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Screening subclinical keratoconus with Placido-based corneal indices

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Abstract

Purpose:

To assess in a sample of normal, keratoconic and keratoconus suspect eyes the performance of a set of new topographic indices computed directly from the digitized images of the Placido rings.

Methods:

This comparative study comprised a total of 124 eyes of 106 patients from the ophthalmic clinics Visum Alicante and Visum Almería (Spain), in three groups: control group (50 eyes), keratoconus group (50 eyes) and keratoconus suspect group (24 eyes). In all cases, a comprehensive examination was performed including the corneal topography with a Placido-based CSO topography system. Clinical outcomes were compared among groups, along with the discriminating performance of the proposed irregularity indices.

Results:

Significant differences at level 0.05 were found on the values of the indices among groups by means of Mann-Witney-Wilcoxon non-parametric test and Fisher's exact test. Additional statistical methods, such as receiver operating characteristic analysis and K-fold cross-validation, confirmed the capability of the indices to discriminate between the three groups.

Conclusions:

Direct analysis of the digitized images of the Placido mires projected on the cornea is a valid and effective tool for detection of corneal irregularities. Although based only on the data from the anterior surface of the cornea, the new indices performed well even when applied to the keratoconus suspect eyes. They have the advantage of simplicity of calculation combined with high sensitivity in corneal irregularity detection, and thus can

be used as supplementary criteria for diagnosing and grading keratoconus that can be added to the current keratometric classifications.

Keywords: Corneal irregularities; subclinical keratoconus; irregularity index; diagnosis; corneal topography; Placido disks

1 Keratoconus (KC) is an ectatic debilitating corneal disorder characterized by a
2 progressive corneal thinning that results in corneal protrusion, irregular astigmatism, and
3 decreased vision¹. Corneal elasticity and rigidity is severely affected in keratoconic eyes²⁻⁴,
4 which become more susceptible to the effect of any pressure, such as the intraocular pressure.
5 Consequently, the corneal shape is more easily distorted (corneal steepening and aberrometric
6 increase in KC). This explains the usual significant increase in the anterior corneal irregularity
7 and a deterioration of the visual quality in KC, aggravated by the high optical relevance of the
8 first surface of the cornea.

9 Several grading systems have been described in the literature in order to classify the
10 severity of KC⁵⁻⁷. Most of these grading systems have been developed taking into account the
11 visual performance of the patient, topographic morphology of the disease, the corneal
12 keratometry readings and corneal aberrometry⁸⁻¹⁰, and have been proven to be an essential
13 tool in the therapeutic approach to the management of KC.

14 Nevertheless, there is a form of this disease, characterized by a milder modification in
15 corneal topography and morphology but without the impairment of the visual function of the
16 patient, that has been defined as an early KC, subclinical KC, or KC suspect. One of the main
17 difficulties in relation to this entity is the lack of its clear definition in the literature¹¹.

18 The topographic analysis of the anterior corneal surface is the main tool that has been
19 used for the KC diagnosis and characterization for years. Several indices, both simple and
20 compound, decision trees and even neural networks based on the corneal topographic data and
21 optical parameters have been developed to provide a more reliable tool to detect abnormal and
22 borderline suspect corneas¹²⁻²⁶. Also the vertical coma of the corneal aberration is one of the
23 simplest direct KC markers used in the clinical practice^{9,13}. However, and even with the
24 advance of the technological tools employed today for the assessment of potential candidates
25 for refractive surgery, subclinical KC is still considered the most important risk factor for

26 developing post LASIK ectasia²⁷⁻²⁸, a devastating condition leading to a significant visual
27 impairment of the patient. Thus, improving the screening strategies, tools and techniques that
28 allow us to identify those cases with the potential hazard of developing such a feared
29 complication has become a major challenge within the ophthalmic community.

30 Most of the corneal indices, published in the literature, are based on the elevation or
31 curvature data of the cornea, as well as pachymetry²⁹ or the epithelial thickness profile³⁰.
32 However, and at least in the case of the dominant Placido-based topographers, these data are
33 not obtained by a direct (and verifiable) measurements, but are an outcome of a mathematical
34 processing of the image of the rings in the keratographic picture by more or less sophisticated
35 (and in the case of commercial devices, by proprietary and not always transparent)
36 algorithms³¹⁻³³. These procedures make important assumptions on the corneal shape
37 (rotational symmetry, approximability by cubic splines, etc.) that are difficult to satisfy in the
38 case of a very complicated or irregular corneal surface. Therefore, numerical approaches
39 developed for KC detection from topographic data using these reconstruction algorithms
40 inherit unnecessarily the complexity of the currently used ring image-to-curvature conversion
41 methods, as well as might be affected by the unavoidable intrinsic errors appearing during
42 such a conversion³⁴⁻³⁵.

43 In order to overcome these shortcomings, as well as to improve and complement the
44 existing set of corneal disease markers, a set of new irregularity indices has been introduced
45 recently³⁶. These indices bypass the conversion to corneal power and use directly the digitized
46 image of the Placido rings.

47 The previous contribution³⁶ had a methodological character, although some
48 preliminary discussion of the performance of the indices was carried out there. The aim of this
49 current study is to assess in a sample of normal, keratoconic and keratoconic suspect eyes a

50 simplified subset of the topographic indices proposed in that paper, evaluating their potential
51 as a tool for KC detection.

52 As a final remark, we should point out that any additional information about a cornea,
53 such as its pachymetry, could improve considerably the screening capability of any marker.
54 The indices analysed here use only the data available to a Placido-based topographer (which
55 are still a vast majority in the clinical practice), but we hope they help to use these data more
56 efficiently.

57
58

Methods

59 This case series comparative study comprised a total of 124 eyes of 106 patients. Two
60 Spanish ophthalmologic centers participated in the recruitment of patients for this study,
61 Vissum Alicante and Vissum Almería, forming part of the Thematic Network of the
62 Cooperative Sanitary Research (RETIC) RD07/0062. All these cases were assigned to one of
63 the following three groups depending on the presence or not of KC: a control group, which
64 included 50 eyes (from 50 patients), a KC group, which included a total of 50 eyes (from 32
65 patients), and a subclinical KC or KC suspect group, with a total of 24 eyes (from 24
66 patients).

67 The inclusion in the KC group was based on the standard criteria for the diagnosis of
68 this corneal condition and the absence of any previous surgical intervention that could have
69 altered the corneal properties. The following signs were considered at diagnosis¹: corneal
70 topography revealing an asymmetric bowtie pattern with or without skewed axes and at least
71 one keratoconus sign on slit-lamp examination, such as stromal thinning, conical protrusion of
72 the cornea at the apex, Fleischer ring, Vogt striae or anterior stromal scar. In those patients
73 wearing contact lenses for the correction of the refractive error, only data obtained after an
74 appropriate contact lens discontinuation were considered: at least 2 weeks for soft contact
75 lenses and at least 4 weeks for rigid gas permeable contact lenses. The exclusion criteria for

76 the KC group were other ocular active pathology at the moment of diagnosis and the presence
77 of an advanced KC (grade 4 according to the Alió-Shabayek grading system⁸). In cases of
78 unilateral KC, the affected eye was always included in the study. However, in bilateral KC
79 only one eye was selected randomly for the study.

80 The group of normal eyes or control group only included eyes with no other ocular
81 pathology, previous ocular surgery or irregular corneal pattern. In this control group, only one
82 eye from each patient was selected randomly (random sampling) for the inclusion in the study
83 in order to avoid the potential bias introduced by the correlation between both eyes of a same
84 patient.

85 The definition of KC suspect cases was based on the following clinical and
86 topographic evaluation: no slit-lamp findings, no scissoring on retinoscopy, and the presence
87 of asymmetric bowtie (AB), inferior steepening (IS), skewed axes (SRAX) or asymmetric
88 bowtie with skewed axes (AB/SRAX) pattern on topography¹⁰.

89 All patients were informed about the study and signed an informed consent document
90 in accordance with the Helsinki Declaration.

91

92 *Examination protocol*

93 The corneal topographic analysis was carried out with the CSO topography system
94 (CSO, Firenze, Italy). This topographer analyses a total of 6144 points of a corneal area
95 enclosed in a circular annulus defined by an inner radius of 0.33 and an outer radius of 10 mm
96 with respect to the corneal vertex. The software of this system, the EyeTop2005 (CSO,
97 Firenze, Italy), performs automatically the conversion of the corneal elevation profile into
98 corneal wavefront data using the Zernike polynomials with an expansion up to the 7th order,
99 although it allows to export the raw data (positions of the digitized mires) as an ASCII file.
100 For the sake of reliability of the analysis of the indices, the standard KPI index as well as the

101 I-S index has been stored for comparative purposes. Both indices are well known and
102 precisely defined in the literature^{7,33}.

103

104 *Definitions of the corneal indices*

105 It is convenient to point out that in the description of the indices we skip the initial
106 discretization step, performed by every commercially available topographer using presumably
107 standard and widely available edge-detection procedures, when the high-contrast black-and-
108 white images of the mires are converted into a discrete points set. Hence, we assume as the
109 input data the coordinates of these points along the edges of consecutive mires, which we
110 consider as positions of the digitized mires. With this information, we have calculated the
111 irregularity indices following the previously discussed methodology³⁶. From the original set
112 of indices, we used a small subset of the best performing indices (also the most robust ones
113 with respect to the misalignment of the eye and other errors), complemented with an
114 additional index as described below.

115 The digitized points P_j captured by the camera of the Placido disk corneal
116 topographer were grouped in $N \in 15$ mires. For the sake of precision, we assume that there
117 were 256 points equally spaced along each ring corresponding to the same number of semi-
118 meridians (a value found in a majority of existing devices). We used only data from complete
119 rings, limiting the number of rings to the maximum of 15. The indices were defined according
120 to the information obtained from all mires as follows.

121

122 For each k , the center C_k and radius R_k of the best-fit circle for the k -th mire was
123 calculated using a standard least squares procedure³⁷, along with the following primary
124 indices (PI):

125 $-PI_1$: the diameter of the set of centers C_k (normalized by the total number of rings N)

126
$$PI_1 = \frac{1}{N} \max_{1 \leq n, m \leq N} \|C_n - C_m\|$$

127 $-PI_2$: the total drift or the deviation in the consecutive centers C_k :

128
$$PI_2 = \frac{1}{N-1} \sum_{1 \leq n \leq N-1} \|C_{n+1} - C_n\|$$

129 These two indices give global information about the deviation of the image of the
130 rings from a concentric pattern.

131 Data from mires were also fit with an ellipse with the aim of capturing the spatial
132 orientation and deformation of each mire (see Figure 1) by means of a simplification³⁷⁻⁴¹ of
133 efficient methods for computation of the best-fit ellipse, rendering the following asymmetry
134 index:

135 $-PI_3$: the dispersion of the values of the axis ratios $r_k = a_k/b_k \geq 1$ of the k -th best fit
136 ellipse by means of the following expressions:

137
$$PI_3 = \sqrt{\frac{1}{N} \sum_{1 \leq k \leq N} (r_k - \bar{r})^2} \quad \text{where} \quad \bar{r} = \frac{1}{N} \sum_{1 \leq k \leq N} r_k$$

138 Indices $PI_1 - PI_3$ coincide with those defined previously³⁶. They were complemented
139 by some additional indices whose definition was modified with respect to that given
140 previously³⁶, seeking better discrimination ability and robustness. In particular, we avoid the
141 use of polar coordinates (sensitive to the apex misalignment), calculating the indices $AR(k)$
142 from the original image of the mires as the radius of the best-fit circle to the k -th ring. In
143 practice, only the fourth mire (index $AR(4)$) was used in the combined model described
144 below, and thus only its individual performance will be analyzed in the next section.

145 We also carried out the standard linear regression of the coordinates of the centers
146 $C_k = (x_k, y_k)$, yielding the coefficients for the linear fit $y = ax + b$. With this approach, high
147 values of a correspond to a vertical alignment of the centers, so its value contains information

148 about their spatial distribution (see Figure 2). These considerations motivate the following
149 index (we use the name of an index defined previously³⁶, but with a new meaning):

150 $-PI_4$: is the absolute value of the slope of the linear regression,

$$151 \quad PI_4 = |a|$$

152 Each of these metrics can be used for KC detection (or at least, as a measure of
153 corneal irregularity), but as it usually happens with the individual indices, none achieves the
154 necessary sensitivity and specificity to meet the standards. For this reason, a combination was
155 used to improve the detection efficiency. We added to our protocol of indices a new
156 additional combined metric called GLPI, which takes continuous values between 0 and 100
157 (0% corresponding to a totally normal, and 100%, to a totally altered cornea).

158 GLPI: is a generalized linear (Placido-based) model combining four of the individual
159 indices mentioned above. Their linear combination (with fixed coefficients) is evaluated in
160 the so-called "probit" link function⁴²⁻⁴³. This yields a quantity between 0 and 1 that is
161 multiplied by 100 for convenience. This value, in the interval [0,100], is a % of irregularity of
162 the cornea. This definition of GLPI is slightly different from the one given previously³⁶: it has
163 been modified to achieve a better accuracy with a smaller number of individual indices and
164 also to include the redefined index PI_4 :

$$165 \quad GLPI=100 \times \text{Probit}(\eta), \quad \text{with}$$

$$166 \quad \eta = 10^{-2}(15.7 + 1043.9 \times PI_1 - 184.2 \times PI_3 - 30.0 \times AR(4) + 0.5 \times PI_4) \quad (1)$$

167

168 *Statistical analysis*

169 In order to determine the homogeneity of the sample, when divided into training and
170 test sets, a Mann-Witney-Wilcoxon non-parametric test⁴⁴⁻⁴⁵ was applied to each of the
171 primary indices. Without assumption of normality, this test checks whether the two samples

172 come from the same population (null hypothesis). It can also be used to analyze the
173 discriminating ability of the indices, checking if it renders different values in each group.

174 Additionally, Fisher's exact test⁴⁶⁻⁴⁷ is a statistical method used when a dichotomous
175 classification process is made. This test checks whether the classifier has enough
176 discrimination ability, and it is valid for any sample size. The idea is to compare the expected
177 proportions of false/true positives/negatives with the actual proportion obtained after
178 classifying. This procedure has been used in this study to check if the true proportions of
179 success of the primary indices when classifying normal and keratoconic eyes are independent
180 and consequently, if the primary indices show classification ability or not.

181 The K-fold cross-validation is a standard statistical tool to assess the global accuracy
182 of a regression or classification model⁴⁸⁻⁴⁹. The main benefit of this method is that it makes
183 use (independently) of the same data to fit the model and to check its performance, which is
184 useful when the sample size is relatively small. The sample is divided into K groups of
185 approximately equal size. Then the regression model is fit (or re-fit, if an initial model was
186 specified) to the data using K-1 of the K subsets, and its accuracy is measured with the
187 predicted values for the remaining group. When K becomes equal to the sample size, this
188 scheme reduces to the well-known leave-one-out cross-validation method. This technique
189 allows estimating the global accuracy of a classification method with only one dataset, but
190 using independently subsets of the sample to fit and to validate the model.

191 Finally, the receiver operating characteristic (ROC) curve analysis is a well-
192 established tool for assessing the discriminating capability of a model. We present the results
193 of this analysis for the redefined primary indices PI_4 and $AR(4)$. The ROC curves for the rest
194 of the indices can be found in the literature³⁶.

195

Results

The primary indices have been computed for all three groups in the database and their means and standard deviations were calculated (see Table 1). The classification ability of the primary indices was assessed in different ways. First, according to the Mann-Witney-Wilcoxon tests, most of the indices are able to discriminate between the three groups (see Table 2), except for PI_2 and $AR(4)$, which being appropriate for discrimination between keratoconic eyes (KC) and the rest of the eyes, do not perform well discriminating between normal (N) and keratoconus suspect (KS) eyes. In addition, Fisher's test for all these indices indicated that the true proportions of positives within the N and KC groups differ (with a significance level of 0.05), so they actually have sensitivity to detect irregularities. Moreover, the ROC curves for PI_4 and $AR(4)$ illustrate the discrimination ability of these indices (see Figure 3); the values of A_2ROC (area under the ROC curve) for all the indices appear on Table 2.

Concerning the combined indices, GLPI index computed using the whole database was able to reach the accuracy value 1 (perfect classifying capability between N and KC groups). The estimations rendered by the K-fold cross-validation method for different values of K are shown in Table 4, exhibiting consistent accuracy values between 0.94 and 0.95.

It is well known that the vertical coma (computed as the absolute value of the Zernike coefficient Z_3^{-1}) is a simple marker for detecting $KC^{9,13}$. It is actually very close in spirit to our irregularity index PI_4 : both measure the upper-down asymmetry, although PI_4 follows the ideology of using only straightforward calculations from the mire images. For comparative reasons, the vertical coma has been also computed for all three groups in our database. According to a previous analysis³⁶, a suitable cut-off value for the vertical coma to discriminate between keratoconus and normal eyes is 3.59×10^{-5} . With this threshold, 8% of the eyes in the KC group of our database were classified as regular and 4% of normal eyes

221 were classified as irregular, which is a good performance. However, within the keratoconus
222 suspect group (KS), the vertical coma was able to classify only 29% of those corneas as
223 irregular. To achieve a success rate of 0.79 within this group (the same as PI_4 , see Table 6),
224 the cut-off value has to be set approximately to 2.00×10^{-5} , yielding that 22% of normal eyes
225 are classified as irregular. This is a much lower accuracy in comparison with PI_4 .

226 There is a clear similarity in the philosophy of the construction of the KPI and the
227 GLPI indices: both are compound indices, indicating a degree of certainty of detection of a
228 corneal irregularity, with moderate to severe cones receiving a KPI score of 100%^{7, 50-51}. Both
229 indices are derived by a variation of discriminant analysis applied to a control group of
230 patients, although GPLI, unlike the KPI, uses only the primary information provided by the
231 keratoscope.

232 A comparison of the new indices with the KPI and I-S renders some interesting
233 conclusions. For the keratoconus suspect group (KS) their values are summarized in Table 5.
234 For the KPI, we used the standard cut-off reported in the literature, considering values equal
235 to or greater than 23 as anomalous (the first two rows in Table 5 fall within the KPI range for
236 normal eyes, while the last two rows correspond to anomalous ones); in the case of the I-S
237 index, values equal or greater than 1.5 were considered anomalous (now, the first two
238 columns in Table 5 correspond to normal eyes, according to the I-S index, and the last two
239 columns correspond to anomalous eyes). It follows from Table 5 that KPI was able to detect
240 only 6 out of 24 keratoconus suspect eyes (25%), while I-S was able to detect 12 out of 24
241 (50%); moreover, 8 out of 24 cases were not detected by either indices (33.3%), and only 4
242 out of 24 cases are detected by both indices simultaneously (16.7%).

243 Finally, Table 6 shows that the classification power of GLPI and KPI are very similar
244 in all three groups: normal eyes, keratoconus eyes and keratoconus suspect eyes. Index PI_4 ,
245 exhibiting a reasonable behavior within the group of normal eyes, has a slightly lower KC

246 detection capability than either GLPI or KPI. However, within the crucial group of KS eyes,
247 both GLPI (accuracy of 0.21) and KPI (accuracy of 0.29) have rather poor results, while the
248 accuracy of PI₄ there is very acceptable (accuracy of 0.79).

249 This suggests the following clinical procedure to examine an individual eye. First, one
250 computes GLPI (which has a high performance, close to the KPI's performance in all three
251 groups) as the main diagnose tool. If the value of GLPI suggests a regular cornea, we look at
252 PI₄: if it renders values above the normal threshold of 1, we classify the patient as a possible
253 keratoconus suspect, requiring further careful examination by the clinician before considering
254 him/her as a candidate for, say, refractive surgery.

255 Discussion

256 The Placido-based anterior corneal topography is an affordable and valuable tool for
257 screening for KC¹. Moderate and advanced KC can be reliably diagnosed by this method,
258 complemented with the biomicroscopic, retinoscopic and pachymetric study¹. Much more
259 challenging is the detection of this ectatic disorder in its very early or preclinical stages. In the
260 last years, much effort has been devoted to improve the analysis of the corneal topography
261 data in order to increase the ability to diagnose early clinical and subclinical KC cases. The
262 importance of an early detection of such cases lies in particular in screening out the candidates
263 for the refractive surgery procedures in these weakened and altered corneas. In this sense, a
264 variety of indices or markers have been proposed in the last three decades. The most well-
265 known and widely used ones are the Rabinowitz and Rabinowitz/McDonnell indices (K, I-S,
266 KISA%), and the Klyce/Maeda indices (KPI, KCI%), along with the vertical coma^{9,13},
267 although some others have also been defined³³. Almost all of them, in accordance with the
268 standard definition of KC, are based on a combination of pachymetry, curvature and corneal
269 power maps obtained by means of corneal topography devices. However, at least in the
270 devices based on Placido disk technology, the corneal power is not the directly measured

271 value but a product of a mathematical processing of the raw data, usually obtained under
272 certain a priori assumptions and by proprietary methods, as explained above. This was one of
273 the motivations for the introduction of new corneal irregularity indices³⁶ for the Placido disk
274 topographers, defined and analyzed in this work. All of them use exclusively the primary
275 data, that is, the image of the reflection of the mires on the anterior surface of the cornea,
276 bypassing the need to calculate the altimetric or curvature data. It should be stressed that these
277 new indices require only elementary arithmetic manipulation of the digitized images of the
278 mires, and do not intend to imitate the reconstruction of the altimetry or local curvature of the
279 cornea³². The aim of the current study was to evaluate in an available sample of normal,
280 keratoconic and preclinical keratoconic eyes these new topographic indices derived directly
281 from the analysis of the digitized images of the Placido rings, and to assess the potential of
282 these indices as a tool for keratoconus detection. We insist that the primary purpose of our
283 markers was not to replace but to complement the standard indices (KPI, KISA%, and others),
284 eventually providing the clinician with an additional information, especially in the borderline
285 and preclinical KC situations, by detecting an irregular cornea, independently of the type of
286 irregularity it presents.

287 Regarding the primary corneal indices defined by our research group, statistically
288 significant differences between the control and the KC groups were found for all indices.
289 Therefore, the primary indices defining different features of the Placido disk images reflected
290 on the cornea were able to discriminate between normal and KC corneas. A careful
291 observation of the ranges of values of the primary indices in the analyzed groups reveals that
292 there was a relevant area of overlapping for all parameter ranges of both groups. Therefore,
293 these two primary indices showed the best discriminating ability among normal and KC eyes.
294 PI_2 represents a measurement of the dispersion in the location of the centers of the fitted
295 circles to the mires projected on the cornea, considering the diameter of the set of centers as

296 well as their drift³². Therefore, it characterizes the behavior of the centers of mass of each
297 ring. The new PI_4 is an indicator of the global asymmetry of the mires. Specifically, this index
298 measures the slope of the regression line for the centers of the mires. In summary, the direct
299 analysis of the asymmetry of the digitized Placido disks projected on the cornea by means of a
300 corneal topography device allows an effective discrimination between normal and
301 keratoconus corneas.

302 In the case of the combined index, an excellent discriminating performance of the
303 GLPI (which can be interpreted as a percentage of irregularity) was observed. It was a perfect
304 classifier between keratoconic and normal eyes, and yielded results comparable to the KPI
305 when discriminating between the normal and subclinical KC eyes. Furthermore, a
306 combination of GLPI with PI_4 allows achieving an excellent capability of detection of
307 irregular corneas, considering as irregular both the keratoconic and the preclinical keratoconic
308 ones, as Table 6 shows. More specifically, all eyes in the KC group, as well as the majority of
309 the eyes in the preclinical KC group, were classified by this combination of indices as
310 irregular corneas. Thus, the use of the primary corneal indices characterizing the asymmetry
311 of the mires seems to be especially useful for KC detection, while their combination yields a
312 classification method with excellent discrimination ability between the three groups.

313 Along with the high sensitivity, another advantages of the corneal indices used in the
314 current study over the standard approaches are (a) their independence from the proprietary
315 algorithms of conversion of the raw ring images into curvature and corneal power, and (b) the
316 mathematical simplicity, with consequent very basic computational requirements. It is
317 convenient to remark that these indices can be easily adapted to any particular commercially
318 available Placido disk topographer; keep in mind that these devices are simple, relatively
319 affordable and easy to use, and represent a vast majority of the topographic devices available
320 in the clinical practice.

321 We should point out also that the primary goal in the design of our markers was not
322 the discrimination between types of pathology but rather a detection of irregularities on the
323 anterior corneal surface. In this sense, we were not trying to replace the standard indices for
324 the detection of KC (such as KPI, I-S or KISA%).

325 Currently, studies are being conducted in order to confirm the effectiveness of the
326 defined indices in the detection and characterization of other corneal conditions. The
327 correlation of these indices with higher order corneal aberrations and other optical quality
328 parameters should be also investigated in the future.

329 In conclusion, the analysis of the digitized images of the Placido disks projected on
330 the cornea is a valid and effective tool for the KC and preclinical KC screening that can be
331 used additionally to the existing keratometric criteria. At this stage of our study, we can
332 recommend them as a complementary screening tool designed to alert the clinician, especially
333 in the borderline cases of irregular corneas for which a more exhaustive examination is
334 recommended.

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345

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497 **Figure Legends**

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499 Figure 1: An example of a digitized mire (dots) and its approximation by the best-fit-
500 circle (left) and the best-fit-ellipse (right).

501

502 Figure 2: Centers C_k and the corresponding linear fit. Consecutive centers are
503 connected in order to visualize better their relative drift, illustrating the different
504 behaviors captured by indices PI_1 (maximum distance) and PI_2 (length of the path).

505

506 Figure 3: ROC curves for the redefined indices: PI_4 (left) and $AR(4)$ (right).

507

Table 1 – Mean and standard deviation values for the primary indices in the three groups in the database: Normal (N), Keratoconus (KC) and Keratoconus Suspect (KS).

| Primary Index | Normal group Mean (SD) | KC group Mean (SD) | KS group Mean (SD) |
|-----------------------|-----------------------------------|-------------------------------|-------------------------------|
| PI₁ | 21 (16) | 194 (131) | 31 (16) |
| PI₂ | 28 (15) | 166 (110) | 27 (13) |
| PI₃ | 28 (17) | 114 (90) | 17 (13) |
| PI₄ | 29 (23) | 208 (219) | 100 (77) |
| AR(4) | 34 (9) | 55 (19) | 52(9) |

Table 2 – Summary of the non-parametric tests of equality of means between the three groups. All values in the table are P-values for the Mann-Witney-Wilcoxon test and * meaning that significant differences (level 0.05) in the values of an index between groups were found.

| Primary Index | N vs KC | KC vs KS | N vs KS |
|-----------------------|----------------|-----------------|----------------|
| PI₁ | < 0.01 * | < 0.01 * | < 0.01 * |
| PI₂ | < 0.01 * | < 0.01 * | 0.47 |
| PI₃ | < 0.01 * | < 0.01 * | < 0.01 * |
| PI₄ | < 0.01 * | < 0.01 * | < 0.01 * |
| AR(4) | < 0.01 * | < 0.01 * | 0.49 |

Table 3 – Value of the area under the ROC curve (A_z ROC) for the indices when classifying between regular eyes (normal group) and irregular eyes (keratoconus group).

| Index | PI₁ | PI₂ | PI₃ | PI₄ | AR(4) | GLPI |
|-------------------------|-----------------------|-----------------------|-----------------------|-----------------------|--------------|-------------|
| A_zROC | 0.987 | 0.989 | 0.880 | 0.936 | 0.837 | 1.000 |

Table 4 – Accuracy estimates (proportion of individuals well-classified) of the GLPI index defined in (1), for Normal and Keratoconus groups.

| Measurement | Accuracy value |
|---|-----------------------|
| 5-fold cross-validation accuracy estimate | 0.95 |
| 10-fold cross-validation accuracy estimate | 0.94 |
| Leave-one-out cross-validation accuracy estimate | 0.94 |

Table 5 – Joint frequency distributions for KPI and I-S values within the Keratoconus Suspect (KS) group. Each cell contains the number of KS eyes with a value of I-S within the interval at the top of that column and a value of KPI within the interval at the left of that row. Non-shaded cells correspond to those eyes diagnosed as normal eyes by both indices KPI and I-S. Light grey cells are the eyes classified as anomalous by one of these indices, whereas dark grey cells are the eyes screened as abnormal by both of them.

| KPI \ I-S | [-0.3, 0.4) | [0.4, 1.5) | [1.5, 2) | [2, 3] |
|------------------|--------------------|-------------------|-----------------|---------------|
| [0,5) | 2 | 7 | 4 | 0 |
| [5, 23) | 0 | 2 | 2 | 1 |
| [23, 45) | 0 | 2 | 0 | 3 |
| [45, 55] | 0 | 0 | 0 | 1 |

Table 6 – Summary of results of classification ability of some of the proposed indices and the KPI. All the values within the table are the accuracy of each index when classifying in the stated group.

| Index | Normal | KC | KC Suspects |
|-----------------------|---------------|-----------|--------------------|
| GLPI | 1.00 | 1.00 | 0.21 |
| KPI | 1.00 | 1.00 | 0.25 |
| PI₄ | 0.87 | 0.90 | 0.79 |

Figure
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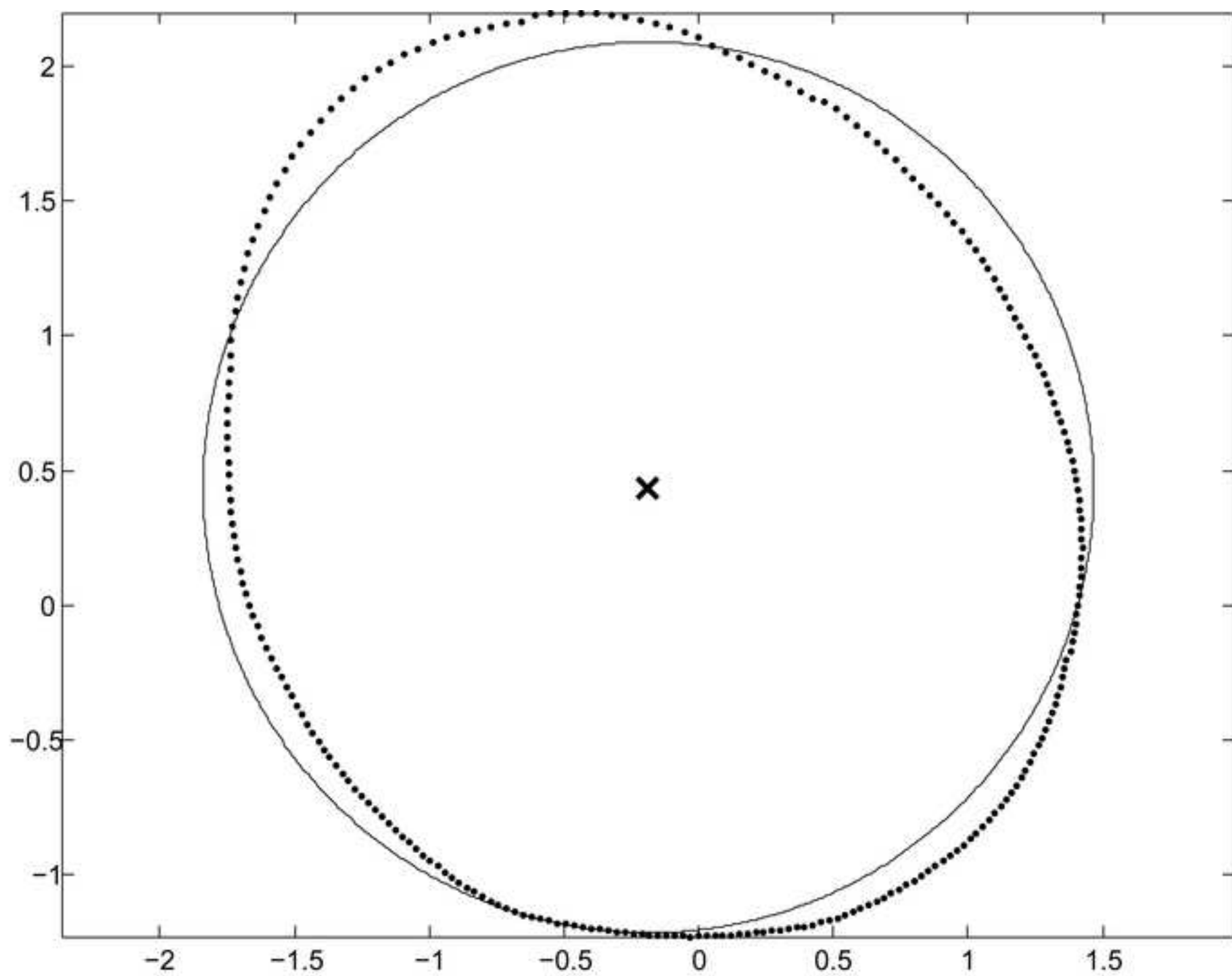


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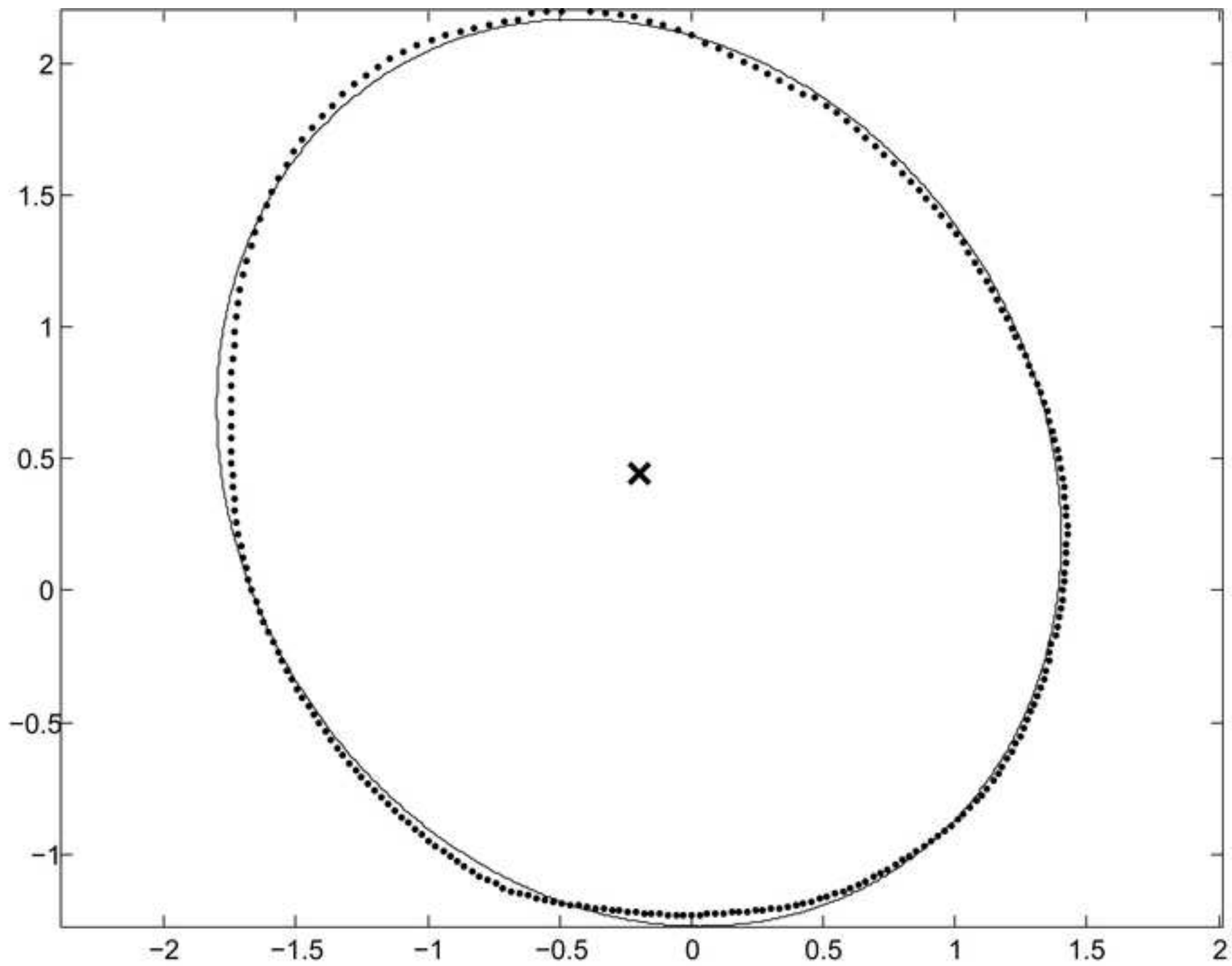


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