

# **Repeatability of corneal elevation maps in keratoconus patients using the tomography matching method**

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## **Financial Support**

This study was supported by the Natural Science Foundation of Zhejiang Province (LY16H120005, LY18A020008), the National Natural Science Foundation of China (81600712, 31771020), the Science and Technology Plan Project of Wenzhou Science and Technology Bureau (Y20170198), Scientific Research Project of Zhejiang Provincial Department of Education (Y201534199) and Projects of medical and health technology development program in ZheJiang Province (2016ZHB012, 2018RC057).

## **Highlights**

KC showed lower repeatability than healthy eyes.

Misalignments influenced more in corenal astigmatism than spherical corneal

curvature measurement.

The severity of KC was an important factor affecting the repeatability of Pentacam in KC patients.

**Running title**

Repeatability of corneal elevation measurement in keratoconus

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Number of words: 2782

1 **Abstract**

2 To assess repeatability of corneal tomography in successive measurements by  
3 Pentacam in keratoconus (KC) and normal eyes based on the Iterative Closest Point  
4 (ICP) algorithm. The study involved 143 keratoconic and 143 matched normal eyes.  
5 ICP algorithm was used to estimate six single and combined misalignment (CM)  
6 parameters, the root mean square (RMS) of the difference in elevation data pre  
7 (PreICP-RMS) and post (PosICP-RMS) tomography matching. Corneal keratometry,  
8 expressed in the form of M, J<sub>0</sub> and J<sub>45</sub> (power vector analysis parameters), was used to  
9 evaluate the effect of misalignment on corneal curvature measurements. The  
10 PreICP-RMS and PosICP-RMS were statistically higher (P <0.01) in KC than normal  
11 eyes. CM increased significantly (p =0.00), more in KC (16.76±20.88 μm) than in  
12 normal eyes (5.43±4.08 μm). PreICP-RMS, PosICP-RMS and CM were correlated  
13 with keratoconus grade (p <0.05). Corneal astigmatism J<sub>0</sub> was different (p=0.01) for  
14 the second tomography measurements with misalignment consideration (-1.11±2.35 D)  
15 or not (-1.18±2.35 D), while M and J<sub>45</sub> kept similar. KC corneas consistently show  
16 higher misalignments between successive tomography measurements and lower  
17 repeatability compared with healthy eyes. The influence of misalignment is evidently  
18 clearer in the estimation of astigmatism than spherical curvature. These higher errors  
19 appear correlated with KC progression.

20

21 **Keywords:** Keratoconus, corneal tomography; repeatability; ICP algorithm

## 22 **Introduction**

23 Keratoconus (KC), is a non-inflammatory progressive condition of the cornea and the  
24 most prevalent form of idiopathic corneal ectasia. It is characterized by localized  
25 thinning and conical protrusion of the cornea which results in regular and irregular  
26 astigmatism and decrease in visual quality <sup>1</sup>. Thinning of the cornea is initially found  
27 in the inferior-temporal and central zones <sup>2</sup> although superior localizations can also  
28 occur <sup>3</sup>. The progression and severity of keratoconus can be monitored by measuring  
29 the distribution of corneal thickness and the degree of protrusion.

30

31 Periodic corneal shape monitoring is currently the main method adopted to determine  
32 the progression of corneal thinning and protrusion in KC, and the effectiveness of  
33 management techniques such as collagen cross-linking (CXL) and rigid gas  
34 permeable lens wear in halting progression. Various corneal shape measurement  
35 methods exist including the Placido <sup>4,5</sup>, Scheimpflug <sup>6, 7</sup>, and Optical coherence  
36 tomography (OCT) <sup>8,9</sup>, all of which need to comply with strict repeatability criteria in  
37 order to provide reliable information on progression. Here the typically irregular  
38 surface of the keratoconic cornea presents a difficult challenge to achieving good  
39 repeatability of tomography measurements. A possible complication is that most  
40 tomography methods provide elevation data at a set of regularly-spaced discrete  
41 points, and therefore misalignment between successive measurements (either taken in  
42 the same setting to check repeatability or separated by a time period to check  
43 progression) can mean a different set of points is measured every time, leading to  
44 considerable differences in results. This study attempts to assess the effectiveness of a  
45 surface matching technology – an Iterative Closest Point (ICP) algorithm, developed  
46 in an earlier study <sup>10,11</sup>. As a feature-based surface matching technique and the  
47 dominant method for image registration, ICP checks the similarities between  
48 overlapping maps to determine the rigid-body transformations needed for the best  
49 possible match. ICP was employed in this study to estimate and correct for

50 misalignment between successive tomography measurements in KC and normal  
51 humans, and determine the effect of misalignment, before and after correction, on  
52 repeatability of tomography data.

53

## 54 **Results**

55 There was a wide range of BCVA (0.0 to 1.4, and -0.2 to 0.1) for KC and normal eyes,  
56 respectively. BCVA in KC was worse than in normal group ( $p < 0.01$ ). The mean  
57 values of RE were  $-5.10 \pm 4.32\text{D}$  ( $-19.50 \sim +4.50\text{D}$ ),  $-4.49 \pm 2.03\text{D}$  ( $-10.50 \sim +0.50\text{D}$ )  
58 for the spherical component, and  $-4.12 \pm 2.23\text{D}$  ( $-8.75 \sim 0.00\text{D}$ ),  $-0.81 \pm 0.55\text{D}$  ( $-2.75$   
59  $\sim 0.00\text{D}$ ) for the cylindrical component in KC and normal eyes, respectively.

60

61 Tomography matching results are shown in Tables 1 and 2. Representative images of  
62 KC case and normal case were provided in Fig. 1. After correcting for misalignment,  
63 PosICP-RMS was significantly lower than PreICP-RMS in both anterior and posterior  
64 surfaces and in both KC and normal eyes ( $p < 0.01$ ). The PreICP-RMS, PosICP-RMS  
65 and the misalignment ratio were significantly higher in the KC group compared with  
66 the control group ( $p < 0.01$ , Table 2). All of the misalignment parameters ( $x_0$ ,  $y_0$ ,  $z_0$ ,  $\alpha$ ,  
67  $\beta$ ,  $\gamma$ ) between successive measurements were not significantly different in the KC  
68 group compared to the control group ( $p > 0.05$ , Table 3), although CM was  
69 significantly higher in the KC group than in the control group ( $p < 0.01$ ).

70

71 The median of keratoconus grade was 3 with a range 1 to 4. Further, in both corneal  
72 surfaces of KC eyes, PreICP-RMS and PosICP-RMS were correlated with KC grade,  
73 and the correlations were much stronger in the anterior surface ( $r = 0.57$ ,  $0.55$ ,  
74 respectively) than in the posterior surface ( $r = 0.51$ ,  $0.41$ ). For the misalignment ratio,  
75 while it remained correlated with KC grade, the correlation was stronger in the  
76 posterior surface ( $r = 0.26$ ) than in the anterior surface ( $r = 0.21$ ) (Table 4). Further,  
77 CM was also significantly correlated with the KC grade ( $r = 0.48$ ) even though the

78 individual misalignment parameters ( $x_0$ ,  $y_0$ ,  $\alpha$ ,  $\beta$ ,  $\gamma$ ) did not show significant  
79 correlation ( $r= 0.06, 0.03, -0.06, 0.15, -0.07$ , respectively) with KC grade except for  $z_0$   
80 ( $r= -0.20$ ).

81

82 Further, while M,  $J_0$  and  $J_{45}$ , obtained before tomography matching were  $51.10\pm 6.21D$ ,  
83  $-1.18\pm 2.35D$  and  $-0.13\pm 1.50D$ , respectively, they slightly changed to  $51.08\pm 6.20D$ ,  
84  $-1.11\pm 2.35D$  and  $-0.11\pm 1.56D$  after correction. These changes were significant in  
85 only the case of  $J_0$  ( $p= 0.01$ ) but were insignificant in M ( $p= 0.64$ ) and  $J_{45}$  ( $p= 0.53$ ).

86

## 87 **Discussion**

88 Corneal shape assessment has evolved over the last few decades and is used  
89 extensively now in the diagnosis, staging and follow-up of keratoconus<sup>12</sup> and  
90 planning of refractive surgeries<sup>13</sup>. It provides anterior, and in some instruments  
91 posterior, surface tomography of the cornea that is derived from true elevation  
92 measurements<sup>14</sup>. The accuracy and repeatability of tomography measurements  
93 assume growing importance with the advent of new prophylactic and therapeutic  
94 corneal interventions such as intrastromal corneal ring segment implantation<sup>15</sup>,  
95 collagen crosslinking<sup>16</sup>, and deep lamellar keratoplasty<sup>17</sup>. The planning of these  
96 applications relies on elevation data that is reliable and repeatable within a few  
97 microns. This requirement is addressed in our study where the repeatability of corneal  
98 elevation measurements is assessed in both keratoconus patients and healthy controls  
99 using the Pentacam, which based on the Scheimpflug technology.

100

101 The literature showed the Scheimpflug system to have excellent repeatability in  
102 measuring corneal curvature in normal eyes<sup>18</sup> but uncertainty remains on its  
103 performance in keratoconic eyes. While some studies reported high reliability in  
104 evaluating the corneal curvature in keratoconus<sup>19,20</sup>, others, based on the examination  
105 of elevation data, showed poor repeatability<sup>21</sup>. In our study, the repeatability of

106 tomography data was significantly lower in keratoconic eyes than in the control group  
107 (Table 1). This finding was true when assessing the anterior and posterior surfaces and  
108 in the estimations of curvature and astigmatism ( $M$ ,  $p= 0.64$ ,  $J_0$ ,  $p=0.01$ ,  $J_{45}$ ,  $p= 0.53$ ).  
109 However, while a high repeatability of an instrument's measurements is an indication  
110 of its precision, measurements with low repeatability should be interpreted with  
111 caution. This is due to the possible misalignment between successive measurements,  
112 which may be due to unavoidable variations in eye alignment with the instrument.

113

114 Analysing the misalignment between successive measurements in our study showed  
115 that while individual misalignment parameters ( $x_0$ ,  $y_0$ ,  $z_0$ ,  $\alpha$ ,  $\beta$  and  $\gamma$ ) were not  
116 statistically different in KC eyes compared with the control group, the combined  
117 misalignment (CM) parameter showed a wide gap between KC and normal corneas  
118 ( $P<0.01$ ). This difference could be due to the particular difficulty in locating the apex  
119 in keratoconic eyes, which may lead to the larger fluctuation observed between  
120 measurement in comparison to the control group. Further, the apex, relative to which  
121 all elevation measurements are made, may not coincide with the corneal geometric  
122 centre in keratoconic eyes because of the typical regional protrusion and skewed  
123 hemi-meridians associated with the disease. Besides, the visual acuity in KC patients  
124 was poorer than in normal eyes ( $p<0.01$ ). The resulting difficulty in fixation and apex  
125 detection could therefore be behind the larger CM, and hence the reduced repeatability,  
126 in KC eyes seen in this study.

127

128 Further, since tomography measurements in the Pentacam system are based on the  
129 Scheimpflug image from the corneal surface, the clarity of the cornea is important to  
130 obtaining accurate measurements<sup>22</sup>. Anatomic changes reported in KC eyes, which  
131 include elongated epithelial cells at corneal apex<sup>23</sup>, alteration of regular arrangement  
132 of collagen fibrils<sup>24</sup>, and clear stromal spaces<sup>25</sup> may influence the optical clarity of  
133 cornea and affect the measurement accuracy for corneal tomography. Similar to  
134 previous studies<sup>26</sup>, the repeatability of Pentacam data observed in this study  
135 decreased in eyes with corneal thinning and contour changes in eyes, both of which

136 phenomenon are associated with KC progression. There is also a decrease in the  
137 corneal transparency secondary to alterations in the optical density of the stroma in  
138 KC which in turn causes increased scattering of light<sup>27</sup>.

139

140 In this study, an ICP algorithm, developed in earlier work<sup>10</sup> was used to estimate  
141 misalignment between each two successive tomography measurements. Correction for  
142 the small misalignments detected resulted in significantly reduced matching errors  
143 between successive maps from  $18.43 \pm 21.54 \mu\text{m}$  to  $6.35 \pm 4.58 \mu\text{m}$  ( $p < 0.01$ ) in anterior  
144 KC maps and from  $29.53 \pm 24.62 \mu\text{m}$  to  $19.62 \pm 11.79 \mu\text{m}$  ( $p < 0.01$ ) in posterior KC  
145 maps. In normal controls, the errors also reduced from  $5.12 \pm 3.07 \mu\text{m}$  to  $2.83 \pm 1.12 \mu\text{m}$   
146 ( $p < 0.01$ ) in anterior maps and from  $12.66 \pm 5.20 \mu\text{m}$  to  $11.08 \pm 4.72 \mu\text{m}$  ( $p < 0.01$ ) in  
147 posterior maps. Therefore, while correcting for misalignment significantly improved  
148 the repeatability of all measurements, there were residual errors which may be caused  
149 by optical distortion (possibly due to aberrations in Pentacam's measuring lens),  
150 measurement noise, and reduced accuracy in peripheral and posterior corneal regions.

151

152 The misalignment ratio, which is intended to quantify the part of the matching error  
153 caused by misalignment, was higher in KC eyes ( $55.20 \pm 19.99\%$  and  $27.01 \pm 16.83\%$  in  
154 anterior and posterior surfaces, respectively), compared with  $38.92 \pm 17.59\%$  and  
155  $12.54 \pm 11.4\%$  in normal controls. A further trend is the lower misalignment ratio seen  
156 in posterior than anterior surfaces, which may be caused by changes in corneal  
157 transparency or corneal refractive index<sup>27</sup>. These changes may have influenced the  
158 image resolution of tomography and amplified the effect of misalignments on corneal  
159 repeatability (PosICP-RMS increased in KC than control groups). The irregular  
160 surface and reduced transparency of the anterior cornea may also affect posterior  
161 region data acquisition and its interpretation<sup>28</sup>.

162

163 All the matching results for anterior corneal surface were correlated with keratoconus  
164 grade demonstrated that the repeatability of tomography measurements on Pentacam  
165 was lower for more advanced keratoconus than for early keratoconus, which was

166 consistent with a previous study<sup>29</sup>. The correlation between repeatability and the  
167 grade of keratoconus needs consideration when attempting to identify disease  
168 progression in order to make decisions for patients in relation to surgical intervention.

169

170 To our knowledge, this is the first report that evaluates the repeatability of corneal  
171 tomography measurements in keratoconic eyes and considers the effect of possible  
172 misalignment. Compared with normal eyes, KC showed higher misalignment errors,  
173 possibly causing which reduced data repeatability. The misalignment's effect was  
174 more pronounced in estimation of astigmatism than spherical curvature. Misalignment  
175 errors also correlated with keratoconus severity.

## 176 **Methods**

### 177 **Study participants**

178 Data were analyzed for 143 eyes of 143 KC patients (108 male and 35 female, age  
179  $21.32 \pm 5.51$  years), and the same number of eyes of 143 gender- and age-matched,  
180 healthy subjects (108 male and 35 female, age  $22.23 \pm 4.32$  years) who were recruited  
181 into the study at the Eye Hospital of Wenzhou Medical University. After complete  
182 clinical and imaging examinations, one independent corneal specialist (SHC)  
183 confirmed the diagnosis of keratoconus based on the criteria<sup>26</sup>: corneal topography  
184 showing an inferior steep spot or an asymmetric bow-tie pattern with or without  
185 skewed axes, at least one slit-lamp findings (apical thinning, Munson sign, Fleischer  
186 ring, Vogt striae and Rizutti sign). All subjects were able to fixate well at the  
187 designated target. The key exclusion criteria for both KC and healthy groups included  
188 wearing soft contact lenses within 2 weeks of involvement in study or wearing rigid  
189 contact lenses within 4 weeks, corneal astigmatism greater than 3.00 diopters (D)  
190 (except in the KC patients), corneal scarring or a prior history of surgical intervention  
191 such as corneal ring implantation, lamellar surgery or penetrating keratoplasty.

192

193 Further, the Tomographic Keratoconus Classification (TKC) system provided by the  
194 Pentacam software (OCULUS Optikgerate GmbH, Wetzlar, Germany) was used for  
195 keratoconus classification as indicated in previous studies<sup>30,31</sup>. The TKC offers a  
196 classification system with 5 grades: 0 (normal) to 4 (severe keratoconus). Where in  
197 some cases intermediate grades (eg, 2-3) are displayed, the lower value was recorded  
198<sup>30,31</sup>. Participants in the KC group had a TKC grade between 1 and 4, while members  
199 of the healthy group had a TKC grade of 0 in addition to satisfying the same gender  
200 and similar age conditions of match with the healthy group.

201

202 Data from only one randomly-selected eye of each participant was collected, where  
203 the randomization was based on a random number sequence (dichotomic sequence, 0  
204 and 1) that was created with Excel 2010. The study followed the tenets of the  
205 Declaration of Helsinki and was approved by the Scientific Committee of the Eye  
206 Hospital of WenZhou Medical University. Signed informed consent for online,  
207 open-access publication of images or information was obtained from all participants  
208 after explaining the procedures to them.

209

## 210 **Data Acquisition**

211 All participants underwent a standard ocular examination including slit-lamp  
212 microscopy, fundus examination, manifest refraction and tomography measurement.  
213 Best corrected visual acuity (BCVA) was recorded in LogMar units, and manifest  
214 refractive error (RE) was measured with a phoropter (Nidek RT-2100; Nidek Inc,  
215 Gamagori, Japan) in the conventional notation of sphere, negative cylinder, and  
216 cylindrical axis. The tomography data included corneal elevation maps of anterior and  
217 posterior surfaces provided by a Pentacam (OCULUS Optikgerate GmbH, Wetzlar,  
218 Germany). During data acquisition, subjects were instructed to fixate on the internal  
219 fixation lamp with room lights switched off. The device was moved back and  
220 realigned again after finishing each acquisition. Tomography measurements were  
221 taken by the same trained examiner (LFH), while the details were described in

222 previous studies <sup>10,32</sup>. All methods were performed in accordance with the relevant  
223 guidelines and regulations.

224

### 225 **Repeatability Analysis**

226 Iterative Closest Point (ICP) method, a feature-based registration and surface  
227 matching technique, was directly applicable to the featureful 3D shape of the corneal  
228 anterior and posterior surfaces. It was utilized to estimate and correct for  
229 misalignment between successive tomography measurements, as described in a  
230 previous study <sup>10</sup>. Misalignment was characterized by three translational parameters  
231 ( $x_0$ ,  $y_0$  and  $z_0$ ) and three rotational parameters ( $\alpha$ ,  $\beta$  and  $\gamma$ ), along with the combined  
232 misalignment parameter (CM) developed to synthesize the effect of all six  
233 misalignment components <sup>10</sup>.

234

235 The root mean square (RMS) of the difference in elevation data pre (PreICP-RMS)  
236 and post (PosICP-RMS) tomography matching based on the ICP algorithm between  
237 two successive tomography measurements was determined <sup>10</sup>. Further, a misalignment  
238 ratio, calculated as  $(1 - \text{PosICP-RMS} / \text{PreICP-RMS})$ , was used to describe the part of  
239 the error between two successive measurements that is caused by misalignment.

240

### 241 **Corneal keratometry calculation**

242 In order to evaluate the effect of misalignment on the corneal tomography  
243 measurements, corneal curvature and astigmatism in the central 3mm zone were  
244 calculated before and after correction for misalignment. According to the principal  
245 curvature method <sup>33,34</sup>, corneal keratometry was expressed in the form of  $M(x,y)$ , the  
246 local spherical equivalent of corneal optical power,  $J_0(x,y)$ , the local cylinder at  
247 0-degree meridian and  $J_{45}(x,y)$ , the local cylinder at 45-degree meridian. The  
248 distribution of corneal power vector across the aperture comprises the power vector  
249 map. A numerical integration method was then adopted to calculate  $M$ ,  $J_0$  and  $J_{45}$ ,  
250 which represent the average values of  $M(x,y)$ ,  $J_0(x,y)$  and  $J_{45}(x,y)$ , respectively, over a  
251 circular corneal aperture of 3 mm in diameter. The three parameters were intended to

252 provide measures of spherical power and astigmatism, and enable comparisons of  
253 corneal curvature before and after correction for misalignment.

## 254 **Statistical analysis**

255 The comparison of tomography matching results between KC and control groups were  
256 tested by the Mann-Whitney U test, while Wilcoxon test was utilized to compare the  
257 RMS and keratometry results before and after correction for misalignment. Data  
258 analysis was conducted using statistical software SPSS 20.0 (Chicago, USA) and a P  
259 value <0.05 was considered to be statistically significant. The correlation between the  
260 keratoconus grade and the tomography matching results was determined by Spearman  
261 correlation analyses. Using software G\*power for Windows (version 3.1.2, Franz Faul,  
262 Christian-Albrechts-Universität Kiel, Kiel, Germany), the sample size was calculated  
263 while an  $\alpha$  of 0.05 and a power of 0.95 for Wilcoxon-Mann-Whitney tests. The  
264 calculations showed that a sample size of at least 110 for each group was needed.

265

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**Author Contributions:**

**YRZ, LFH and YPZ:** analyzed data and drafted the manuscript.

**JJW, XBZ, WH:**and **BG** analyzed data and revised the draft.

**YRZ, LFH,** captured the elevation images of corneal surface and analyzed the data.

**QMW, SHC and AE:** revised the draft, proposed the idea and supervised the project.

**FJB:** designed the experiment, built initial constructs, analyzed data, proposed the idea and supervised the project.

All authors have read and approved the final manuscript.

**Additional Information:****Conflict of Interest**

The authors indicate no financial conflict of interest.

## Figure Captions:

**Figure 1** Distribution of elevation differences between successive corneal topography maps recorded before and after elimination of misalignment using ICP algorithm. The analysis was carried out for a randomly-selected KC case (A-D) and a gender- and age-matched (age difference less than 5 years) Normal case (E-H). Contour maps (A, B, E, F) show the elevation differences in the common region of two successive anterior corneal topographies recorded before (A, E) and after (B, F) elimination of misalignment, while contour maps (C, D, G, H) show corresponding elevation differences in the common region of posterior topographies recorded before and after elimination of misalignment. The eight contour maps share the same colour scale (upright in  $\mu\text{m}$ ). Before ICP correction of misalignment in the KC case, the RMS of fit error was  $87.11 \mu\text{m}$  for both anterior and posterior surfaces, considered simultaneously, and reduced to  $52.39 \mu\text{m}$  following the ICP correction. This can be compared to the Normal case where the RMS of fit error before ICP correction was  $9.09 \mu\text{m}$  for both anterior and posterior surfaces, considered simultaneously, and reduced to  $6.64 \mu\text{m}$  following the ICP correction.

**Table Captions:**

**Table 1** Matching errors between successive tomography measurements for keratoconic and normal eyes

**Table 2** Comparison of matching error results of the first and second measurement between keratoconus and control groups

**Table 3** Translational and rotational misalignments between successive tomography measurements

**Table 4** Correlation of keratoconus grade with matching error results of two successive tomography measurements

Table 1 Matching errors between successive tomography measurements for keratoconic and normal eyes

Group	Corneal surface	PreICP-RMS, $\mu\text{m}$	PosICP-RMS, $\mu\text{m}$	Misalignment ratio, %
Control	Anterior	5.12 $\pm$ 3.07	2.83 $\pm$ 1.12	38.92 $\pm$ 17.59
	Posterior	12.66 $\pm$ 5.20	11.08 $\pm$ 4.72	12.54 $\pm$ 11.40
Keratoconus	Anterior	18.43 $\pm$ 21.54	6.35 $\pm$ 4.58	55.20 $\pm$ 19.99
	Posterior	29.53 $\pm$ 24.62	19.62 $\pm$ 11.79	27.01 $\pm$ 16.83

PreICP-RMS and PosICP-RMS represent the root-mean-square of the elevation data obtained for corneal surfaces in successive measurements and presented both before and after tomography matching; Misalignment ratio =  $1 - (\text{PosICP-RMS} / \text{PreICP-RMS})$

Table 2 Comparison of matching error results of the first and second measurement between keratoconus and control groups

Corneal surface	PreICP-RMS, $\mu\text{m}$	PosICP-RMS, $\mu\text{m}$	Misalignment ratio
Anterior	0.000**	0.000**	0.000**
Posterior	0.000**	0.000**	0.000**

Mann-Whitney U test was used to compared the tomography matching results of control and keratoconus groups. PreICP-RMS and PosICP-RMS represent the root-mean-square error of the coordinate differences of corneal surface between two successive measurement before and after tomography matching, respectively; Misalignment ratio=  $1 - (\text{PosICP-RMS} / \text{PreICP-RMS})$ ; \* means  $P < 0.05$ , \*\* means  $P < 0.01$

Table 3 Translational and rotational misalignments between successive tomography measurements

Group	$\alpha$ , degree	$\beta$ , degree	$\gamma$ , degree	$x_0$ , $\mu\text{m}$	$y_0$ , $\mu\text{m}$	$z_0$ , $\mu\text{m}$	CM, $\mu\text{m}$
Control	-0.04±0.77	0.09±0.45	-0.37±2.42	12.49±60.77	4.36±99.77	-0.85±3.29	5.43±4.08
Keratoconus	-0.07±0.88	0.14±0.75	-0.21±3.81	16.1±81.4	5.14±85.34	-1.42±4.7	16.76±20.88
Comparison	0.527	0.518	0.053	0.662	0.699	0.171	0.000**

Mann-Whitney U test was used to compared the tomography matching results of control and keratoconus groups;  $\alpha$ ,  $\beta$ ,  $\gamma$  represent the rotational misalignments about the three main axes x, y and z, respectively, calculated for both the anterior and posterior corneal surfaces;  $x_0$ ,  $y_0$ ,  $z_0$  represent the translational displacements of anterior and posterior corneal surfaces; Combined misalignment parameter (CM) was developed to combine the effects of all six misalignment components; \* means  $P < 0.05$ , \*\* means  $P < 0.01$ .

Table 4 Correlation of keratoconus grade with matching error results of two successive tomography measurements

Periods	Corneal surface	PreICP-RMS (μm)	PosICP-RMS (μm)	Misalignment ratio (%)
Keratoconus grade	Anterior	0.57**	0.55**	0.21**
	Posterior	0.51**	0.41**	0.26**

PreICP-RMS and PosICP-RMS represent the root-mean-square differences between the elevation data of two successive measurements taken before and after tomography matching; Misalignment ratio =  $1 - (\text{PosICP-RMS} / \text{PreICP-RMS})$ ; Keratoconus grade is based on the Tomographic Keratoconus Classification system (TKC) provided by the Pentacam software, which allows classification into 5 grades: 0 (normal) to 4 (severe keratoconus). \* means  $P < 0.05$ , \*\* means  $P < 0.01$ .