christoph Lwowski MD³ Thomas Kohnen MD PhD³ Erik Mertens MD⁴ Karel Van Keer MD PhD^{5,6}

Affiliations

- 1. Yatiris Group, PLADEMA Institute. Universidad Nacional del Centro de la Provincia de Buenos Aires (UNICEN), Tandil, Buenos Aires, Argentina.
- 2. Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Tandil, Buenos Aires, Argentina.
- 3. Department of Ophthalmology, Goethe-University, Frankfurt Am Main, Germany
- 4. Medipolis, Antwerp, Belgium.
- 5. Department of Ophthalmology, University Hospitals UZ Leuven, Leuven, Belgium
- 6. Biomedical Sciences Group, Department of Neurosciences, Research Group Ophthalmology, KU Leuven, Leuven, Belgium.

Financial disclosures

Leandro Rocamora	none.
José I. Orlando	none.
Christoph Lwowski	none.
Thomas Kohnen	Alcon/Novartis, Allergan, Avedro, Bausch & Lomb, Dompé,
	Geuder, J&J, Lensgen, Med Update, Nevarkar, Oculentis,
	Oculus, Presbia, Santen, Schwind, Staar Surgical, Tear Lab,
	Thieme, Zeiss, Ziemer.
Erik Mertens	Allotex, CSO, Ellex, Excel-lens, Hoya, Medicontur,
	MicroSurgical Technology, Novoxel, PhysIOL, Staar Surgical,
	TearLab.
Karel Van Keer	DORC, IMEC, Recordati, Zeiss.

Acknowledgements of grant support

PICT 2019-00070 (FONCyT, Agencia I+D+i, Argentina) PICT Startup 2021-00023 (FONCyT, Agencia I+D+i, Argentina) PIP GI 2021-2023 - 11220200102472CO (CONICET, Argentina) Horlait-Dapsens Medical Foundation

Corresponding author

Name: Karel van Keer Address: Herestraat 49, 3000 Leuven, BELGIUM Telephone: 0032 016 33 22 11 e-mail address: karel.vankeer@uzleuven.be

ABSTRACT

Purpose: To develop and evaluate reliable formulae for predicting post-operative vault more accurately after implantable collamer lens (ICL) surgery in a Caucasian patient population of varying degrees of ammetropia.

Setting: Private clinical practice.

Design: Retrospective analysis on dataset split in separate training and test set.

Methods: One hundred fifteen eyes of 59 patients were used to train regression models predicting post-operative vault based on anterior segment optical coherence tomography parameters (LASSO-OCT formula), ocular biometry data (LASSO-Biometry formula) or data from both devices (LASSO-Full formula). The performance of these models was evaluated against the manufacturer's nomogram (OCOS) and Nakamura 1 (NK1) and 2 (NK2) formulae on a matched separate test set of 37 eyes of 19 patients.

Results: Mean preoperative spherical equivalent was -5.32 \pm 3.37 (range: +3.75D to -17.375D). The mean absolute errors of the estimated versus achieved postoperative vault for the LASSO-Biometry, LASSO-OCT and LASSO-Full were 144.1 \pm 107.9µm, 145.6 \pm 100.6µm and 132.0 \pm 86.6µm, respectively. These results were significantly lower compared to the OCOS, NK1 and NK2 formulae (p < 0.006). Postoperative vault could be estimated within 500µm in 97.3% (LASSO-Biometry) to 100% of cases (LASSO-OCT and LASSO-Full).

Conclusions: The LASSO suite provides a set of powerful, reproducible yet convenient ICL sizing formulae with state of the art performance in Caucasian patients, including those with low to moderate degrees of myopia. The calculator can be accessed at http://icl.emmetropia.be.

MANUSCRIPT

Introduction

Implantable collamer lens (ICL) surgery offers a compelling surgical alternative for patients who are not eligible for, or prefer to avoid, corneal refractive laser surgery. Several studies have demonstrated the excellent safety and efficacy profile of ICL surgery^{1–5}. In order to minimize the risks of ICL surgery, maximal effort should be made to avoid the need for reinterventions.

Inadequate postoperative vault is the leading cause for ICL exchange/explantation⁶⁻⁹. Vault refers to the sagittal distance between the posterior surface of the ICL and the anterior capsule of the crystalline lens. Within the range of 250 to 750µm, the risks for developing anterior subcapsular cataract (due to insufficient vaulting), as well for secondary glaucoma due to iris pigment dispersion and endothelial cell loss (due to excessive vaulting) are very low^{2,3,10-13}. Post-operative vault is determined by the ocular anatomy and the dimensions of the implanted ICL. The anatomy of the eye influences the vault in two major ways: first, sagittal dimensions (anterior chamber depth, crystalline lens rise,...) determine the anteroposterior distance between the resting position of the ICL in the ciliary sulcus and the anterior lens capsule. Second, the coronal dimension of the eye (sulcus to sulcus diameter) determines the degree by which the ICL is compressed in the ciliary sulcus¹⁴⁻¹⁶. The STAAR V4c ICL (Staar Surgical AG, Nidau, Switzerland) is designed in such a way that lateral compression of the ICL will lead to an anterior bowing of the lens¹⁵. For a given sulcus to sulcus diameter, increasing the ICL size will therefore increase the vault.

Choosing the optimal ICL size remains challenging. The STAAR V4c ICL comes in 4 sizes (diameter of 12.1 mm, 12.6 mm, 13.2 mm or 13.7 mm). Based on preoperative data, the surgeon should choose the diameter with the highest probability of resulting in an adequate vault. The manufacturer's official Online Calculation & Ordering System (OCOS) formula selects the preferred ICL size based on the corneal diameter (white to white, WTW) and anterior chamber depth (ACD). While achieving excellent average results, this formula is notable for its outliers^{15,17}. Moreover, the formula only reports the preferred ICL size, but does not estimate the achieved vault for the selected ICL. In an effort to improve the predictability of ICL sizing, several formulae have been developed, with their own strengths and weaknesses with regards to precision, accuracy, external validity and ease of use^{14,18–24}. Of particular importance, the vast majority of these new ICL sizing formulae have been trained on Asian datasets with high proportion of strongly myopic eyes^{19–21,23,24}. Racial differences in ocular anatomy may limit the performance of these formulae in patients of other ethnicities^{25,26}.

The aim of this study is to develop and share a convenient suite of ICL sizing formulae, optimally suited for a less myopic population of Caucasian descent.

Methods

Patients

The study was conducted using retrospective data of patients undergoing same-day bilateral ICL surgery at the Medipolis Eye Center, Antwerp, Belgium. In total, 78 patients, aged 18 – 52 years, were retrieved, of whom both eyes were included. Only eyes in which all pre- and post-operative measurements were available were retained for further analysis, leaving a total of 152 eyes of 78 patients. Each patient was randomly assigned to a training (80%) or a test set (20%), ensuring a similar distribution of postoperative vault values in both sets. Eyes corresponding to the same patient were assigned to the same set, resulting in a training set of N=115 eyes (59 patients) and a test set of N=37 eyes (19 patients). The training set was used for learning the vault prediction formulae and to calibrate their hyperparameters, while the test set was kept strictly separate and used only for evaluating the final models and the existing formulae.

Measurements

All patients underwent extensive ophthalmological pre-/ and post-operative examinations. Intraocular pressure, autorefraction, visual acuity and subjective refraction was assessed by a trained optometrist. An experienced technician performed endothelial cell count, optical biometry (IOLmaster 700 (Carl Zeiss Meditec AG, Jena, Germany)) and corneal topography + anterior segment optical coherence tomography (AS-OCT/MS-39) (Costruzione Strumenti Oftalmici, Firenze, Italy)) in standardized mesopic conditions. A list of the relevant parameters that were used in the models, as well as their mean and standard deviation in the training set, can be found in Supplemental Table 1. Anamnesis, slit lamp biomicroscopy and fundoscopy was performed by the operating surgeon (E.M.). The decision on the ICL size was made at the discretion of the surgeon, and was guided by the OCOS and Nakamura 1 and 2 formulae (Supplemental Figure 2)^{19,20}. Post-operative vault was measured at 12 ± 4 weeks after surgery using the provided caliper tool of the OCT software. All OCT images were aquired under stable, mesopic light conditions, to minimize the influence of pupil dilation or accomodation on the vault measurement²⁷.

Surgical procedure

All surgeries were performed by the same experienced surgeon (E.M.) under topical (preservative-free oxybuprocaine HCl 0.4%) + intracameral (preservative-free lidocaine 1%) anesthesia. Left eyes were operated first and right eyes second. A 1.0 mm side-port was made at 5 o'clock (right eye) or 10 o'clock (left eye), followed by intracameral injection of lidocaine and methylcellulose (ocucoat, B+L, Rochester, USA). A temporal 2.6 mm clear corneal incision was made, followed by the implantation of the ICL. After unfolding, the lens was positioned in the ciliary sulcus. Non-toric ICLs were alligned along the horizontal meridian, toric ICLs were rotated to the required axis. After verification of lens centration and alignment, the viscoelastic material was rinced with saline, incisions were sealed, intracameral preservative-free antibiotics (0.1 ml cefuroxime

(10mg/ml) were injected and one drop of dorzolamide 20% and timolol 5% was administred topically. In the recovery room, patients were given a tablet of acetazolamide 250 mg.

Model development

Models were developed to predict post-operative vault based on patient demographics (age, refraction and implanted ICL) and AS-OCT parameters (LASSO-OCT formula), optical biometry parameters (LASSO-Biometry formula) or a combination of both (LASSO-Full formula). Rather than resorting to a classical multivariate linear regression approach, the Least Absolute Shrinkage and Selection Operator (LASSO) technique was used²⁸. This technique is an alternative linear regression model widely applied in the field of machine learning for predictive tasks with a high number of independent variables. It holds a major advantage over traditional multivariate linear regression in its ability to automatically discard irrelevant parameters that do not significantly contribute to the accuracy of the model. For a more in-depth description of this technique, as well as for a better understanding of the following paragraph, we refer to the reference article in the specialized literature²⁸.

To control the effect of the L1 penalty in the optimization objective, α values in the set {10⁻⁴, 10⁻³, 10⁻², 10⁻¹, 1, 10, 10², 10³, 10⁴} were explored by evaluating their resulting mean absolute error on a 5-fold cross-validation scheme on the training set. The optimal α configuration was then applied to retrain the model on the entire training set. To reduce the effect of differences in feature scalings, data samples were standardized by subtracting each feature's individual mean and dividing the result by its corresponding standard deviation before training and prediction, as estimated from the training set. The corresponding mean and standard deviation values are reported in Supplemental Table 1 for reproducibility purposes. All data preprocessing and model adjustments were performed using Python 3 (version 3.9.9), Scikit-learn3 (version 1.0.1) and SciPy4 (version 1.7.1) modules^{29,30}.

7

Evaluation metrics and statistical analysis

The resulting models were evaluated on the separated test set to avoid biases in the results. The performance of the constructed models was also benchmarked against the OCOS, Nakamura's et al. formula 1 (NK1)¹⁹ and 2 (NK2)²⁰. Since these alternative models are predictors for the ideal diameter of the ICL to implant, they were adapted to perform post-operative vault prediction using the equation proposed by Nakamura et al¹⁹:

Predicted vault = 0.5 + 1.1 (Implanted ICL size - Optimal ICL size calculated from each formula)

Differences between the predicted vault value obtained by each formula and the corresponding ground truth postoperative vault were evaluated on a per-eye basis on the test set, using Mean Absolute Error (MAE), Rooted Mean Squared Error (RMSE) and the coefficient of determination R-squared values as obtained using Scikit-learn.²⁹ Non-parametric paired Wilcoxon signed-rank tests with level of significance of 0.05 were used to statistically compare the distributions of vault predictions obtained by each formula with respect to the ground truth (two-tailed) and to evaluate differences in the error distribution (one-tailed), using SciPy.³⁰

Results

Model design and coefficients

Table 1 summarizes the main characteristics of the patient cohort after splitting the database into training and test sets. No statistical significant differences between training and test measurements were observed (Wilcoxon signed-rank test, p > 0.05). Supplemental Figure 1 illustrates the distribution of spherical equivalent values in the training set.

A comparison in the distribution of ICL diameters recommended by the OCOS formula and the actual implanted ICL diameter as chosen by the surgeon is depicted in Supplemental Figure 2. The

postoperative vault achieved in the entire dataset was $482.5 \pm 230.1 \mu m$ (range $46 - 1376 \mu m$). A correlation analysis between pairs of measurements was performed using only the training set, to avoid data leakage in model design. Supplemental Figure 3 presents a heatmap with the R values corresponding to each pair of features, with those associated to the postoperative vault highlighted in blue (first column/row).

Figure 1 depicts the coefficients of each of the 3 different LASSO models. Notice that the learning algorithm automatically assigned an associated weight of zero (0) to several features. This indicates that their contribution to minimize the objective error in the training set is minimal and that these features can thus be ignored in the model. On the other hand, parameters that are important to the model are attributed a positive or negative coefficient, the magnitude of which relates to the relative importance of the parameter.

Model evaluation

Performance statistics of the different models are listed in Table 2, together with ground truth measurements and results from OCOS, NK1 and NK2. All models predicted vault values whose distribution is not statistically different from the achieved vault measurements (two-tailed paired Wilcoxon signed-rank test, p > 0.05). However, there exist significant differences in their error rates. The distributions of MAEs obtained by each formula are depicted as box plots in Figure 2. The LASSO formulae report the lowest errors, both in terms MAE, maximal absolute error and RMSE. From the three LASSO models, the LASSO-Full formula was the most accurate, with the lowest MAE in terms of magnitude and standard deviation.

Figure 3 depicts a cumulative bar chart showing the percentage of eyes in the test set with Absolute Errors (AE) smaller than 50 microns, 100 microns, 200 microns and 500 microns, for each of the proposed and baseline formulae. The LASSO-Full model obtained AEs below 100µm for 40% of the test eyes, 70% under 200µm and 100% under 500µm. In contrast, NK1, NK2 and OCOS formulae

9

obtained consistently higher error rates, with the majority of the test eyes reporting errors exceeding 200µm. Evaluating the cases with suboptimal postoperative vault in the test set (6 eyes <250µm, 6 eyes > 750µm), the LASSO formulae would have resulted in a 50% (LASSO-Biometry, 3 eyes <250µm, 3 eyes > 750µm) tot 75% (LASSO-OCT and LASSO-Full, both 5 eyes <250µm and 4 eyes > 750µm) reduction of excessive low or excessive high vault.

One-tailed Wilcoxon signed-rank tests were performed comparing the MAEs reported by the LASSO-Full model and each of the baseline formulae (Table 2). This analysis shows that the LASSO-Full model reported consistently lower errors than the OCOS, NK1 and NK2 formulae (p < 0.05). There were no statistically significant difference between the LASSO-Full and the LASSO-OCT or LASSO-Biometry models (p > 0.05).

Figure 4 presents a Bland-Altman plot demonstrating the differences in the vault prediction in the test set between the LASSO-Full and the NK2 formulae. Vault predictions by the LASSO-Full model report a mean signed difference with the achieved vault of 2.61 and are narrowly spread around zero. The NK2 formula has an even smaller mean signed difference of only -0.25, but is characterized by much more spreaded results. Supplemental Figure 4 depicts this data in a different perspective, showing the scatter plot and regression lines between achieved and predicted vault for the LASSO-Full model ($R^2 = 0.68$) and NK2 formula ($R^2 = 0.11$).

Discussion

In this paper, we describe the development and performance of the LASSO formulae, a convenient suite of ICL sizing formulae that can assist refractive surgeons in further improving the safety of ICL surgery. The elective nature of refractive surgery demands the most stringent safety standards. Over the years, studies have shown that in the hands of an experienced surgeon, ICL implantation has an excellent efficacy and safety profile with a very low risk for sight-treatening

complications^{1–5}. Postoperative vault is considered one of the most important risk factor for complications after ICL surgery. Accordingly, inadequate vault is reported as the major reason for ICL exchange/explantation^{6–9}. Improving the process of ICL sizing is therefore of key importance to further improve the safety profile of ICL surgery^{2,4}. The LASSO suite contributes to this evolution in 3 major areas: accuracy and precision, external validity and convenience.

The LASSO models are characterized by a high accuracy and precision compared to the standard and state-of-the-art models. With the favorable postoperative vault range between 250 and 750µm, the recommended target vault for the STAAR V4c ICL is 500µm². To improve the predictability of ICL sizing, not only should the average estimated vault be close to the average achieved postoperative vault (overall accuracy), the *individual* estimates should also be as close as possible to the individual achieved postoperative vaults (precision)³¹. The latter is important to reduce the risk of achieving a vault outside the favorable range. When evaluating the performance of an ICL formula, one should therefore not only compare the average estimated vs achieved vault, but more importantly, assess the prediction error of the individual cases. The most relevant metrics in this regard are the MAE (the mean absolute error between the estimated and achieved vault in an individual case) and its standard deviation, together with the maximal absolute error (the largest absolute difference between the estimated and achieved vault in the dataset). As can be observed in Table 2, on average, all the formulae that were used in this manuscript were able to estimate the postoperative vault fairly well, with no significant differences between estimated and achieved vault for any of the models. The OCOS formula however is characterized by a high MAE (284.5 \pm 217.5 μ m) and high maximal absolute error. This illustrates a known shortcoming of the OCOS formule and explains why this formula is prone to outliers who fall outside the favourable range^{15,17}. In agreement with previous studies, the NK1 and especially the NK2 formulae show improved MAE ± SD and maximal absolute errors in our test dataset^{19,20}. The LASSO models further improve the precision, as evident from the significantly smaller MAE, SDs and maximal absolute errors. Where the maximal absolute error of the OCOS formula in our test set was 841.0µm, this error was only 347.6µm in the LASSO-

Full model. Figure 3 illustrates how these findings translate into clinical practise: following the OCOS formula would have resulted in an error of more then 500µm in 10.8% of cases, whereas the LASSO-Full, LASSO-OCT and LASSO-Biometry formulae predicted respectively 100%, 100% and 97.3% of cases within 500µm. For the LASSO-Full model, over 90% of cases could be estimated within 200µm. These results put the performance of the LASSO-Full model on par with the recently published state-of-the-art formulae by Kang et al. and Kamiya et al^{23,24}.

In contrast to most other recent formulae, the LASSO models were trained on a European dataset, comprising a considerable amount of patients with low and moderate myopia. Supplemental Table 2 lists an overview of previously published publicly available formulae. The majority of them were trained on an Asian, more myopic population. Racial differences in the anatomy of the anterior segment are known to have an impact on ICL sizing^{25,26}. This translates to a very different distribution of implanted ICL sizes between Asian and European studies (Supplemental Figure 5). In the study from Kamiya et al. and Kang et al., the 13.7 mm diameter ICL was only implanted in respectively 2 out of 1745 eyes (0.1%) and 1 out of 2756 eyes (0.04%). The second largest 13.2mm ICL accounts to less than 10% in both studies, with the vast majority of patients receiving a 12.6 mm or 12.1 mm ICL^{23,24}. Our study is in line with other recently published European studies and shows an opposite pattern with few 12.1 mm implantations but a much higher percentage of the larger 13.2 mm and 13.7 mm lenses^{22,32}. These differences between Asian and Caucasian eyes may limit the external validity of the Asian models when used in Caucasian patients. Having almost no 13.7mm ICLs in their training dataset, the models trained on an Asian population cannot be expected to be as accurate for the larger ICL sizes as they are for the 12.1 mm and 12.6 mm lenses. Moreover, the training set used for the LASSO models is also considerably less myopic compared to most other studies (Supplemental Table 2). As ICL surgery is becoming more and more popular in patients with mild and moderate myopia, it is important that new formulae follow this trend³³. The level of myopia has a significant influence on several anterior chamber parameters of relevance in ICL sizing including crystaline lens rise, ACD and WTW^{34,35}. The training set used in this study included patients across the ametropic spectrum (manifest refractive sphere ranging from - 17.00 to +4.75D), with a particular large percentage of eyes with low (> -3D) and moderate (> -6D) myopia (Supplemental Figure 1). This sets the LASSO models apart from previously published formulae and makes them particularly suited for Caucasian patients with low to moderate myopia.

The LASSO suite is convenient and can be easily implemented into clinical practice. First, the models rely largely on automatically captured measurements. In comparison to ultrasound imaging, the ocular biometry and AS-OCT imaging techniques used in this study are less operator-dependent³⁶. Secondly, by providing three different formulae, the LASSO suite allows the user to tailor the formula to the available equipment. The LASSO-Biometry model offers a compelling option for surgeons without access to an AS-OCT device to improve the accuracy of their ICL calculations over the OCOS formula. Third, the models are provided as linear regression formulae which can be easily implented by the end user in a spreadcheat calculator without the need for programming skills or special software.

The study should be read in the context of its limitations. Although the training set is of respectable size, the performance of the models could likely be improved by increasing the dataset, especially for the extreme ICL sizes of 12.1 mm and 13.7 mm, of which only few cases were included in this study. Secondly, the monocentric, retrospective nature of this study may overestimate the performance of the models when used in a different setting. Given the contraints of the study setting, we took measures to minimize its impact by strictly separating the training and test set at the patient level, thus avoiding data leakage between both eyes of the same patient. Future studies should examine if the high level of performance achieved in our test set can be matched on external datasets.

In conclusion, the LASSO suite is a set of powerful ICL sizing formulae that were trained on a Caucasian population including a large portion of low to moderate myopia. Both the LASSO-Biometry, the LASSO-OCT and the LASSO-Full model report excellent accuracy and precision over a

wide range of refractive errors and show especially improved results in the low myopic range. The formulae can be accessed via the url http://icl.emmetropia.be. Based on the available equipment, refractive surgeons can easily implement one of the formulae in their clinical practise. By refining the postoperative vault prediction, the LASSO suite may ultimately help to further improve the safety profile of ICL surgery.

ACKNOWLEDGMENTS

/

VALUE STATEMENT

What was known

- Implantable collamer lens (ICL) provides a safe and effective alternative to corneal refractive surgery.

- Inadequate postoperative vault is the major reason for ICL explantation.

- The majority of recently published ICL sizing formulae are trained on Asian datasets with predominantly highly myopic patients.

What this paper adds

- The LASSO models offer excellent performance for prediciting postoperative vault in Caucasian patients, also in those with low to moderate myopia.

Supplemental Figure 1-<u>http://links.lww.com/JRS/A718</u>

Supplemental Figure 2-<u>http://links.lww.com/JRS/A719</u>

Supplemental Figure 3-<u>http://links.lww.com/JRS/A720</u>

Supplemental Figure 4-<u>http://links.lww.com/JRS/A721</u>

Supplemental Figure 5-<u>http://links.lww.com/JRS/A722</u>

Supplemental Tables-http://links.lww.com/JRS/A723

REFERENCES

- 1. Choi JH, Lim DH, Nam SW, Yang CM, Chung ES, Chung TY. Ten-year clinical outcomes after implantation of a posterior chamber phakic intraocular lens for myopia. *Journal of Cataract & Refractive Surgery*. 2019;45(11):1555-1561.
- 2. Packer M. Meta-analysis and review: effectiveness, safety, and central port design of the intraocular collamer lens. *Clinical Ophthalmology (Auckland, NZ)*. 2016;10:1059.
- 3. Alfonso JF, Fernández-Vega-Cueto L, Alfonso-Bartolozzi B, Montés-Micó R, Fernández-Vega L. Five-year follow-up of correction of myopia: posterior chamber phakic intraocular lens with a central port design. *Journal of refractive surgery*. 2019;35(3):169-176. doi:10.3928/1081597X-20190118-01
- 4. Montés-Micó R, Ruiz-Mesa R, Rodríguez-Prats JL, Tañá-Rivero P. Posterior-chamber phakic implantable collamer lenses with a central port: a review. *Acta Ophthalmol.* 2021;99(3). doi:10.1111/aos.14599
- 5. Repplinger B, Kohnen T. Intraocular pressure after implantation of an ICL with aquaport: development of intraocular pressure after implantation of an ICL (model V4c) with aquaport without iridotomy. *Der Ophthalmologe: Zeitschrift der Deutschen Ophthalmologischen Gesellschaft*. 2018;115(1):29-33. doi:10.1007/s00347-017-0556-1
- 6. Zeng QY, Xie XL, Chen Q. Prevention and management of collagen copolymer phakic intraocular lens exchange: causes and surgical techniques. *Journal of Cataract & Refractive Surgery*. 2015;41(3):576-584.
- 7. AlSabaani NA, Behrens A, Jastanieah S, Al Malki S, Al Jindan M, Al Motowa S. Causes of phakic implantable collamer lens explantation/exchange at King Khaled Eye Specialist Hospital. *Middle East African Journal of Ophthalmology*. 2016;23(4):293.
- 8. Kaur M, Titiyal JS, Falera R, Sinha R, Sharma N. Indications for explant of implantable collamer lens. *Eye*. 2018;32(4):838-840.
- 9. Alhamzah A, Alharbi SS, Alfardan F, Aldebasi T, Almudhaiyan T. Indications for exchange or explantation of phakic implantable collamer lens with central port in patients with and without keratoconus. *International Journal of Ophthalmology*. 2021;14(11):1714.
- 10. Yu Y, Zhang C, Zhu Y. Femtosecond laser assisted cataract surgery in a cataract patient with a "0 vaulted" ICL: a case report. *BMC ophthalmology*. 2020;20(1):1-5. doi:10.1186/s12886-020-01440-x
- 11. Strungaru MH, Rodríguez JG, Weisbrod DJ, Tayfour F, Buys YM. Acute angle closure following implantable collamer lens for myopia. *Journal of Glaucoma*. 2020;29(7):e74-e76.
- 12. Chen X, Wang X, Xu Y, Cheng M, Han T, Wang X, Zhou X. Long-term Comparison of Vault and Complications of Implantable Collamer Lens with and without a Central Hole for High Myopia Correction: 5 Years. *Current Eye Research*. Published online 2021:1-7.

- 13. Córdoba A, Graue-Hernández EO, Gómez-Bastar A, Navas A. Long-term follow-up of persistent low vault after implantable collamer lens exchange. *Journal of Cataract & Refractive Surgery*. 2019;45(4):519-522.
- 14. Kojima T, Yokoyama S, Ito M, Horai R, Hara S, Nakamura T, Ichikawa K. Optimization of an implantable collamer lens sizing method using high-frequency ultrasound biomicroscopy. *American journal of ophthalmology*. 2012;153(4):632-637. e1.
- 15. Nam SW, Lim DH, Hyun J, Chung ES, Chung TY. Buffering zone of implantable Collamer lens sizing in V4c. *BMC ophthalmology*. 2017;17(1):1-6.
- 16. Gargallo-Martinez B, Garcia-Medina JJ, Rubio-Velazquez E, Fernandes P, Villa-Collar C, Gonzalez-Meijome JM, Gutierrez-Ortega R. Vault changes after cyclopentolate instillation in eyes with posterior chamber phakic intraocular lens. *Scientific Reports*. 2020;10(1):1-9.
- 17. Lee DH, Choi SH, Chung ES, Chung TY. Correlation between preoperative biometry and posterior chamber phakic Visian Implantable Collamer Lens vaulting. *Ophthalmology*. 2012;119(2):272-277.
- 18. Dougherty PJ, Rivera RP, Schneider D, Lane SS, Brown D, Vukich J. Improving accuracy of phakic intraocular lens sizing using high-frequency ultrasound biomicroscopy. *Journal of Cataract & Refractive Surgery*. 2011;37(1):13-18.
- 19. Nakamura T, Isogai N, Kojima T, Yoshida Y, Sugiyama Y. Implantable collamer lens sizing method based on swept-source anterior segment optical coherence tomography. *American journal of ophthalmology*. 2018;187:99-107.
- 20. Nakamura T, Isogai N, Kojima T, Yoshida Y, Sugiyama Y. Optimization of implantable collamer lens sizing based on swept-source anterior segment optical coherence tomography. *Journal of Cataract & Refractive Surgery*. 2020;46(5):742-748.
- 21. Igarashi A, Shimizu K, Kato S, Kamiya K. Predictability of the vault after posterior chamber phakic intraocular lens implantation using anterior segment optical coherence tomography. *Journal of Cataract & Refractive Surgery*. 2019;45(8):1099-1104.
- 22. Trancón AS, Manito SC, Sierra OT, Baptista AM, Serra PM. Determining vault size in implantable collamer lenses: preoperative anatomy and lens parameters. *Journal of Cataract & Refractive Surgery*. 2020;46(5):728-736.
- 23. Kamiya K, Ryu IH, Yoo TK, Kim JS, Lee IS, Kim JK, Ando W, Shoji N, Yamauchi T, Tabuchi H. Prediction of Phakic Intraocular Lens Vault Using Machine Learning of Anterior Segment Optical Coherence Tomography Metrics. *American Journal of Ophthalmology*. 2021;226:90-99.
- 24. Kang EM, Ryu IH, Lee G, Kim JK, Lee IS, Jeon GH, Song H, Kamiya K, Yoo TK. Development of a Web-Based Ensemble Machine Learning Application to Select the Optimal Size of Posterior Chamber Phakic Intraocular Lens. *Translational Vision Science & Technology*. 2021;10(6):5-5.
- 25. Qin B, Tang M, Li Y, Zhang X, Chu R, Huang D. Anterior segment dimensions in Asian and Caucasian eyes measured by optical coherence tomography. *Ophthalmic Surgery, Lasers and Imaging Retina*. 2012;43(2):135-142.
- 26. Chang JS, Meau AY. Visian Collamer phakic intraocular lens in high myopic Asian eyes. *Journal* of refractive surgery. 2007;23(1):17-25.

- 27. Xiong Y, Mao Y, Li J, Wan X, Li M, Zhang J, Wang J, Sun X. Vault changes and pupillary responses to light in myopic and toric implantable collamer lens. *BMC Ophthalmol.* 2021;21(1):366. doi:10.1186/s12886-021-02119-7
- 28. Tibshirani R. Regression Shrinkage and Selection Via the Lasso. *Journal of the Royal Statistical Society: Series B (Methodological)*. 1996;58(1):267-288. doi:10.1111/j.2517-6161.1996.tb02080.x
- 29. Pedregosa F, Varoquaux G, Gramfort A, Michel V, Thirion B, Grisel O, Blondel M, Prettenhofer P, Weiss R, Dubourg V. Scikit-learn: Machine learning in Python. *the Journal of machine Learning research*. 2011;12:2825-2830.
- 30. Virtanen P, Gommers R, Oliphant TE, Haberland M, Reddy T, Cournapeau D, Burovski E, Peterson P, Weckesser W, Bright J. SciPy 1.0: fundamental algorithms for scientific computing in Python. *Nature methods*. 2020;17(3):261-272.
- 31. Streiner DL, Norman GR. "Precision" and "Accuracy": Two Terms That Are Neither. *Journal of Clinical Epidemiology*. 2006;59(4):327-330. doi:10.1016/j.jclinepi.2005.09.005
- 32. Reinstein DZ, Vida RS, Archer TJ. Visual Outcomes, Footplate Position and Vault Achieved with the Visian Implantable Collamer Lens for Myopic Astigmatism. *Clinical Ophthalmology* (*Auckland, NZ*). 2021;15:4485.
- 33. Kamiya K, Shimizu K, Igarashi A, Kitazawa Y, Kojima T, Nakamura T, Oka Y, Matsumoto R. Posterior chamber phakic intraocular lens implantation: comparative, multicentre study in 351 eyes with low-to-moderate or high myopia. *British Journal of Ophthalmology*. 2018;102(2):177-181.
- 34. Chen Z, Li T, Li M, Xu Y, Zhou X. Effect of Tropicamide on crystalline Lens rise in low-tomoderate myopic eyes. *BMC ophthalmology*. 2020;20(1):1-6.
- 35. Xu G, Wu G, Du Z, Zhu S, Guo Y, Yu H, Hu Y. Distribution of White-to-White Corneal Diameter and Anterior Chamber Depth in Chinese Myopic Patients. *Frontiers in Medicine*. 2021;8.
- 36. Wan T, Yin H, Yang Y, Wu F, Wu Z, Yang Y. Comparative study of anterior segment measurements using 3 different instruments in myopic patients after ICL implantation. *BMC ophthalmology*. 2019;19(1):1-8.

TABLES and FIGURES

Table 1 Patient demographics and characteristics

The P-value corresponds to the results of a Wilcoxon signed-rank test comparing the statistical differences in the distribution of each characteristic in training and test set.

Table 1. Patient demographics and characteristics

	Training set		Test set		P-value	
	Mean ± SD	Range	Mean ± SD	Range		
Number of patients (eyes)	59 (115)		19 (37)			
Age	32.09 ± 7.00	(18.00, 52.00)	31.46 ± 7.53	(21.00, 43.00)	0.813	
Manifest refractive sphere (D)	-4.86 ± 3.37	(-17.00, 4.75)	-4.76 ± 2.65	(-14.00, 0.25)	0.463	
Manifest refractive cylinder (D)	-0.92 ± 1.01	(-5.50, 0.00)	-1.01 ± 1.19	(-6.00, 0.00)	0.377	
Axial length (mm)	25.50 ± 1.55	(21.08, 31.63)	25.55 ± 1.06	(24.19, 29.05)	0.473	
Anterior chamber depth (mm)	3.70 ± 0.23	(3.24, 4.36)	3.71 ± 0.24	(3.27, 4.28)	0.470	
Scleral spur to scleral spur (mm)	12.40 ± 0.47	(11.62, 13.58)	12.39 ± 0.27	(11.91, 12.99)	0.384	
Crystalline lens rise (mm)	-0.24 ± 0.16	(-0.69, 0.25)	-0.21 ± 0.14	(-0.55, 0.04)	0.226	
Implanted ICL power (D)	-5.93 ± 3.52	(-16.50, 4.75)	-5.93 ± 2.63	(-13.5, -0.75)	0.445	
Toric ICL (%)	43		38	_	0.549	
Postoperative achieved vault (µm)	479.51 ± 224.15	(80.00, 1376.00)	491.78 ± 253.47	(46.00, 1127.00)	0.476	

Table 2. Postoperative vault prediction error

From left to right. Mean and standard deviation (SD) postoperative vault values as measured in the test set and predicted by OCOS, NK1 and NK2 formulae and our three proposed models. Mean absolute error (MAE) and standard deviation (SD), maximal absolute error and root of the mean square error (RMSE) as reported by each formula.

* P value comparing formula-estimated vault to measured value

** P value comparing formula's MAE to MAE of LASSO-Full formula

Table 2. Postoperative vault prediction error

	Vault (mean ± SD)	MAE ± SD	Maximal absolute error	RMSE	Two-tailed P Value*	One-tailed P Value**
Measured postoperative vault	491.8 ± 250.0	-	-	-		
ocos	538.6 ± 369.0	285.4 ± 217.5	841.0	358.8	0.414	0.0011
NK1	544.6 ± 255.8	269.5 ± 173.5	707.6	320.5	0.330	0.0003
NK2	491.5 ± 241.4	239.7 ± 242.8	550.6	286.9	0.922	0.0017
LASSO-Biometry	479.3 ± 126.2	144.1 ± 107.9	524.8	180.0	0.729	0.381
LASSO-OCT	506.8 ± 121.6	145.6 ± 100.6	437.8	177.0	0.449	0.376
LASSO-Full	494.3 ± 134.7	132.0 ± 86.6	347.6	157.9	0.673	-

Supplemental Table 1 Distribution of predictive parameters.

Mean and standard deviation (SD) values of each characteristic identified as relevant by the LASSO models, as estimated from the training set.

Supplemental Table 2. Overview of previously published formulae.

Data not reported /analyzed are indicated by NA UBM, ultrasound biomicroscopy; AS-OCT, anterior segment Optical Coherence Tomography; SEQ, preoperative spherical equivalent.

Figure 1. Model regression coefficients.

Coefficients learned by the Full-model (left), OCT-model (right, top) and Biometry-model (right, bottom).



Figure 2. Distribution of absolute errors in the postoperative vault prediction.





Left: Cumulative bar chart with the percentages of eyes in the test with absolute errors smaller than 50µm, 100µm, 200µm and 500µm, for each of the LASSO models and the baseline formulae. Right: Percentage of eyes in the test with absolute errors higher than 500µm.



Figure 4. Bland-Altman plot comparing LASSO-Full and NK2.

Agreement between the measured postoperative vault values in the test set and the predictions from the LASSO-Full model and NK2 formula



Supplemental Figure 1. Distribution of spherical equivalent.

Supplemental Figure 2. Distribution of implanted ICL diameter.

ICL diameter recommended by the OCOS formula (grey) and the actual implanted size (purple)

Supplemental Figure 3. Correlation between measurements.

Heatmap of R values representing the correlation between pairs of features in the training set. Numbers in each box (i,j) represent the corresponding R value between features i and j. The R values between the measured postoperative vault and the remaining features are highlighted in blue.

Supplemental Figure 4. Scatter plot and regression lines comparing LASSO-Full and NK2.

Predicted versus actual measured postoperative vault for the LASSO-Full model and the NK2 formula.

Supplemental Figure 5. Distribution of implanted ICL sizes in recent publications.

Distribution of implanted ICL sizes in recent Asian (Kang et al., Kamiya et al. ^{23,24}, highlighted in grey) and European studies (Trancón et al., Reinstein et al., LASSO ^{22,32}, highlighted in blue) Note the pronounced difference for the 12.1mm and 13.7mm sizes between the Asian and European studies.