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Performance of Updated Stress-Strain Index in Differentiating between Normal, Forme-Fruste, Subclinical and Clinical Keratoconic Eyes

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Abstract:	Purpose: This study seeks to evaluate the ability of the updated stress strain index (SSIv2) and other Corvis ST biomechanical parameters in distinguishing between keratoconus with different disease stages, and normal eyes. Design: Diagnostic accuracy analysis to distinguish disease stages. Methods: 1084 eyes were included and divided into groups of normal (199 eyes), forme fruste keratoconus (FFKC, 194 eyes), subclinical keratoconus (SKC, 113 eyes), mild clinical keratoconus (CKC-I, 175 eyes), moderate clinical keratoconus (CKC-II, 204 eyes) and severe clinical keratoconus (CKC-III, 199 eyes). Each eye was subjected to a Corvis ST examination to determine the central corneal thickness (CCT), biomechanically corrected intraocular pressure (bIOP), SSIv2 and other eight Corvis parameters including the SSIv1, SP-A1, A1T, ARTh, IIR, DAM, DARatio2 and CBI. The sensitivity and specificity of these parameters in diagnosing keratoconus were analyzed through receiver operating characteristic curves. Results: Before and after correction for CCT and bIOP, SSIv2 and ARTh were significantly higher, and IIR and CBI were significantly lower in the normal group than in the FFKC group, SKC group and the 3 CKC groups (all $P<0.05$). There were also significant correlations between the values of SSIv2, ARTh, IIR, CBI and the CKC severity (all $P<0.05$). AUC of SSIv2 was significantly higher than all other Corvis parameters in distinguishing normal eyes from FFKC, followed by IIR, ARTh and CBI. Conclusion: Corvis ST's updated SSI demonstrated superior performance in differentiating between normal and keratoconic corneas, and between corneas with different keratoconus stages. Similar, but less pronounced, performance was demonstrated by the IIR, ARTh and CBI.
Opposed Reviewers:	J. Crawford Downs cdowns@uab.edu

	Due to a direct competition and conflict of interest
Response to Reviewers:	Response to Reviewers' comments: If you could please make the following minor edits, your manuscript will be ready for acceptance: Submitted Design section in the Abstract: Design: This is a retrospective observational study. Suggested Design section for the Abstract: Design: Diagnostic accuracy analysis to distinguish disease stages. R: The text has been modified as suggested.

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Dear Editor,

We would like to resubmit the manuscript entitled "Performance of Corvis ST Parameters including Updated SSI in Differentiating between Normal, Forme-Fruste, Subclinical and Keratoconic Eyes" for publication in American Journal of Ophthalmology. Based on the recommendations of the reviewers, we rechecked and reanalyzed the data, which resulted in a change in the sample size in each group and addition of a new group-SKC. This article focuses on the ability of key biomechanical parameters from the Corvis ST to differentiate between different grades of conical corneas and finds that the updated stress-strain index demonstrates superior diagnostic efficacy. This study points to more reliable biomechanical indicators for the clinical diagnosis of early keratoconus, including forme fruste keratoconus and subclinical keratoconus. Based on the contributions in revision, we have changed the sequence of the authors. Requested information is listed below:

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We would like to suggest several potential referees who are experts in related fields:

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Due to a direct competition and conflict of interest, we request that J. Crawford Downs (cdowns@uab.edu) from Department of Ophthalmology, School of Medicine, University of Alabama at Birmingham, 1670 University Blvd., VH 390A, Birmingham, AL 35294, USA., is not considered as reviewer. With thanks for your consideration. If you need any information on our study, please let us know. We look forward to hearing from you.

Yours sincerely

ShiHao Chen, M.D, O.D.

FangJun Bao, M.D, Ph.D.

Response to Reviewers' comments:

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Performance of Corvis ST Parameters including Updated Stress-Strain Index in Differentiating between Normal, Forme-Fruste, Subclinical and Clinical Keratoconic Eyes

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Running title

Updated Stress-Strain Index in distinguishing Keratoconus

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Conclusion: Corvis ST's updated SSI demonstrated superior performance in differentiating between normal and keratoconic corneas, and between corneas with different keratoconus stages. Similar, but less pronounced, performance was demonstrated by the IIR, ARTh and CBI.

Keywords: forme fruste keratoconus; subclinical keratoconus, corneal biomechanics; updated stress-strain Index; Corvis ST

Background:

Keratoconus (KC) is considered a binocular asymmetric corneal ectatic disorder characterized by progressive corneal thinning and protrusion, resulting in compromised vision [1,2]. The pathogenesis of KC is still unclear, it was generally recognized that its progression was influenced by a combination of genetic and environmental factors [3]. Traditional hypotheses suggested that it was a non-inflammatory origin [4], however, some studies found higher inflammation-related cytokines in keratoconic corneas than in normal subjects [5,6]. Current consensus indicates that the occurrence and development of KC are closely related to regional changes in corneal biomechanical properties [7].

Although KC is a bilateral condition, it may take years for patients to show clinical symptoms in the fellow "normal" eye [8], which most researchers currently describe it as forme fruste KC (FFKC) or subclinical KC (SKC). We defined FFKC as the fellow eye of clinical keratoconus with normal slit-lamp biomicroscopy and no manifestation of topographic abnormalities [9]. We also defined SKC as the fellow eye of clinical keratoconus with normal slit-lamp biomicroscopy but slight manifestation of topographic abnormalities such as inferior–superior asymmetry and/or bow-tie pattern with skewed radial axes [9].

The detection of FFKC or SKC, which represents the condition of the fellow eye in KC patients with no clinical signs of manifest KC or obvious tomographic changes remains a challenge [10-12]. Previous studies further found that biomechanics deterioration occurs before the tomographic changes and development of evident clinical symptoms [13,14]. For these reasons, the in-vivo quantification of corneal biomechanics is of paramount importance for the timely introduction of treatments to halt disease progression before tomographic distortion, and associated vision deterioration take place, especially in SKC and FFKC cases [15-17].

The Ocular Response Analyzer (ORA, Reichert Technologies, Depew, NY) was the

first clinical device to assess corneal biomechanics in vivo [18]. It was followed by the Corvis ST (CVS, Oculus Optikgeräte GmbH, Wetzlar, Germany) which uses an air jet to apply a concentrated pressure on corneal apex, and a Scheimpflug camera to record the corneal response [19,20]. While the biomechanical parameters recorded by ORA and Corvis ST provided useful insight into corneal biomechanical performance, these parameters were found to be affected by central corneal thickness (CCT) [21,22] and intraocular pressure (IOP) [23,24].

More recently, a new Corvis ST parameter, the stress-strain index (SSIv1), was introduced to represent the corneal material stiffness, rather than the overall stiffness estimated by other Corvis ST parameters such as the stiffness parameter (SP) and the integrated inverse radius (IIR) [25]. The SSI was validated in healthy corneas, and found to be less affected by CCT and IOP than other parameters [25]. In a later development, a method was developed to convert the SSI from a single value into a map of corneal biomechanical stiffness, and this method can be used for both healthy and KC eyes [23]. The SSI was recently updated to better track the progression of KC and quantify the stiffening effect of cross-linking (CXL) [26]. This article sought to put this updated SSI (SSIv2) through another challenge and assess its ability to discriminate between normal and KC corneas, as well as distinguishing different disease stages including FFKC and SKC.

Patients and Methods:

In this retrospective, single-center study, the biometric parameters of 1084 eyes from 938 patients of the Refractive Surgery Center of the Eye Hospital were recorded. All the subjects were divided into six groups: a normal group (199 eyes), a forme fruste KC group (FFKC, 194 eyes), a subclinical KC group (SKC, 113 eyes) and three clinical keratoconus (CKC) groups. The CKC groups included a mild CKC group (CKC-I, 175 eyes), a moderate CKC group (CKC-II, 204 eyes) and a severe CKC group (CKC-III, 199 eyes). In normal group, one eye was randomly selected from each of the 199

patients with normal corneas who came to accept refractive surgery. On the other hand, the FFKC group included 194 eyes of 194 KC patients, with manifest KC in the fellow eye. All patients had a comprehensive ophthalmic examination, including the Corvis ST (CVS, software version 1.3b1445, OCULUS Optikgeräte, Wetzlar, Germany) and Pentacam HR examinations (Oculus Optikgeräte GmbH). Only measurements with acceptable quality were used in analysis.

Group criteria was listed in Table 1. The inclusion criteria for the normal group were that the general eye examination of both eyes showed normal corneas with normal slit-lamp biomicroscopy, corrected distance visual acuity of 20/20 or higher, an overall subjective normal topography map, and no history of ocular surgeries or trauma. The criteria for the CKC groups included distortion topographic characteristics (eg, skewed asymmetric bow-tie or inferior steepening) and at least one slit-lamp finding (eg, Munson's sign, Vogt's striae, Fleischer's ring, apical thinning, or Rizutti's sign) [27]. CKC was classified into three groups (Table 1, CKC-I, CKC-II and CKC-III) according to the topographic keratoconus classification (TKC) system [28,29] provided by Pentacam. 0, poss, 1, 1-2, 2, 2-3, 3, 3-4 and 4 are the different grades in TKC system. 0 means normal, poss means KC possible, and 1 to 4 describe mild KC to advanced KC with different severity in sequence. Patients classified as advanced keratoconus (TKC=3-4, 4) were not included in this study due to the limited number of cases after excluding corneal scars or opacities. The SKC group consisted of the fellow eyes of CKC corneas with slight abnormal corneal tomography, including inferior-superior localized steepening or an asymmetric bowtie pattern, but without detectable clinical signs on slit-lamp biomicroscopy and retinoscopy [30], and KC percentage index (KISA%) between 60 and 100 [31] or TKC= poss. The FFKC group consisted of the fellow eyes of CKC corneas, in which there were normal topography and normal slit-lamp examination including mean keratometry < 47.00 D [32], a KC percentage index (KISA%) score lower than 60 [31], a paracentral inferior–superior (I-S value) asymmetry value below 1.40 [32] and TKC= 0. Exclusion criteria included previous ocular surgery,

significant corneal scars, opacities, or any significant systemic diseases may potentially affect the outcomes. Soft contact lens wear was discontinued for at least 2 weeks before taking part in study, and rigid contact lens wear discontinued for at least 4 weeks.

Biomechanical evaluation

The Corvis ST examinations produced values of 11 variables, including the CCT, biomechanically corrected IOP (bIOP) and nine CVS parameters (Table S1), including SSIv2, SSIv1, the stiffness parameter at first applanation (SP-A1), first applanation time (A1T), Ambrósio relational thickness (ARTh), IIR, the maximum deformation amplitude (DAM), ratio between deformation amplitude at apex and at 2 mm nasal and temporal (DARatio2) and Corvis biomechanical Index (CBI). The SSIv1 was developed to measure corneal material stiffness in healthy corneas [25]. The later development of SSIv2 was based on a more comprehensive set of numerical models that incorporated changes in abnormal corneas. Theoretically, local corneal softening in a condition such as keratoconus and stiffening after treatments such as CXL as indicatded in previous studies based on other measurement methods [33,34] could be reflected by SSIv2 with more precision and greater repeatability than SSIv1 [26].

Statistical Analysis:

Statistical analysis was performed using the SPSS software (version 25, IBM Corp., Armonk, NY, USA) and Medcalc software (version 20.0.4, Medcalc Software bvba). Chi-square test was used to evaluate the gender ratio between groups, and one-way analysis of variance (one-way ANOVA) or Kruskal-Wallis tests was included to compare means of Corvis ST parameters among the 6 groups according to the results of the normality test. Bonfferoni correction was applied to the significance test results in the post hoc analysis. Analysis of covariance was performed to compare the biomechanical parameters of the 6 groups after controlling for the effect of CCT and bIOP through analysis of covariance (ANCOVA). The receiver operating characteristic (ROC) curve analysis was employed to identify the prediction accuracy of Corvis ST

parameters. The diagnostic efficiency of each parameter according to the corresponding area under the ROC curve (AUROC) was determined. Then the threshold, sensitivity, and specificity of each ROC curve were determined by identifying the point that was closest to point (0, 1) on the ROC curve. Delong test was used to compare the areas under curves (AUCs) of different parameters and AUCs of the same parameter in keratoconus at different stages. In this study, $P < 0.05$ indicated statistical significance.

Results:

The baseline data of the 6 groups are presented in Table 2, showing a match in age and gender ratio (all $P>0.05$). The differences in CCT were statistically significant between the three CKC groups and the normal group or the FFKC group (all $P < 0.05$). There were no statistically significant differences in CCT and bIOP between the FFKC and normal groups. There were no statistically significant differences in bIOP between the SKC, the CKC-I groups and the normal group (all $P>0.05$). There were statistically significant differences in CCT between SKC group and normal group as well as bIOP between CKC-II, CKC-III and normal group (all $P < 0.05$).

Between FFKC and normal group, no significant differences were found in SSIv1, SP-A1, DAM, DARatio2 and CBI (all $P > 0.05$, Tables 3 and 4). After correction for CCT and bIOP, SP-A1, DAM and CBI became significantly different ($P = 0.001$, $P = 0.013$ and $P < 0.001$, respectively), while SSIv1 and DARatio2 remained non-statistically significant. The SSIv2, A1T and ARTh were significantly lower, and IIR was significantly higher (all indicating lower stiffness) in the FFKC group than in the normal group (all $P < 0.05$), and similar results were found after correction for CCT and bIOP (Tables 3 and 4).

The differences in all parameters in the SKC and normal groups were statistically significant before correcting CCT and bIOP, and the trends in all parameters remained unchanged after correction except for the differences in SP-A1 and DARatio2 (all P =

1.000). The differences in SSIv2, SP-A1, ARTh, IIR and CBI were statistically significant between the SKC group and the FFKC group with or without correction. In contrast, there was no statistically significant difference between SSIv1 and A1T with or without correction (all $P < 0.05$). In addition, DAM and DARatio2 were statistically different before correcting CCT and bIOP, but the differences were not statistically significant after the correction (all $P > 0.05$, Table 4).

Furthermore, the SSIv2, SSIv1, SP-A1 and ARTh were significantly lower (indicating lower stiffness) in CKC groups than normal or FFKC groups (all $P < 0.05$, Tables 4). After correction for CCT and bIOP, similar trends were observed, while the difference in SP-A1 between the CKC-I and normal groups was not statistically significant (P=1.000). The difference in A1T was not statistically significant in the CKC-I group and the FFKC group, but was statistically significant in the CKC-II, CKC-III and the FFKC groups. After correction for CCT and bIOP, the differences in A1T between the CKC groups and FFKC group became non-significant (all $P = 1.000$). However, the differences in A1T between the CKC groups and normal group were statistically significant before and after correction (all $P<0.05$). The IIR, DAM, DARatio2 and CBI in the 3 CKC groups were also significantly higher (indicating lower stiffness) than the normal or FFKC groups (all $P < 0.05$, Tables 4). The exception after correcting for CCT and bIOP was in comparing DAM between the CKC-I group and FFKC group ($P = 1.000$) and the DARatio2 between CKC-I group and the FFKC gruop or normal group ($P = 0.555$, 1.000, respectively).

The differences in all parameters were not statistically significant when distinguishing between the SKC group and CKC-I group, either before or after correction (all $P <0.05$). The SSIv2, SSIv1, SP-A1 and ARTh were significantly lower in the CKC-II and CKC-III groups than in the SKC group before and after correction for CCT and bIOP (all $P<0.05$). The difference in A1T was not statistically significant in the CKC-II and the SKC groups (P=0.358), this result kept similar after correction (P=1.000). The

difference in A1T was statistically significant in the CKC-III group versus the SKC group ($P < 0.05$), and the result changed after correction for CCT and bIOP ($P=1.000$). The IIR, DAM, DARatio2, and CBI were significantly higher in the CKC-II and CKC-III groups than in the SKC group ($P < 0.05$), and the results were unchanged after correction for CCT and bIOP except for the comparison between CKC-II and SKC groups ($P = 1.000$).

Among the three CKC groups, all parameters showed significant differences in post-hoc analysis comparisons before correction except for the CBI of the CKC-II group and the CKC-III group before correction ($P = 0.117$). The A1T became non-significant after correcting for CCT and bIOP (all $P = 1.000$) but the difference of CBI between the CKC-II group and the CKC-III group became statistically significant. Meanwhile, CBI was not statistically significant in the comparison between CKC-I and CKC-III ($P = 1.000$) after correction. Further, DAM and DARatio2 changed significantly (all changes indicating stiffness decreases) with CKC severity (all $P < 0.01$) except when comparing CKC-I with CKC-II after correction for CCT and bIOP ($P = 1.000$, 0.133, respectively).

Overall, the results demonstrated that all stiffness parameters considered correlated significantly with CKC severity (all $P < 0.01$) including SSIv2 ($r = -0.788$), SSIv1 ($r = -0.579$), SP-A1 ($r = -0.641$), A1T ($r = -0.412$), ARTh ($r = -0.848$), IIR ($r = 0.811$), DAM ($r = 0.549$), DARatio2 ($r = 0.645$) and CBI ($r = 0.787$).

Table 5 shows the predictive accuracy of each Corvis parameter as well as the optimum cutoff value for each, leading to the highest overall sensitivity and specificity. To discriminate FFKC from normal eyes, the CVS parameter with the highest AUC was SSIv2 (0.915, 95% confidence interval (CI): 0.883-0.941), followed by IIR (0.731), ARTh (0.727), A1T (0.637), CBI (0.631), while DAM (0.595), SSIv1 (0.572), SP-A1 (0.519) and DARatio2 (0.514) had lower predictive accuracy. The SSIv2 also showed excellent ability to distinguish SKC from normal eyes with an AUC of 0.931, specificity

and sensitivity of 93.47% and 85.84%, respectively. In differentiating CKC-I from normal eyes, SSIv2, ARTh, IIR and CBI showed excellent ability (Table 5, AUC = 0.952, 0.928, 0.893, 0.881). For the diagnostic efficiency in differentiating CKC-II from normal eyes, the AUC values obtained for the SSIv2, ARTh, IIR and CBI were 0.998 (0.987-1.000), 0.994 (0.980-0.999), 0.984 (0.967-0.994) and 0.976 (0.956-0.989), respectively (all $P < 0.001$). Furthermore, in terms of the ability to distinguish CKC-III from normal eyes, the SSIv2 showed perfect performance with 1.000 AUC, 100% sensitivity, and 99.50% specificity. Also, all other seven biomechanical parameters showed excellent diagnostic ability except for A1T for which AUC = 0.850.

Moreover, SSIv2 provided excellent ability to distinguish FFKC from normal eyes, but its diagnostic efficiency was lower than that observed in differentiating SKC group (AUC=0.931), the CKC groups (AUC=0.952, 0.998, 1.000, respectively) from normal eyes. The same trend was noted with the other eight CVS parameters. The ROC curve analysis of normal corneas and clinical keratoconus at different disease stages showed that the AUCs of SSIv2 for all disease stages were > 0.95. Comparative analysis between these parameters showed that the AUC values of SSIv2 were also significantly higher than for all other eight CVS parameters ($P < 0.01$) in distinguishing normal eyes from FFKC eyes (Table 6). For these eight parameters, the efficiency in diagnosing FFKC was relatively low, but all the AUCs increased with higher keratoconus severity.

Discussion:

In the course of recognizing and exploring conical cornea, new parameters were constantly proposed and considered to excel in identifying FFKC or KC. For example, the CBI proposed by Riccardo et al. [19] in 2016 showed 98.4% specificity and 100% sensitivity in diagnosing KC, and the Tomographic and Biomechanical Index (TBI) proposed by Renato et al. [35] in 2017 showed 96.0% specificity and 90.4% sensitivity in distinguishing FFKC, which demonstrated progressive efforts to stage KC in its subclinical stages. In this study, we assessed Corvis ST parameters for diagnosing and

staging KC by comparing their values at different KC severity levels. Our results showed that corneal stiffness, as measured by these parameters was consistently lower in KC patients than in normal subjects. However, while many of the parameters effectively distinguished severe KC, only a few, such as SSIv2, IIR, ARTh and CBI performed well in identifying FFKC, SKC and mild CKC from normal subject.

The results of the study showed that some parameters (ARTh, IIR, and CBI) were good at diagnosing CKC with high accuracy (AUC > 0.9). However, when it comes to diagnosing FFKC, these same parameters were not as accurate (AUC < 0.75), which is consistent with what other studies have found [36]. Nevertheless, when comparing FFKC patients to normal individuals, there were significant differences in these parameters, indicating that they can still be useful in distinguishing between the two groups, but there is wide overlap between the two groups, making it harder to diagnose FFKC accurately. In addition, the CBI parameter was not good at diagnosing FFKC (AUC of 0.606), which was not surprising given the findings of other recent studies that also found CBI to be not effective at diagnosing FFKC (AUC of 0.667 [36], 0.710 [37], and 0.632 [38]). This means that more research is needed to determine if CBI is useful in diagnosing FFKC.

To differentiate SKC from normal subjects, SSIv2, ARTh, IIR, and CBI had superior performance (all AUC > 0.85), SSIv1, DAM and A1T showed moderate diagnostic efficacy for SKC eyes, while SP-A1 and DARatio2 behaved the lowest efficacy. SP-A1 and DARatio2 presented no statistically significant difference in between-group comparisons after correcting for CCT and bIOP.

Moreover, the A1T showed lower diagnostic efficacy compared to previous studies. Elham el al identified A1T's excellent ability to detect KC with AUC of 0.955, and when controlled for CCT, A1T still demonstrated excellent diagnostic ability with AUC of 0.904 [39]. Other studies indicated that the diagnostic ability of A1T for FFKC was

limited with AUC of 0.594 [37] and 0.660 [36]. Tommy et al. compared the Corvis ST parameters of the SKC and normal groups and found that A1T had an AUC of 0.750 with a specificity of 82.4% and a sensitivity of 46.9% [40]. Another prospective diagnostic test study found an AUC of 0.697 for A1T diagnosis of SKC [27]. Our study showed a similar trend, with AUC values of 0.673, 0.775 and 0.850 for A1T in distinguishing CKC-I to CKC-III from the normal group, and 0.637 and 0.698 for distinguishing FFKC and SKC from the normal group. The differences in results may be caused by variations in bIOP and CCT distributions in different studies.

Kataria et al [41] reported that SP-A1 had a good ability to diagnose mild KC (AUC = 0.913) and Heidari el al [27] reported a reasonable ability to diagnose SKC (AUC = 0.779). The ability to identify FFKC was not as high, with AUC of 0.716 [42]. In our study, the corresponding AUC values were 0.519, 0.647, 0.679, 0.859 and 0.967 for diagnosing FFKC, SKC, CKC-I, CKC-II, CKC-III and FFKC eyes. Furthermore, the diagnostic efficacy of SP-A1 in our study for detecting FFKC and SKC was lower than the 0.7 level found in previous studies.

An earlier study stated that DARatio2 played a limited role in the diagnosis of FFKC, with AUC values of 0.648, sensitivity of 48.9% and specificity of 79.70% [38]. Previous studies have shown moderate efficacy of DARatio2 in the diagnosis of SKC, with AUC values of 0.742 [27] and 0.613 [43]. However, the efficacy of this parameter was significantly higher in the diagnosis of KC with AUC values up to 0.921 [44] and 0.946 [45]. Our research showed a similar trend with AUC of 0.514, 0.678, 0.701, 0.856 and 0.956 in the diagnosis of FFKC, SKC, CKC-I, CKC-II and CKC-III.

Pablo Peña-García et al concluded that DAM was the best-isolated discriminant variable to diagnose FFKC eyes with an AUC of 0.775 [46]. However, Tian et al [47] and Lu et al [38] mentioned that DAM alone could not reliably distinguish FFKC from normal individuals with AUC of 0.603, 0.676, sensitivity of 27.8%/58.70% and specificity of

98.0%/71.10%. In our study, we found DAM had poor ability to diagnose FFKC with an AUC of 0.595. A retrospective, consecutive, non-randomized study by Cristina Peris-Martínez et al. found that the AUC value of the DAM in differentiating between SKC and normal samples was 0.805 before matching CCT and IOP, and the AUC value decreased to 0.663 after matching [12]. In our study, the AUC value of DAM was 0.704. Considering that our SKC group and normal group was matched with bIOP but not CCT, it might explain such a difference in results.

The SSI parameter was first introduced by Eliasy et al in 2019 as a corneal material stiffness parameter that was relatively independent of IOP and CCT, and showed positive correlation with age [25]. Although SSI was not introduced to distinguish between healthy and KC corneas, a prior study detected an average SSI reduction of 5% ($P = 0.173$) between healthy eyes and fellow eyes suffering from subclinical ectasia (fellow-eye with normal topography of very asymmetric ectasia, VAE-NT). There were also mean SSI reductions of 38.1% and 43.3% ($P < 0.01$) in moderate and severe KC subgroups, respectively, relative to VAE-NT [48]. Other studies had also supported the role of SSI in describing corneal stiffness and its deterioration in CKC [49]. However, in our study, SSIv1's diagnostic ability for FFKC was limited (AUC = 0.572), and its diagnostic efficacy in the SKC group and the three CKC subgroups with topographic changes was not as strong as with other parameters, such as IIR and ARTh.

An updated version of the SSI (SSIv2) was proposed by Eliasy [26] in 2020 to reduce correlation with CCT and bIOP. In our study, SSIv2 demonstrated superior diagnostic efficacy for all KC groups including the detection of FFKC, and maintained the same trends after correcting for CCT and bIOP. The AUC values of SSIv2 for CKC-I, CKC-II, and CKC-III were all over 0.95. For FFKC, it was 0.915 with remarkable high sensitivity (79.38%) and specificity (93.47%), and a notably lower false positive rate (FPR) of 6.53%. For SKC, it was 0.931 with sensitivity and specificity of 85.84% and 93.47%.

Accounting for the influence of CCT and bIOP on Corvis ST parameters [49,50], we matched CCT and bIOP, as well as gender ratio and age, in FFKC and normal groups. We matched bIOP, gender ratio and age in SKC and normal groups. In the CKC groups, the tomographical changes made it difficult to match in CCT and bIOP with normal, thus we were only able to match age and gender ratio. This partly explains the difference between our results and previous studies, which had varying matching requirements for CCT and bIOP. However, by including a larger sample size, we sought to minimize randomness and error, enhancing the reliability of our findings.

A previous study comparing Corvis ST biomechanical properties between Chinese and Caucasians found that the differences in SP-A1, ARTh, and SSI were statistically significant and that the properties were lower in Chinese populations [51]. Furthermore, the CBI which was created using data from Caucasian and South American populations [19], was also different in Chinese and Caucasians [51]. There are also differences in corneal morphology. A study using the Pentacam found that in healthy populations, the Chinese had smaller corneal diameters than North Americans, and higher anterior elevation at the thinnest point (BFS 8.0 mm) than North Americans, with statistically significant differences [52]. Also, that study found correlations between corneal diameter and Final D and the Progression Index [52]. Furthermore, the TBI parameter incorporated Final D as one of the machine learning factors [35]. We hypothesized that this racial difference in corneal morphology and material properties may directly or indirectly influence the efficacy of biomechanical parameters provided by Corvis ST, and make them behave a different range of sensitivity and specificity for one specific population versus another.

The main limitation of this study is that there was no long-term follow-up of the patients included in the study, resulting in a lack of longitudinal verification for the biomechanical parameters to establish their diagnostic effectiveness in different grades of keratoconus. This point will be considered in future studies.

To our knowledge, this is the first study comparing the diagnostic effectiveness of Corvis ST parameters including the updated stress-strain index in distinguishing between KC and normal eyes while matching data for multiple confounders. Our results show that some of the main Corvis ST parameters, particularly SSIv2, ARTh, IIR, and CBI, are correlated with keratoconus severity, indicating their excellent ability in classifying KC. As the disease worsens, the changes in between parameter values increase, making diagnosis easier. Relative to all other parameters, the updated SSI provides superior ability to distinguish between normal and keratoconic corneas and between the different stages of keratoconus including FFKC and SKC. On the other hand, ARTh, IIR, and CBI show similar but less pronounced performance in the FFKC and SKC group. Further validation is needed to determine SSIv2's potential for detecting FFKC and SKC in clinical settings. We also encourage peer researchers around the world to perform heterogeneous testing of SSIv2 across races and populations to better determine its specificity, sensitivity, and normal range.

Declarations

Ethics approval:

The study involves human participants and was approved by the Ethics Committee of the Eye Hospital, Wenzhou Medical University (ID: H2023-017-K-14).

Patient consent for publication:

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

Prof Elsheikh is a consultant to Oculus Optikgeräte GmbH

Authors' contributions

Design and conduct of the study (SHC, AElsheikh, FJB), data collection, analysis and interpretation (YYM, XMM, ZXQ, AEliasy, BWW, HX, PW, XBZ, JJW, YFY, FJB); Manuscript preparation and review (YYM, XMM, ZXQ, AEliasy, BWW, HX, PW, XBZ, JJW, YFY, SHC, AElsheikh, FJB). All authors read and approved the final manuscript.

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Table Captions

Table 1 Inclusion criteria for different keratoconus group

Table 2 Baseline biometric variable analysis

Table 3 Comparison of SSIv2, SSIv1 and other Corvis parameters among 6 different groups

Table 4 Post-hoc comparison of P values for each Corvis parameter for 6 different groups

Table 5 The diagnostic efficiency of SSIv2, SSIv1 and other Corvis parameters for different groups

Table 6 Comparison between AUC of Corvis parameters for Differentiating Forme Fruste Keratoconus, Subclinical Keratoconus, clinical Keratoconus and Normal cornea group

Table S1 Description of Corvis output parameters

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Performance of Corvis ST Parameters including Updated Stress-Strain Index in Differentiating between Normal, Forme-Fruste, Subclinical and Clinical Keratoconic Eyes

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Running title

Updated Stress-Strain Index in distinguishing Keratoconus

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Abstract

Purpose: This study seeks to evaluate the ability of the updated stress strain index (SSIv2) and other Corvis ST biomechanical parameters in distinguishing between keratoconus with different disease stages, and normal eyes.

Design: Diagnostic accuracy analysis to distinguish disease stages.

Methods: 1084 eyes were included and divided into groups of normal (199 eyes), forme fruste keratoconus (FFKC, 194 eyes), subclinical keratoconus (SKC, 113 eyes), mild clinical keratoconus (CKC-I, 175 eyes), moderate clinical keratoconus (CKC-II, 204 eyes) and severe clinical keratoconus (CKC-III, 199 eyes). Each eye was subjected to a Corvis ST examination to determine the central corneal thickness (CCT), biomechanically corrected intraocular pressure (bIOP), SSIv2 and other eight Corvis parameters including the SSIv1, SP-A1, A1T, ARTh, IIR, DAM, DARatio2 and CBI. The sensitivity and specificity of these parameters in diagnosing keratoconus were analyzed through receiver operating characteristic curves.

Results: Before and after correction for CCT and bIOP, SSIv2 and ARTh were significantly higher, and IIR and CBI were significantly lower in the normal group than in the FFKC group, SKC group and the 3 CKC groups (all $P<0.05$). There were also significant correlations between the values of SSIv2, ARTh, IIR, CBI and the CKC severity (all $P<0.05$). AUC of SSIv2 was significantly higher than all other Corvis parameters in distinguishing normal eyes from FFKC, followed by IIR, ARTh and CBI.

Conclusion: Corvis ST's updated SSI demonstrated superior performance in differentiating between normal and keratoconic corneas, and between corneas with different keratoconus stages. Similar, but less pronounced, performance was demonstrated by the IIR, ARTh and CBI.

Keywords: forme fruste keratoconus; subclinical keratoconus, corneal biomechanics; updated stress-strain Index; Corvis ST

Background:

Keratoconus (KC) is considered a binocular asymmetric corneal ectatic disorder characterized by progressive corneal thinning and protrusion, resulting in compromised vision [1,2]. The pathogenesis of KC is still unclear, it was generally recognized that its progression was influenced by a combination of genetic and environmental factors [3]. Traditional hypotheses suggested that it was a non-inflammatory origin [4], however, some studies found higher inflammation-related cytokines in keratoconic corneas than in normal subjects [5,6]. Current consensus indicates that the occurrence and development of KC are closely related to regional changes in corneal biomechanical properties [7].

Although KC is a bilateral condition, it may take years for patients to show clinical symptoms in the fellow "normal" eye [8], which most researchers currently describe it as forme fruste KC (FFKC) or subclinical KC (SKC). We defined FFKC as the fellow eye of clinical keratoconus with normal slit-lamp biomicroscopy and no manifestation of topographic abnormalities [9]. We also defined SKC as the fellow eye of clinical keratoconus with normal slit-lamp biomicroscopy but slight manifestation of topographic abnormalities such as inferior–superior asymmetry and/or bow-tie pattern with skewed radial axes [9].

The detection of FFKC or SKC, which represents the condition of the fellow eye in KC patients with no clinical signs of manifest KC or obvious tomographic changes remains a challenge [10-12]. Previous studies further found that biomechanics deterioration occurs before the tomographic changes and development of evident clinical symptoms [13,14]. For these reasons, the in-vivo quantification of corneal biomechanics is of paramount importance for the timely introduction of treatments to halt disease progression before tomographic distortion, and associated vision deterioration take place, especially in SKC and FFKC cases [15-17].

The Ocular Response Analyzer (ORA, Reichert Technologies, Depew, NY) was the

first clinical device to assess corneal biomechanics in vivo [18]. It was followed by the Corvis ST (CVS, Oculus Optikgeräte GmbH, Wetzlar, Germany) which uses an air jet to apply a concentrated pressure on corneal apex, and a Scheimpflug camera to record the corneal response [19,20]. While the biomechanical parameters recorded by ORA and Corvis ST provided useful insight into corneal biomechanical performance, these parameters were found to be affected by central corneal thickness (CCT) [21,22] and intraocular pressure (IOP) [23,24].

More recently, a new Corvis ST parameter, the stress-strain index (SSIv1), was introduced to represent the corneal material stiffness, rather than the overall stiffness estimated by other Corvis ST parameters such as the stiffness parameter (SP) and the integrated inverse radius (IIR) [25]. The SSI was validated in healthy corneas, and found to be less affected by CCT and IOP than other parameters [25]. In a later development, a method was developed to convert the SSI from a single value into a map of corneal biomechanical stiffness, and this method can be used for both healthy and KC eyes [23]. The SSI was recently updated to better track the progression of KC and quantify the stiffening effect of cross-linking (CXL) [26]. This article sought to put this updated SSI (SSIv2) through another challenge and assess its ability to discriminate between normal and KC corneas, as well as distinguishing different disease stages including FFKC and SKC.

Patients and Methods:

In this retrospective, single-center study, the biometric parameters of 1084 eyes from 938 patients of the Refractive Surgery Center of the Eye Hospital were recorded. All the subjects were divided into six groups: a normal group (199 eyes), a forme fruste KC group (FFKC, 194 eyes), a subclinical KC group (SKC, 113 eyes) and three clinical keratoconus (CKC) groups. The CKC groups included a mild CKC group (CKC-I, 175 eyes), a moderate CKC group (CKC-II, 204 eyes) and a severe CKC group (CKC-III, 199 eyes). In normal group, one eye was randomly selected from each of the 199

patients with normal corneas who came to accept refractive surgery. On the other hand, the FFKC group included 194 eyes of 194 KC patients, with manifest KC in the fellow eye. All patients had a comprehensive ophthalmic examination, including the Corvis ST (CVS, software version 1.3b1445, OCULUS Optikgeräte, Wetzlar, Germany) and Pentacam HR examinations (Oculus Optikgeräte GmbH). Only measurements with acceptable quality were used in analysis.

Group criteria was listed in Table 1. The inclusion criteria for the normal group were that the general eye examination of both eyes showed normal corneas with normal slit-lamp biomicroscopy, corrected distance visual acuity of 20/20 or higher, an overall subjective normal topography map, and no history of ocular surgeries or trauma. The criteria for the CKC groups included distortion topographic characteristics (eg, skewed asymmetric bow-tie or inferior steepening) and at least one slit-lamp finding (eg, Munson's sign, Vogt's striae, Fleischer's ring, apical thinning, or Rizutti's sign) [27]. CKC was classified into three groups (Table 1, CKC-I, CKC-II and CKC-III) according to the topographic keratoconus classification (TKC) system [28,29] provided by Pentacam. 0, poss, 1, 1-2, 2, 2-3, 3, 3-4 and 4 are the different grades in TKC system. 0 means normal, poss means KC possible, and 1 to 4 describe mild KC to advanced KC with different severity in sequence. Patients classified as advanced keratoconus (TKC=3-4, 4) were not included in this study due to the limited number of cases after excluding corneal scars or opacities. The SKC group consisted of the fellow eyes of CKC corneas with slight abnormal corneal tomography, including inferior-superior localized steepening or an asymmetric bowtie pattern, but without detectable clinical signs on slit-lamp biomicroscopy and retinoscopy [30], and KC percentage index (KISA%) between 60 and 100 [31] or TKC= poss. The FFKC group consisted of the fellow eyes of CKC corneas, in which there were normal topography and normal slit-lamp examination including mean keratometry < 47.00 D [32], a KC percentage index (KISA%) score lower than 60 [31], a paracentral inferior–superior (I-S value) asymmetry value below 1.40 [32] and TKC= 0. Exclusion criteria included previous ocular surgery,

significant corneal scars, opacities, or any significant systemic diseases may potentially affect the outcomes. Soft contact lens wear was discontinued for at least 2 weeks before taking part in study, and rigid contact lens wear discontinued for at least 4 weeks.

Biomechanical evaluation

The Corvis ST examinations produced values of 11 variables, including the CCT, biomechanically corrected IOP (bIOP) and nine CVS parameters (Table S1), including SSIv2, SSIv1, the stiffness parameter at first applanation (SP-A1), first applanation time (A1T), Ambrósio relational thickness (ARTh), IIR, the maximum deformation amplitude (DAM), ratio between deformation amplitude at apex and at 2 mm nasal and temporal (DARatio2) and Corvis biomechanical Index (CBI). The SSIv1 was developed to measure corneal material stiffness in healthy corneas [25]. The later development of SSIv2 was based on a more comprehensive set of numerical models that incorporated changes in abnormal corneas. Theoretically, local corneal softening in a condition such as keratoconus and stiffening after treatments such as CXL as indicatded in previous studies based on other measurement methods [33,34] could be reflected by SSIv2 with more precision and greater repeatability than SSIv1 [26].

Statistical Analysis:

Statistical analysis was performed using the SPSS software (version 25, IBM Corp., Armonk, NY, USA) and Medcalc software (version 20.0.4, Medcalc Software bvba). Chi-square test was used to evaluate the gender ratio between groups, and one-way analysis of variance (one-way ANOVA) or Kruskal-Wallis tests was included to compare means of Corvis ST parameters among the 6 groups according to the results of the normality test. Bonfferoni correction was applied to the significance test results in the post hoc analysis. Analysis of covariance was performed to compare the biomechanical parameters of the 6 groups after controlling for the effect of CCT and bIOP through analysis of covariance (ANCOVA). The receiver operating characteristic (ROC) curve analysis was employed to identify the prediction accuracy of Corvis ST

parameters. The diagnostic efficiency of each parameter according to the corresponding area under the ROC curve (AUROC) was determined. Then the threshold, sensitivity, and specificity of each ROC curve were determined by identifying the point that was closest to point (0, 1) on the ROC curve. Delong test was used to compare the areas under curves (AUCs) of different parameters and AUCs of the same parameter in keratoconus at different stages. In this study, $P < 0.05$ indicated statistical significance.

Results:

The baseline data of the 6 groups are presented in Table 2, showing a match in age and gender ratio (all $P>0.05$). The differences in CCT were statistically significant between the three CKC groups and the normal group or the FFKC group (all $P < 0.05$). There were no statistically significant differences in CCT and bIOP between the FFKC and normal groups. There were no statistically significant differences in bIOP between the SKC, the CKC-I groups and the normal group (all $P>0.05$). There were statistically significant differences in CCT between SKC group and normal group as well as bIOP between CKC-II, CKC-III and normal group (all $P < 0.05$).

Between FFKC and normal group, no significant differences were found in SSIv1, SP-A1, DAM, DARatio2 and CBI (all $P > 0.05$, Tables 3 and 4). After correction for CCT and bIOP, SP-A1, DAM and CBI became significantly different ($P = 0.001$, $P = 0.013$ and $P < 0.001$, respectively), while SSIv1 and DARatio2 remained non-statistically significant. The SSIv2, A1T and ARTh were significantly lower, and IIR was significantly higher (all indicating lower stiffness) in the FFKC group than in the normal group (all $P < 0.05$), and similar results were found after correction for CCT and bIOP (Tables 3 and 4).

The differences in all parameters in the SKC and normal groups were statistically significant before correcting CCT and bIOP, and the trends in all parameters remained unchanged after correction except for the differences in SP-A1 and DARatio2 (all P =

1.000). The differences in SSIv2, SP-A1, ARTh, IIR and CBI were statistically significant between the SKC group and the FFKC group with or without correction. In contrast, there was no statistically significant difference between SSIv1 and A1T with or without correction (all $P < 0.05$). In addition, DAM and DARatio2 were statistically different before correcting CCT and bIOP, but the differences were not statistically significant after the correction (all $P > 0.05$, Table 4).

Furthermore, the SSIv2, SSIv1, SP-A1 and ARTh were significantly lower (indicating lower stiffness) in CKC groups than normal or FFKC groups (all $P < 0.05$, Tables 4). After correction for CCT and bIOP, similar trends were observed, while the difference in SP-A1 between the CKC-I and normal groups was not statistically significant (P=1.000). The difference in A1T was not statistically significant in the CKC-I group and the FFKC group, but was statistically significant in the CKC-II, CKC-III and the FFKC groups. After correction for CCT and bIOP, the differences in A1T between the CKC groups and FFKC group became non-significant (all $P = 1.000$). However, the differences in A1T between the CKC groups and normal group were statistically significant before and after correction (all $P<0.05$). The IIR, DAM, DARatio2 and CBI in the 3 CKC groups were also significantly higher (indicating lower stiffness) than the normal or FFKC groups (all $P < 0.05$, Tables 4). The exception after correcting for CCT and bIOP was in comparing DAM between the CKC-I group and FFKC group ($P = 1.000$) and the DARatio2 between CKC-I group and the FFKC gruop or normal group ($P = 0.555$, 1.000, respectively).

The differences in all parameters were not statistically significant when distinguishing between the SKC group and CKC-I group, either before or after correction (all $P <0.05$). The SSIv2, SSIv1, SP-A1 and ARTh were significantly lower in the CKC-II and CKC-III groups than in the SKC group before and after correction for CCT and bIOP (all $P<0.05$). The difference in A1T was not statistically significant in the CKC-II and the SKC groups (P=0.358), this result kept similar after correction (P=1.000). The

difference in A1T was statistically significant in the CKC-III group versus the SKC group ($P < 0.05$), and the result changed after correction for CCT and bIOP ($P=1.000$). The IIR, DAM, DARatio2, and CBI were significantly higher in the CKC-II and CKC-III groups than in the SKC group ($P < 0.05$), and the results were unchanged after correction for CCT and bIOP except for the comparison between CKC-II and SKC groups ($P = 1.000$).

Among the three CKC groups, all parameters showed significant differences in post-hoc analysis comparisons before correction except for the CBI of the CKC-II group and the CKC-III group before correction ($P = 0.117$). The A1T became non-significant after correcting for CCT and bIOP (all $P = 1.000$) but the difference of CBI between the CKC-II group and the CKC-III group became statistically significant. Meanwhile, CBI was not statistically significant in the comparison between CKC-I and CKC-III ($P = 1.000$) after correction. Further, DAM and DARatio2 changed significantly (all changes indicating stiffness decreases) with CKC severity (all $P < 0.01$) except when comparing CKC-I with CKC-II after correction for CCT and bIOP ($P = 1.000$, 0.133, respectively).

Overall, the results demonstrated that all stiffness parameters considered correlated significantly with CKC severity (all $P < 0.01$) including SSIv2 ($r = -0.788$), SSIv1 ($r = -0.579$), SP-A1 ($r = -0.641$), A1T ($r = -0.412$), ARTh ($r = -0.848$), IIR ($r = 0.811$), DAM ($r = 0.549$), DARatio2 ($r = 0.645$) and CBI ($r = 0.787$).

Table 5 shows the predictive accuracy of each Corvis parameter as well as the optimum cutoff value for each, leading to the highest overall sensitivity and specificity. To discriminate FFKC from normal eyes, the CVS parameter with the highest AUC was SSIv2 (0.915, 95% confidence interval (CI): 0.883-0.941), followed by IIR (0.731), ARTh (0.727), A1T (0.637), CBI (0.631), while DAM (0.595), SSIv1 (0.572), SP-A1 (0.519) and DARatio2 (0.514) had lower predictive accuracy. The SSIv2 also showed excellent ability to distinguish SKC from normal eyes with an AUC of 0.931, specificity

and sensitivity of 93.47% and 85.84%, respectively. In differentiating CKC-I from normal eyes, SSIv2, ARTh, IIR and CBI showed excellent ability (Table 5, AUC = 0.952, 0.928, 0.893, 0.881). For the diagnostic efficiency in differentiating CKC-II from normal eyes, the AUC values obtained for the SSIv2, ARTh, IIR and CBI were 0.998 (0.987-1.000), 0.994 (0.980-0.999), 0.984 (0.967-0.994) and 0.976 (0.956-0.989), respectively (all $P < 0.001$). Furthermore, in terms of the ability to distinguish CKC-III from normal eyes, the SSIv2 showed perfect performance with 1.000 AUC, 100% sensitivity, and 99.50% specificity. Also, all other seven biomechanical parameters showed excellent diagnostic ability except for A1T for which AUC = 0.850.

Moreover, SSIv2 provided excellent ability to distinguish FFKC from normal eyes, but its diagnostic efficiency was lower than that observed in differentiating SKC group (AUC=0.931), the CKC groups (AUC=0.952, 0.998, 1.000, respectively) from normal eyes. The same trend was noted with the other eight CVS parameters. The ROC curve analysis of normal corneas and clinical keratoconus at different disease stages showed that the AUCs of SSIv2 for all disease stages were > 0.95. Comparative analysis between these parameters showed that the AUC values of SSIv2 were also significantly higher than for all other eight CVS parameters ($P < 0.01$) in distinguishing normal eyes from FFKC eyes (Table 6). For these eight parameters, the efficiency in diagnosing FFKC was relatively low, but all the AUCs increased with higher keratoconus severity.

Discussion:

In the course of recognizing and exploring conical cornea, new parameters were constantly proposed and considered to excel in identifying FFKC or KC. For example, the CBI proposed by Riccardo et al. [19] in 2016 showed 98.4% specificity and 100% sensitivity in diagnosing KC, and the Tomographic and Biomechanical Index (TBI) proposed by Renato et al. [35] in 2017 showed 96.0% specificity and 90.4% sensitivity in distinguishing FFKC, which demonstrated progressive efforts to stage KC in its subclinical stages. In this study, we assessed Corvis ST parameters for diagnosing and

staging KC by comparing their values at different KC severity levels. Our results showed that corneal stiffness, as measured by these parameters was consistently lower in KC patients than in normal subjects. However, while many of the parameters effectively distinguished severe KC, only a few, such as SSIv2, IIR, ARTh and CBI performed well in identifying FFKC, SKC and mild CKC from normal subject.

The results of the study showed that some parameters (ARTh, IIR, and CBI) were good at diagnosing CKC with high accuracy (AUC > 0.9). However, when it comes to diagnosing FFKC, these same parameters were not as accurate (AUC < 0.75), which is consistent with what other studies have found [36]. Nevertheless, when comparing FFKC patients to normal individuals, there were significant differences in these parameters, indicating that they can still be useful in distinguishing between the two groups, but there is wide overlap between the two groups, making it harder to diagnose FFKC accurately. In addition, the CBI parameter was not good at diagnosing FFKC (AUC of 0.606), which was not surprising given the findings of other recent studies that also found CBI to be not effective at diagnosing FFKC (AUC of 0.667 [36], 0.710 [37], and 0.632 [38]). This means that more research is needed to determine if CBI is useful in diagnosing FFKC.

To differentiate SKC from normal subjects, SSIv2, ARTh, IIR, and CBI had superior performance (all AUC > 0.85), SSIv1, DAM and A1T showed moderate diagnostic efficacy for SKC eyes, while SP-A1 and DARatio2 behaved the lowest efficacy. SP-A1 and DARatio2 presented no statistically significant difference in between-group comparisons after correcting for CCT and bIOP.

Moreover, the A1T showed lower diagnostic efficacy compared to previous studies. Elham el al identified A1T's excellent ability to detect KC with AUC of 0.955, and when controlled for CCT, A1T still demonstrated excellent diagnostic ability with AUC of 0.904 [39]. Other studies indicated that the diagnostic ability of A1T for FFKC was

limited with AUC of 0.594 [37] and 0.660 [36]. Tommy et al. compared the Corvis ST parameters of the SKC and normal groups and found that A1T had an AUC of 0.750 with a specificity of 82.4% and a sensitivity of 46.9% [40]. Another prospective diagnostic test study found an AUC of 0.697 for A1T diagnosis of SKC [27]. Our study showed a similar trend, with AUC values of 0.673, 0.775 and 0.850 for A1T in distinguishing CKC-I to CKC-III from the normal group, and 0.637 and 0.698 for distinguishing FFKC and SKC from the normal group. The differences in results may be caused by variations in bIOP and CCT distributions in different studies.

Kataria et al [41] reported that SP-A1 had a good ability to diagnose mild KC (AUC = 0.913) and Heidari el al [27] reported a reasonable ability to diagnose SKC (AUC = 0.779). The ability to identify FFKC was not as high, with AUC of 0.716 [42]. In our study, the corresponding AUC values were 0.519, 0.647, 0.679, 0.859 and 0.967 for diagnosing FFKC, SKC, CKC-I, CKC-II, CKC-III and FFKC eyes. Furthermore, the diagnostic efficacy of SP-A1 in our study for detecting FFKC and SKC was lower than the 0.7 level found in previous studies.

An earlier study stated that DARatio2 played a limited role in the diagnosis of FFKC, with AUC values of 0.648, sensitivity of 48.9% and specificity of 79.70% [38]. Previous studies have shown moderate efficacy of DARatio2 in the diagnosis of SKC, with AUC values of 0.742 [27] and 0.613 [43]. However, the efficacy of this parameter was significantly higher in the diagnosis of KC with AUC values up to 0.921 [44] and 0.946 [45]. Our research showed a similar trend with AUC of 0.514, 0.678, 0.701, 0.856 and 0.956 in the diagnosis of FFKC, SKC, CKC-I, CKC-II and CKC-III.

Pablo Peña-García et al concluded that DAM was the best-isolated discriminant variable to diagnose FFKC eyes with an AUC of 0.775 [46]. However, Tian et al [47] and Lu et al [38] mentioned that DAM alone could not reliably distinguish FFKC from normal individuals with AUC of 0.603, 0.676, sensitivity of 27.8%/58.70% and specificity of

98.0%/71.10%. In our study, we found DAM had poor ability to diagnose FFKC with an AUC of 0.595. A retrospective, consecutive, non-randomized study by Cristina Peris-Martínez et al. found that the AUC value of the DAM in differentiating between SKC and normal samples was 0.805 before matching CCT and IOP, and the AUC value decreased to 0.663 after matching [12]. In our study, the AUC value of DAM was 0.704. Considering that our SKC group and normal group was matched with bIOP but not CCT, it might explain such a difference in results.

The SSI parameter was first introduced by Eliasy et al in 2019 as a corneal material stiffness parameter that was relatively independent of IOP and CCT, and showed positive correlation with age [25]. Although SSI was not introduced to distinguish between healthy and KC corneas, a prior study detected an average SSI reduction of 5% ($P = 0.173$) between healthy eyes and fellow eyes suffering from subclinical ectasia (fellow-eye with normal topography of very asymmetric ectasia, VAE-NT). There were also mean SSI reductions of 38.1% and 43.3% ($P < 0.01$) in moderate and severe KC subgroups, respectively, relative to VAE-NT [48]. Other studies had also supported the role of SSI in describing corneal stiffness and its deterioration in CKC [49]. However, in our study, SSIv1's diagnostic ability for FFKC was limited (AUC = 0.572), and its diagnostic efficacy in the SKC group and the three CKC subgroups with topographic changes was not as strong as with other parameters, such as IIR and ARTh.

An updated version of the SSI (SSIv2) was proposed by Eliasy [26] in 2020 to reduce correlation with CCT and bIOP. In our study, SSIv2 demonstrated superior diagnostic efficacy for all KC groups including the detection of FFKC, and maintained the same trends after correcting for CCT and bIOP. The AUC values of SSIv2 for CKC-I, CKC-II, and CKC-III were all over 0.95. For FFKC, it was 0.915 with remarkable high sensitivity (79.38%) and specificity (93.47%), and a notably lower false positive rate (FPR) of 6.53%. For SKC, it was 0.931 with sensitivity and specificity of 85.84% and 93.47%.

Accounting for the influence of CCT and bIOP on Corvis ST parameters [49,50], we matched CCT and bIOP, as well as gender ratio and age, in FFKC and normal groups. We matched bIOP, gender ratio and age in SKC and normal groups. In the CKC groups, the tomographical changes made it difficult to match in CCT and bIOP with normal, thus we were only able to match age and gender ratio. This partly explains the difference between our results and previous studies, which had varying matching requirements for CCT and bIOP. However, by including a larger sample size, we sought to minimize randomness and error, enhancing the reliability of our findings.

A previous study comparing Corvis ST biomechanical properties between Chinese and Caucasians found that the differences in SP-A1, ARTh, and SSI were statistically significant and that the properties were lower in Chinese populations [51]. Furthermore, the CBI which was created using data from Caucasian and South American populations [19], was also different in Chinese and Caucasians [51]. There are also differences in corneal morphology. A study using the Pentacam found that in healthy populations, the Chinese had smaller corneal diameters than North Americans, and higher anterior elevation at the thinnest point (BFS 8.0 mm) than North Americans, with statistically significant differences [52]. Also, that study found correlations between corneal diameter and Final D and the Progression Index [52]. Furthermore, the TBI parameter incorporated Final D as one of the machine learning factors [35]. We hypothesized that this racial difference in corneal morphology and material properties may directly or indirectly influence the efficacy of biomechanical parameters provided by Corvis ST, and make them behave a different range of sensitivity and specificity for one specific population versus another.

The main limitation of this study is that there was no long-term follow-up of the patients included in the study, resulting in a lack of longitudinal verification for the biomechanical parameters to establish their diagnostic effectiveness in different grades of keratoconus. This point will be considered in future studies.

To our knowledge, this is the first study comparing the diagnostic effectiveness of Corvis ST parameters including the updated stress-strain index in distinguishing between KC and normal eyes while matching data for multiple confounders. Our results show that some of the main Corvis ST parameters, particularly SSIv2, ARTh, IIR, and CBI, are correlated with keratoconus severity, indicating their excellent ability in classifying KC. As the disease worsens, the changes in between parameter values increase, making diagnosis easier. Relative to all other parameters, the updated SSI provides superior ability to distinguish between normal and keratoconic corneas and between the different stages of keratoconus including FFKC and SKC. On the other hand, ARTh, IIR, and CBI show similar but less pronounced performance in the FFKC and SKC group. Further validation is needed to determine SSIv2's potential for detecting FFKC and SKC in clinical settings. We also encourage peer researchers around the world to perform heterogeneous testing of SSIv2 across races and populations to better determine its specificity, sensitivity, and normal range.

Declarations

Ethics approval:

The study involves human participants and was approved by the Ethics Committee of the Eye Hospital, Wenzhou Medical University (ID: H2023-017-K-14).

Patient consent for publication:

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

Prof Elsheikh is a consultant to Oculus Optikgeräte GmbH

Authors' contributions

Design and conduct of the study (SHC, AElsheikh, FJB), data collection, analysis and interpretation (YYM, XMM, ZXQ, AEliasy, BWW, HX, PW, XBZ, JJW, YFY, FJB); Manuscript preparation and review (YYM, XMM, ZXQ, AEliasy, BWW, HX, PW, XBZ, JJW, YFY, SHC, AElsheikh, FJB). All authors read and approved the final manuscript.

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b. Financial Disclosures:

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c. Other acknowledgements:

Not applicable.

Table Captions

Table 1 Inclusion criteria for different keratoconus group

Table 2 Baseline biometric variable analysis

Table 3 Comparison of SSIv2, SSIv1 and other Corvis parameters among 6 different groups

Table 4 Post-hoc comparison of P values for each Corvis parameter for 6 different groups

Table 5 The diagnostic efficiency of SSIv2, SSIv1 and other Corvis parameters for different groups

Table 6 Comparison between AUC of Corvis parameters for Differentiating Forme Fruste Keratoconus, Subclinical Keratoconus, clinical Keratoconus and Normal cornea group

Table S1 Description of Corvis output parameters

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Table 1: Inclusion criteria for different keratoconus group

Group	Inclusion criteria		
	Clinical sign criteria	Topographic criteria	TKC staging
FFKC	1. The fellow eyes of CKC corneas. 2. Without detectable clinical signs on slit-lamp, biomicroscopy and retinoscopy [30].	1. Normal topography examination including: a. Mean keratometry < 47.00 D [32]. b. KC percentage index (KISA%) score lower than 60 [31]. c. Paracentral inferior–superior (I-S value) asymmetry value below 1.40 [32].	TKC = 0
SKC		1. Slight abnormal corneal tomography, including at least one of below: a. inferior-superior localized steepening. b. an asymmetric bowtie pattern. 2. KC percentage index (KISA%) between 60 and 100 [31].	with or without TKC = poss
CKC-I	At least one slit-lamp finding including Munson's sign, Vogt's striae, Fleischer's ring, apical thinning, or Rizutti's sign [27].	Distortion topographic characteristics (eg, skewed asymmetric bow-tie or inferior steepening) [27].	TKC = 1 [28,29]
CKC-II			TKC = 1–2, 2 [28,29]
CKC-III			TKC = 2–3, 3 [28,29]

FFKC: forme fruste group, SKC: subclinical keratoconus group, CKC-I: mild clinical keratoconus group, CKC-II: moderate clinical keratoconus group; CKC-III: severe clinical keratoconus group. TKC means Topographic keratoconus classification (TKC) system provided by Pentacam. 0, poss, 1, 1-2, 2, 2-3, 3, 3-4 and 4 are the different grades in TKC system. 0 means normal, poss means KC possible, and 1 to 4 describe mild KC to advanced KC with different severity in sequence.

Table 2 Baseline biometric variable analysis

Variable	Groups						Comparison among 6 groups
	Normal	FFKC	SKC	CKC-I	CKC-II	CKC-III	
	Mean±SD/ Median(IQR)	Mean±SD/ Median(IQR)	Mean±SD/ Median(IQR)	Mean±SD/ Median(IQR)	Mean±SD/ Median(IQR)	Mean±SD/ Median(IQR)	P Value
Age (years)	22.75(4.99)	22.76(4.99)	21.46(7.65)	21.39(10.03)	22.92(9.10)	23.16±6.08	0.307
CCT (μm)	529.33(27.95)	526.00(42.95)	512.98±31.76	509.61±31.96	488.60±33.10	470.57±32.99	<0.001
bIOP (mmHg)	14.16±1.75	13.81(2.69)	13.85±2.17	13.88±1.86	13.60±2.09	12.73±2.38	<0.001
Gender Ratio (Female:Male)	56:143	48:146	31:82	54:121	52:152	61:138	0.687

CCT: central corneal thickness; bIOP: biomechanically-corrected Intraocular pressure; SD: standard deviation; IQR: Interquartile range, Normal: normal group; FFKC: forme fruste group, SKC: subclinical keratoconus group, CKC-I: mild clinical keratoconus group, CKC-II: moderate clinical keratoconus group; CKC-III: severe clinical keratoconus group

Table 3 Comparison of SSIv2, SSIv1 and other Corvis parameters among 6 different groups

Variable	Groups						Comparison among 6 groups
	Normal	FFKC	SKC	CKC-I	CKC-II	CKC-III	
	Mean±SD/ Median(IQR)	Mean±SD/ Median(IQR)	Mean±SD/ Median(IQR)	Mean±SD/ Median(IQR)	Mean±SD/ Median(IQR)	Mean±SD/ Median(IQR)	P Value
SSIv2	0.84(0.08)	0.72±0.08	0.68±0.11	0.66±0.09	0.59±0.08	0.51±0.09	<0.001
SSIv1	0.94±0.14	0.91±0.13	0.87±0.14	0.85±0.13	0.76(0.16)	0.67±0.12	<0.001
SP-A1	86.72(20.68)	88.19(25.66)	77.54±20.34	73.52(25.76)	61.62(22.38)	44.68±16.69	<0.001
A1T [ms]	7.37(0.27)	7.27±0.25	7.21±0.26	7.23±0.26	7.15±0.25	7.02±0.28	<0.001
ARTh	451.00(107.92)	387.61(103.48)	313.47±84.27	298.57(111.70)	216.29±73.57	151.43(54.74)	<0.001
IIR [mm^-1]	8.99(1.25)	9.56(1.26)	10.28(1.79)	10.69±1.16	12.05±1.27	13.96±1.87	<0.001
DAM	1.08±0.09	1.11±0.09	1.15±0.11	1.15±0.09	1.19±0.09	1.27(0.17)	<0.001
DARatio2	4.66(0.59)	4.76(0.61)	5.13±0.67	5.24(0.85)	5.76(0.98)	6.57(1.34)	<0.001
CBI	0.18(0.43)	0.40(0.68)	0.89(0.37)	0.96(0.33)	1.00(0.01)	1.00(0)	<0.001

SD: standard deviation; IQR: Interquartile range, Normal: normal group; FFKC: forme fruste group, SKC: subclinical keratoconus group, CKC-I: mild clinical keratoconus group, CKC-II: moderate clinical keratoconus group; CKC-III: severe clinical keratoconus group

Table 4 Post-hoc comparison of P values for each Corvis parameter for 6 different groups

Variable		P Value								
		FFKC VS Normal	SKC VS Normal	CKC-I VS Normal	CKC-II VS Normal	CKC-III VS Normal	SKC VS FFKC	CKC-I VS FFKC	CKC-II VS FFKC	CKC-III VS FFKC
SSIv2	Before correction	<0.001	<0.001	<0.001	<0.001	<0.001	0.042	<0.001	<0.001	<0.001
	After correction	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
SSIv1	Before correction	0.902	0.001	<0.001	<0.001	<0.001	0.207	0.004	<0.001	<0.001
	After correction	0.065	<0.001	<0.001	<0.001	<0.001	0.565	0.009	<0.001	<0.001
SP-A1	Before correction	1.000	0.002	<0.001	<0.001	<0.001	0.001	<0.001	<0.001	<0.001
	After correction	0.001	1.000	1.000	<0.001	<0.001	0.001	<0.001	<0.001	<0.001
A1T [ms]	Before correction	<0.001	<0.001	<0.001	<0.001	<0.001	0.696	1.000	<0.001	<0.001
	After correction	<0.001	<0.001	<0.001	<0.001	<0.001	1.000	1.000	1.000	1.000
ARTh	Before correction	0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	After correction	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
IIR [mm^-1]	Before correction	<0.001	<0.001	<0.001	<0.001	<0.001	0.001	<0.001	<0.001	<0.001
	After correction	<0.001	<0.001	<0.001	<0.001	<0.001	0.030	<0.001	<0.001	<0.001
DAM [mm]	Before correction	0.108	<0.001	<0.001	<0.001	<0.001	0.007	0.004	<0.001	<0.001
	After correction	0.013	<0.001	<0.001	<0.001	<0.001	0.198	1.000	0.036	<0.001
DARatio2	Before correction	1.000	<0.001	<0.001	<0.001	<0.001	0.001	<0.001	<0.001	<0.001

	After correction	1.000	1.000	1.000	0.010	<0.001	1.000	0.555	<0.001	<0.001
CBI	Before correction	1.000	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	After correction	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Normal: normal group; FFKC: forme fruste group, SKC: subclinical keratoconus group, CKC-I: mild clinical keratoconus group, CKC-II: moderate clinical keratoconus group; CKC-III: severe clinical keratoconus group

Table 5 The diagnostic efficiency of SSIv2, SSIv1 and other Corvis parameters for different groups

Variable	FFKC VS Normal group								
	AUC	95% CI	SE	Cut-off point	Sensitivity (%)	Specificity (%)	FPR (%)	FNR (%)	P
SSIv2	0.915	0.883-0.941	0.0137	≤0.773	79.38	93.47	6.53	20.62	<0.0001
SSIv1	0.572	0.521-0.621	0.0288	≤1.047	88.14	27.14	72.86	11.86	0.0128
SP-A1	0.519	0.468-0.569	0.0294	>91.490	44.56	65.66	34.34	55.44	0.5246
A1T [ms]	0.637	0.588-0.685	0.0277	≤7.424	76.29	44.72	55.28	23.71	<0.0001
ARTh	0.727	0.680-0.771	0.0256	≤405.202	61.86	77.39	22.61	38.14	<0.0001
IIR [mm^-1]	0.731	0.684-0.774	0.0249	>9.139	74.23	58.79	41.21	25.77	<0.0001
DAM [mm]	0.595	0.545-0.644	0.0286	>1.124	45.88	74.37	25.63	54.12	0.0009
DARatio2	0.514	0.463-0.564	0.0294	>4.676	57.73	52.02	47.98	42.27	0.6353
CBI	0.631	0.581-0.679	0.0281	>0.545	41.45	80.90	19.10	58.55	<0.0001

Variable	SKC VS Normal group								
	AUC	95% CI	SE	Cut-off point	Sensitivity (%)	Specificity (%)	FPR (%)	FNR (%)	P
SSIv2	0.931	0.897-0.956	0.0186	≤0.773	85.84	93.47	6.53	14.16	<0.0001
SSIv1	0.656	0.601-0.709	0.0321	≤0.967	83.19	40.20	59.80	16.81	<0.0001
SP-A1	0.647	0.592-0.701	0.0339	≤74.967	48.67	79.80	20.20	51.33	<0.0001
A1T [ms]	0.698	0.643-0.748	0.0321	≤7.251	58.04	74.87	25.13	41.96	<0.0001
ARTh	0.892	0.853-0.924	0.0201	≤390.473	84.07	81.41	18.59	15.93	<0.0001
IIR [mm^-1]	0.867	0.824-0.903	0.0222	>9.625	78.57	80.40	19.60	21.43	<0.0001
DAM [mm]	0.704	0.650-0.754	0.0319	>1.163	51.33	84.42	15.58	48.67	<0.0001
DARatio2	0.678	0.623-0.729	0.0324	>4.869	62.83	66.67	33.33	37.17	<0.0001
CBI	0.858	0.814-0.895	0.0231	>0.590	77.68	83.92	16.08	22.32	<0.0001
Variable	CKC-I VS Normal group								
	AUC	95% CI	SE	Cut-off point	Sensitivity (%)	Specificity (%)	FPR (%)	FNR (%)	P

SSIv2	0.952	0.926-0.972	0.0113	≤0.763	88.57	95.98	4.02	11.43	<0.0001
SSIv1	0.690	0.641-0.737	0.0271	≤0.855	57.14	72.86	27.14	42.86	<0.0001
SP-A1	0.679	0.629-0.726	0.0284	≤75.140	55.17	79.29	20.71	44.83	<0.0001
A1T [ms]	0.673	0.623-0.720	0.0279	≤7.254	53.71	74.37	25.63	46.29	<0.0001
ARTh	0.928	0.897-0.952	0.0133	≤368.200	83.43	88.44	11.56	16.57	<0.0001
IIR [mm^-1]	0.893	0.857-0.922	0.0167	>9.972	74.14	93.47	6.53	25.86	<0.0001
DAM [mm]	0.712	0.663-0.757	0.0265	>1.125	58.29	74.87	25.13	41.71	<0.0001
DARatio2	0.701	0.651-0.747	0.0273	>4.885	66.67	67.68	32.32	33.33	<0.0001
CBI	0.881	0.844-0.912	0.0178	>0.735	72.41	92.46	7.54	27.59	<0.0001

Variable	CKC-II VS Normal group								
	AUC	95% CI	SE	Cut-off point	Sensitivity (%)	Specificity (%)	FPR (%)	FNR (%)	P
SSIv2	0.998	0.987-1.000	0.0014	≤0.747	100.00	97.49	2.51	0.00	<0.0001
SSIv1	0.820	0.779-0.856	0.0206	≤0.860	79.41	70.85	29.15	20.59	<0.0001
SP-A1	0.859	0.821-0.892	0.0189	≤65.840	66.50	93.94	6.06	33.50	<0.0001

A1T [ms]	0.775	0.731-0.815	0.0228	≤7.250	66.67	74.87	25.13	33.33	<0.0001
ARTh	0.994	0.980-0.999	0.0024	≤332.171	97.06	94.97	5.03	2.94	<0.0001
IIR [mm^-1]	0.984	0.967-0.994	0.0060	>10.173	94.12	96.98	3.02	5.88	<0.0001
DAM [mm]	0.819	0.778-0.856	0.0208	>1.128	78.33	75.38	24.62	21.67	<0.0001
DARatio2	0.856	0.818-0.889	0.0192	>5.296	70.44	88.89	11.11	29.56	<0.0001
CBI	0.976	0.956-0.989	0.0074	>0.750	97.06	92.96	7.04	2.94	<0.0001

Variable	CKC-III VS Normal group								
	AUC	95% CI	SE	Cut-off point	Sensitivity (%)	Specificity (%)	FPR (%)	FNR (%)	P
SSIv2	1.000	0.990-1.000	0.0002	≤0.700	100.00	99.50	0.50	0.00	<0.0001
SSIv1	0.932	0.903-0.955	0.0123	≤0.763	81.91	92.96	7.04	18.09	<0.0001
SP-A1	0.967	0.944-0.982	0.0076	≤64.835	88.89	94.95	5.05	11.11	<0.0001
A1T [ms]	0.850	0.811-0.884	0.0190	≤7.160	71.86	85.43	14.57	28.14	<0.0001
ARTh	1.000	0.990-1.000	0.0003	≤307.240	100.00	98.49	1.51	0.00	<0.0001

IIR [mm^-1]	0.995	0.981-0.999	0.0050	>10.173	100.00	96.98	3.02	0.00	<0.0001
DAM [mm]	0.921	0.889-0.945	0.0132	>1.189	81.91	89.95	10.05	18.09	<0.0001
DARatio2	0.956	0.931-0.974	0.0109	>5.296	93.97	88.89	11.11	6.03	<0.0001
CBI	0.992	0.977-0.998	0.0041	>0.960	97.92	96.98	3.02	2.08	<0.0001

AUC: area under curve; CI: confidence interval; SE: standard error; P: probability. FPR: False positive rate; FNR: False negative rate, Normal: normal group; FFKC: forme fruste group, SKC: subclinical keratoconus group, CKC-I: mild clinical keratoconus group, CKC-II: moderate clinical keratoconus group; CKC-III: severe clinical keratoconus group

Table 6 Comparison between AUC of Corvis Parameters for Differentiating Forme Fruste Keratoconus, Subclinical Keratoconus, clinical Keratoconus and Normal cornea group

Parameter		SSIv2	SSIv1	SP-A1	A1T [ms]	ARTh	IIR [mm^-1]	DAM [mm]	DARatio2	CBI
FFKC VS Normal group	SSIv2	-	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	SSIv1	-	-	0.2901	0.0259	<0.0001	<0.0001	0.3133	0.1244	0.0716
	SP-A1	-	-	-	0.0246	<0.0001	<0.0001	0.1405	0.9740	0.0241
	A1T [ms]	-	-	-	-	0.0062	0.0003	0.1004	0.0003	0.9507
	ARTh	-	-	-	-	-	0.9989	0.0003	<0.0001	0.0001
	IIR [mm^-1]	-	-	-	-	-	-	<0.0001	<0.0001	0.0003
	DAM [mm]	-	-	-	-	-	-	-	0.0136	0.2077
	DARatio2	-	-	-	-	-	-	-	-	<0.0001
	CBI	-	-	-	-	-	-	-	-	-
SKC VS Normal group	SSIv2	-	<0.0001	<0.0001	<0.0001	0.1691	0.0001	0.0001	<0.0001	0.0119
	SSIv1	-	-	0.8528	0.1890	<0.0001	<0.0001	0.0565	0.3715	<0.0001
	SP-A1	-	-	-	0.0477	<0.0001	<0.0001	0.0643	0.2877	<0.0001
	A1T [ms]	-	-	-	-	<0.0001	<0.0001	0.8895	0.5470	<0.0001

	ARTh	-	-	-	-	-	0.2830	<0.0001	<0.0001	0.0847
	IIR [mm^-1]	-	-	-	-	-	-	<0.0001	<0.0001	0.8464
	DAM [mm]	-	-	-	-	-	-	-	0.6193	<0.0001
	DARatio2	-	-	-	-	-	-	-	-	<0.0001
	CBI	-	-	-	-	-	-	-	-	-
CKC-I VS Normal group	SSIv2	-	<0.0001	<0.0001	<0.0001	0.1659	<0.0001	<0.0001	<0.0001	<0.0001
	SSIv1	-	-	0.8128	0.5963	<0.0001	<0.0001	0.2708	0.5582	<0.0001
	SP-A1	-	-	-	0.7069	<0.0001	<0.0001	0.2146	0.3647	<0.0001
	A1T [ms]	-	-	-	-	<0.0001	<0.0001	0.1067	0.3459	<0.0001
	ARTh	-	-	-	-	-	0.0206	<0.0001	<0.0001	0.0004
	IIR [mm^-1]	-	-	-	-	-	-	<0.0001	<0.0001	0.4394
	DAM [mm]	-	-	-	-	-	-	-	0.8045	<0.0001
	DARatio2	-	-	-	-	-	-	-	-	<0.0001
	CBI	-	-	-	-	-	-	-	-	-
CKC-II VS	SSIv2	-	<0.0001	<0.0001	<0.0001	0.1377	0.0264	<0.0001	<0.0001	0.0087
	SSIv1	-	-	0.0999	0.0888	<0.0001	<0.0001	0.9787	<0.0001	<0.0001
	SP-A1	-	-	-	<0.0001	<0.0001	<0.0001	0.0298	0.8857	<0.0001

Normal group	A1T [ms]	-	-	-	-	<0.0001	<0.0001	0.0315	0.0022	<0.0001
	ARTh	-	-	-	-	-	0.1299	<0.0001	<0.0001	0.0196
	IIR [mm^-1]	-	-	-	-	-	-	<0.0001	<0.0001	0.5490
	DAM [mm]	-	-	-	-	-	-	-	0.0857	<0.0001
	DARatio2	-	-	-	-	-	-	-	-	<0.0001
	CBI	-	-	-	-	-	-	-	-	-
CKC-III VS Normal group	SSIv2	-	<0.0001	<0.0001	<0.0001	0.5061	0.3059	<0.0001	0.0001	0.0975
	SSIv1	-	-	0.0035	0.0001	<0.0001	<0.0001	0.4047	0.0711	<0.0001
	SP-A1	-	-	-	<0.0001	<0.0001	0.0038	<0.0001	0.3017	0.0001
	A1T [ms]	-	-	-	-	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	ARTh	-	-	-	-	-	0.3315	<0.0001	0.0001	0.1222
	IIR [mm^-1]	-	-	-	-	-	-	<0.0001	0.0011	0.9678
	DAM [mm]	-	-	-	-	-	-	-	0.0094	<0.0001
	DARatio2	-	-	-	-	-	-	-	-	0.0002
	CBI	-	-	-	-	-	-	-	-	-

Normal: normal group; FFKC: forme fruste group, SKC: subclinical keratoconus group, CKC-I: mild clinical keratoconus group, CKC-II: moderate clinical keratoconus group; CKC-III: severe clinical keratoconus group

Table S1: Description of Corvis output parameters.

Parameters short name	Description
SSIv2	updated stress-strain index
SSIv1	The stress-strain index
SP-A1	Stiffness parameter at first applanation
A1T	First applanation time
ARTh	Ambrósio relational thickness to the horizontal profile
IIR	Integrated inverse radius
DAM	Maximum deformation amplitude
DARatio2	Ratio between deformation amplitude at apex and at 2 mm nasal and temporal
CBI	Corvis Biomechanical Index

Table of Contents Statement

This article focuses on the ability of key biomechanical parameters from the Corvis ST to differentiate between different grades of conical corneas and finds that the updated stress-strain index demonstrates superior diagnostic efficacy. This study points to more reliable biomechanical indicators for the clinical diagnosis of early keratoconus, including forme fruste keratoconus and subclinical keratoconus.

FangJun Bao graduated with a PhD degree at Wenzhou Medical University (WMU) in 2015, worked in Eye Hospital, WMU as a refractive surgeon. He received “Richard C. Troutman Prize” from International Society of Refractive Surgery (ISRS) in 2022. His research interests include the investigation of keratoconus on imaging and corneal biomechanical properties, the assessment of the effects of regional variation of corneal constitutive parameters in keratoconus before and after corneal cross linking therapy and others.

Brief Introduction

Yuanyuan Miao received the M.D. degree from Wenzhou Medical University, Zhejiang, China in 2021. She is currently working toward the M.S. degree in Ophthalmology with the School of Ophthalmology & Optometry, Wenzhou Medical University, Zhejiang, China. Her research interests include biomechanical characteristic of keratoconus and early diagnosis of keratoconus.

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