An Exploratory Analysis of Forme Fruste Keratoconus Sensitivity Diagnostic Parameters

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Abstract

Purpose: To re-statistical analysis of the Pentacam or Corvis ST parameters from literatures, and to obtain more sensitive diagnostic parameters for clinical keratoconus (CKC) and forme fruste keratoconus (FFKC), respectively.

Methods: The parameters and the corresponding area of ROC curve (AUC) in previous studies were extracted and screened to obtain the database of CKC (Data-CKC) and FFKC (Data-FFKC), respectively. Two different importance evaluation methods (%IncMSE and IncNodePurity) of random forest were used to preliminary select the important parameters. Then, based on the partial dependency analysis, the sensitive diagnostic parameters that had promotion to the diagnostic performance were obtained. Data-FFKC was analyzed in the same way. Finally, a diagnostic test meta-analysis on the sensitive parameter of interest was conducted to verify the reliability of the above analysis methods.

Results: There were 88 parameters with 766 records in Data-CKC, 57 parameters with 346 records in Data-FFKC. Based on two importance evaluation methods, 60 important parameters were obtained, of which 20 were further screened as sensitive parameters of keratoconus, and most of these parameters were related to the thinnest point of cornea. The stiffness parameter at first applanation (SPA1) was the only Corvis ST output parameter sensitive to FFKC except the Tomographic and Biomechanical Index (TBI) and the Corvis Biomechanical Parameter (CBI). A total of 4 records were included in the meta-analysis of diagnostic tests on SPA1. The results showed that there was threshold effect, but no significant heterogeneity ($I^2=33\%$), and the area under the SROC curve was 0.87 (95% CI, 0.84-0.90).

Conclusions: the sensitive diagnostic parameters of keratoconus mainly include the 7 categories. The diagnostic value of SPA1, which represents the biomechanical properties of cornea, is worthy of further attention in the diagnosis of keratoconus in forme fruste keratoconus. Moreover, the morphological parameters based on the typical position of the thinnest point of corneal thickness have potential special significance for the diagnosis of disease.

Introduction

Keratoconus is a blinding eye disease characterized by corneal dilatation, thinning and forward conical protrusion. It often occurs in adolescence and usually presents bilateral asymmetry^[1, 2]. Despite extensive research in this field, the exact etiology of the disease is not clear.

For a long time, the diagnosis of keratoconus mainly depends on the typical morphological changes of cornea and the symptoms and signs^[3]. However, in recent years, it has been gradually proposed that the abnormality of corneal biomechanical behavior may be the main factor of the disease, and the change of corneal geometry is its secondary manifestation^[4]. Therefore, in addition to the analysis of the influence of morphological characteristics on the diagnosis of keratoconus, there are more and more studies on the diagnosis of keratoconus based on the biomechanical characteristics.

In clinics, Pentacam (Oculus, Optikgeräte GmbH, Wetzlar, Germany) and Corneal Visualization Scheimpflug Technology (Corvis ST; Oculus, Optikgeräte GmbH, Wetzlar, Germany) are currently the most widely used corneal morphological examination device and *in vivo* corneal biomechanics detection device, respectively. Among them, Pentacam has a good description for the measurement of corneal anterior and posterior surface elevation ^[5], curvature, and Corvis ST can better reflect the changes of corneal biomechanical characteristics by recording the whole process of corneal deformation in real time ^[6]. Although there were quite a lot of researches on the diagnosis and analysis of keratoconus using the above two devices, almost the parameters included in each study were different, and the stage, definition, sample size of keratoconus analyzed were also diverse. Thus, whether the results of each study are consistent, and which parameters are truly better sensitive diagnostic parameters, we still lack an overall analysis of these conclusions.

Therefore, this study is mainly to make a re-statistical analysis of the diagnostic performance of the parameters reported in the literature, that is, to screen out the better sensitive diagnostic parameters for clinical keratoconus (CKC) and forme fruste keratoconus (FFKC) respectively, based on the morphological heterogeneity reflected by Pentacam and the mechanical heterogeneity reflected by Corvis ST, so as to provide a reference for the early diagnosis of keratoconus.

Methods

Search strategy

We searched foreign language electronic databases of PubMed, Web of science and Chinese electronic databases of CNKI and Wanfang to collect the published studies on the evaluation of diagnostic efficiency of CKC or FFKC using Pentacam or Corvis ST devices. Since the diagnosis of CKC was relatively mature, as long as there was a clear description of its diagnosis and inclusion criteria in the literature, the CKC studied in the literature met the inclusion criteria of CKC in this study.

Due to the differences in the definition and inclusion criteria of early keratoconus in different literatures, the FFKC included in this study was restricted to the contralateral normal eyes of CKC and have no clinical and topographical features ^[3,7]. That is, at least two of the following conditions must be met: (1) a normal-appearing cornea on slit-lamp examination, retinoscopy, and ophthalmoscopy; (2) topography was normal with no asymmetric bowtie and no focal or inferior steepening pattern; (3) the level of topographic keratoconus classification (TKC) provided by Pentacam was normal, namely, it was “-”.

The retrieval languages were restricted to English and Chinese, in which the English search terms included: “keratoconus”, “Pentacam”, “Corvis ST”, “ROC”, and these search words were connected by using “and” or “or” for retrieval. The references of related articles were retrieved for additional publications. The publication period was from Jan. 2005 to Feb. 2020. Two investigators (HZ and XZ) independently searched the studies, screened identified abstracts and articles in duplicate, and extracted the available data from eligible studies.

Inclusion and exclusion criteria

Inclusions for analysis were restricted to: 1) Participants included in each literature were examined by Pentacam or Corvis ST; 2) The output parameters of Pentacam or Corvis ST and their corresponding AUC values were given in the literature; 3) The AUC values were either based on normal cornea and CKC, or based on normal cornea and FFKC.

Exclusion criteria applied were as follows: 1) Only Pentacam or Corvis ST were mentioned, but they were not the main analysis devices; 2) It did not belong to the analysis of the comparison between the CKC and the normal cornea or between the FFKC and the normal; 3) No explicit AUC value provided; 4) Other aspects of keratoconus were studied, such as repeatability and asymmetry; 5) reviews; 6) abstracts or full-text documents were not available; 5) studies reported by other language (non-Chinese, non- English).

Database establishment and organization

The following available information was extracted from the included literatures: title, the name of first author, the year of publication, two comparative research groups on which AUC was based, devices, parameters and their corresponding AUC values. And an initial information table was been developed to ensure the traceability of relevant information. Any differences in information abstraction were resolved by consensus and discussion with the other authors.

The databases of CKC (Data-CKC) and FFKC (Data-FFKC) were respectively obtained by sorting and filtering the data in the initial information table as follows:

1. Unified abbreviations for parameters with the same definition. Such as, the abbreviations of parameters characterizing the thickness of the thinnest point of cornea were unified as TP (corneal thickness at the thinnest point), the abbreviations of parameters characterizing the maximum indentation deformation amplitude are unified as HCDA (deformation amplitude at the highest concavity).
2. Merged parameters with similar definitions. Such as, except for the thickness of the thinnest point, the other corneal thickness parameters (central corneal thickness, corneal apex thickness, central pupil thickness) were classified as corneal thickness at the apex (AP).
3. Removed derived parameters from calculations, that is, if a parameter was not directly output by the device, but obtained by the researcher through calculation, it was removed.
4. Deleted the parameters with ambiguous definitions. Such as, some parameters were defined as the height of the anterior or posterior surface, but it is not clear whether they belonged to the maximum height of the cornea surface, the height at the apex of the cornea, or the height at the thinnest point of the cornea.
5. Deleted the parameters with only one record, that is, if a parameter had only one corresponding record, it was deleted.
6. For the parameters of diopter or radius of curvature, if it was not clearly indicated whether it belonged to the anterior or posterior surface of the cornea, it was the anterior surface by default.

The database was composed of parameters and their corresponding AUC values, among which, the former mainly represented the existence of parameters and belonged to the discrete variable. The existence of the parameter depended on whether the literature could provide the specific corresponding AUC value of the parameter. If it could be provided, it represented the existence of the parameter, and the value of the cross intersection was assigned as "1"; if not, it was "0". For Data-CKC, AUC value was obtained by comparing CKC with normal cornea, while for Data-FFKC, AUC value was obtained by comparing FFKC with normal cornea.

Statistical analysis

First of all, %IncMSE and IncNodePurity^[8, 9], these two different importance evaluation methods of Random Forest regression algorithm were used to preliminarily select the important parameters that had great influence on the AUC. Then, based on the partial dependence^[10], the preliminarily selected parameters were analyzed again, and the sensitive parameters that had positive promotion effect on the diagnosis of disease were obtained. Finally, we conducted a meta-analysis of the diagnostic test on the sensitive parameter of interest, which further demonstrated the high diagnostic ability of the parameter, and confirmed the validity and reliability of the method in this study.

In this study, Data-CKC was randomly divided into five groups, four of which were selected each time for Random Forest regression, and a total of five regressions were carried out. After each regression, the importance values of all parameters based on the two parameter importance evaluation methods were output respectively. We defined the weight of each parameter by using the ratio of the importance values of each parameter obtained each time and the maximum importance value in the result. Finally, the final importance values of each parameter in different importance evaluation methods were obtained by adding the five times weight values of each parameter. The first 30 important parameters of the important results obtained based on the two methods of %IncMSE and IncNodePurity (CKC-MSE, CKC-NP) were extracted respectively, and then the above parameters were analyzed in turn by using partial dependence analysis, so as to obtain the sensitive parameters for the keratoconus based on the existing studies. Take the same approach for Data-FFKC.

The threshold effect analysis was carried out for the eligible studies, that is, the Spearman correlation coefficient between sensitivity and specificity of the included studies was calculated, meanwhile, I^2 was used to test the heterogeneity^[11]. When there was no threshold effect and the heterogeneity was not obvious, the sensitivity and specificity were combined. When there was threshold effect, summary receiver operator characteristic (SROC) was drawn for subsequent evaluation. When there was moderate or above heterogeneity, the possible sources of heterogeneity can be explored from the aspects of research design, methodology and statistical methods. The publication bias was evaluated by using the Deek's funnel plot.

Modeling analysis and drawing were performed using R 3.6.1 software (R Foundation, Vienna, Austria; <https://www.R-project.org/>) and GraphPad Prism software version 8.0 respectively. Meta-analysis of diagnostic tests was performed by Stata software version 16.0 (Stata Corp, College Station, TX, USA).

Results

Literature retrieval and database construction

The detailed retrieval and inclusion and exclusion process was shown in Fig. 1. Data-CKC contained 88 parameters and 766 records, including 59 Pentacam output parameters and 539 records, 29 Corvis ST output parameters and 212 records, 1 combined parameters and 15 records. Among them, there were 105 records with AUC value of 0.99 and above, corresponding to 25 Pentacam output parameters, 4 Corvis ST output parameters and 1 combined parameter (Fig. 2A1&A2), and 587 records with AUC value of 0.80 and above, corresponding to 52 Pentacam output parameters, 25 Corvis ST output parameters and 1 combined parameter. Data-FFKC included 57 parameters and 346 records, including 41 Pentacam output parameters and 256 records, and 15 Corvis ST output parameters and 52 records, 1 combined parameters and 13 records. Among them, there were 114 records with AUC value of 0.80 and above, involving 25 Pentacam output parameters, 5 Corvis ST output parameters and 1 combined parameter (Fig. 2B1&B2). Definitions of all parameters included in this study were given in the *supplementary section*.

Screening results of sensitive diagnostic parameters

CKC-MSE and CKC-NP were the top 30 important parameters obtained by the two different importance evaluation methods of %IncMSE and IncNodePurity respectively, with a total of 36 parameters. Among them, CKC-MSE contained 19 Pentacam output parameters, 10 Corvis ST output parameters and 1 combined parameter, while CKC-NP contained 14 Pentacam output parameters, 15 Corvis ST output parameters and 1 combined parameter. Based on the partial dependence analysis of the above 36 parameters, 11 were found to be sensitive diagnostic parameters of CKC, that is, they had a positive promotion effect on AUC (Fig. 3A), and among them, parameter of surface variance (ISV), parameter of height decentration (IHD), BAD-D, the Tomographic and Biomechanical Index (TBI) and the Corvis Biomechanical Parameter (CBI) were both screened out in CKC-MSE and CKC-NP.

Similarly, FFKC-MSE and FFKC-NP contained 34 Pentacam output parameters, 6 Corvis ST parameters and 1 combined parameter TBI, totaling 41 parameters, of which 19 were sensitive diagnostic parameters for FFKC (Fig. 3B). And among these 19 parameters, 7 were both screened out from FFKC-MSE and FFKC-NP, namely maximum pachymetric progression parameter (PPI_{max}), IHD, BAD-D, Elevation of Back Surface in Thinnest Location (B.Ele.Th), TBI, the stiffness parameter at first applanation (SPA1) and CBI.

In summary, a total of 60 important parameters were obtained based on two importance evaluation methods, of which 20 were further screened as sensitive parameters of keratoconus. Of these 20 sensitive parameters, 8 were selected by two different importance evaluation methods, they are ISV, IHD, BAD-D, TBI, CBI, B.Ele.Th, PPI_{max}, and SPA1. Among them, IHD, BAD-D, TBI, CBI were all sensitive diagnostic parameters for FFKC and CKC, while PPI_{max}, B.Ele.Th and SPA1 were only sensitive diagnostic parameters for FFKC, and SPA1 was the only Corvis ST output parameter.

The results of the diagnostic test meta-analysis for SPA1

We used Stata software to conduct a meta-analysis of the diagnostic test on SPA1, which was the only Corvis ST output parameter that was sensitive to FFKC besides the TBI and CBI.

In Data-FFKC, there were 4 records related to SPA1, involving two articles (Table 1). The threshold effect was evaluated by the Spearman correlation coefficient (-0.949), with the *P* value of 0.051, showing that the threshold effect existed to certain extent. The summary receiver operator characteristic (SROC) curve based on the bivariate random effects model showed the AUC was 0.87 (95% CI, 0.84-0.90; Fig. 4A), indicating that it had good diagnostic performance. In addition, no obvious heterogeneity was found ($I^2=33\%$), and the ratio of heterogeneity possibly caused by threshold effect was 1, so there was no excessive analysis of other heterogeneity sources. There was no significant asymmetry in the Deek's funnel plot, indicating that the probability of publication bias was fairly small ($p=0.28$; Fig. 4B).

Table 1
Characteristics of studies included in the meta-analysis

Name	Year	Country	Cutoff	True Positive	False Positive	False Negative	True Negative
Kataria_a	2019	Indian	≤ 93.74	66	17	34	83
Kataria_b	2019	Indian	≤ 93.61	24	17	26	83
Liu_a	2018	China	≤ 97.1	26	3	3	27
Liu_b	2018	China	≤ 89.6	22	4	7	26

Discussion

Despite most of the studies have analyzed the diagnostic efficiency of the included parameters for the disease, we are still not sure whether there is a big deviation in the diagnostic efficiency of the parameters obtained in the existing studies, and which parameters are really considered as more meaningful parameters. Therefore, the main purpose of this study was to re-analyze the diagnostic parameters of keratoconus presented in published articles based on Pentacam, a typical morphological device, or Corvis ST, a device reflecting corneal biomechanical characteristics, to screen out the better sensitive diagnostic parameters for CKC and FFKC respectively, and to provide a further reference for the early diagnosis of keratoconus.

In this study, the 20 sensitive diagnostic parameters obtained by partial dependence analysis of important diagnostic parameters could be divided into the following 7 categories: mixed parameters (TBI, BAD-D), thickness progression parameters (ARTavg, ARTmax, PPIavg, PPImax and PPImin), typical thickness parameters (Thinnest point of the cornea, TP), surface morphological parameters (IVA, ISV, IHD,

KI), corneal volume parameters (CV 3), height parameters (F.Ele.Th, B.Ele.Th, AED_TP, PED_TP and PEmax), dynamic response parameters (CBI, SPA1).

In general, most of the 20 sensitive diagnostic parameters screened out in this study were related to the thinnest point of the cornea, such as thickness progression parameters, height parameters based on the thinnest cornea (F.Ele.Th, B.Ele.Th, AED_TP and PED_TP), and even TP itself was also selected as the sensitive diagnostic parameters of FFKC. It is well known that pachymetric progression index (PPI) is calculated as the progression value at different pachymetric rings, and Ambrósio's Relational Thickness (ART) expresses the ratio of the thinnest pachymetry and the respective pachymetric progression^[12, 13]. Moreover, AED_TP and PED_TP were the relative difference between the best fit sphere (BFS) elevation map and the enhanced elevation map at the thinnest point on the front and back surface of the cornea, in which the enhanced BFS has been modified to accentuate ectatic or conical regions (with exclusion of a 3.5 mm optical zone in the thinnest portion of the cornea)^[5, 12]. In summary, all these further indicated that various morphological parameters based on the typical position of the thinnest point of corneal thickness might have special significance for the diagnosis of keratoconus.

SPA1, as a stiffness parameter to resist corneal deformation under the action of air puff^[14], was found to be the only Corvis ST output parameter that was sensitive to forme fruste keratoconus but not sensitive to clinical keratoconus. Clinically, the morphology of FFKC is generally considered to be normal, so the function of the parameter SPA1 reflecting the overall corneal stiffness is easier to show. For CKC, in view of the obvious changes in its morphology, the parameters describing corneal morphology given by Pentacam play a major role in the diagnosis^[15]. This suggested that the parameters related to corneal biomechanics properties might indeed had potential importance in the diagnosis of forme fruste keratoconus.

In addition, the diagnostic test meta-analysis of SPA1 not only verified the diagnostic performance of SPA1 again, but also verified effectiveness and credibility of secondary screening of sensitive parameters by random forest regression to a certain extent. Furthermore, despite both the secondary parameter screening method and diagnostic test meta-analysis can comprehensively evaluate the diagnostic performance of an parameter, the latter is not convenient for the situation with a large number of parameters, while the former can analyze multiple parameters at one time, therefore, the secondary parameter screening method used in this study is also worthy of affirmation and application.

Of course, our study also had certain limitations. First of all, the number of morphological parameters and biomechanical parameters contained in the same database was quite different, that is, the former was often two or three times higher than the latter, mainly because the development of Corvis ST was several years later than Pentacam. Also, the purpose of this study was to obtain particularly sensitive parameters that could be used to diagnose CKC and FFKC respectively based on the information in the literature, rather than merely to analyze the consistency of the diagnostic performance of the same parameter in literatures. Therefore, those parameters with relatively common diagnostic performance had not been screened out.

In a word, the sensitive diagnostic parameters of keratoconus mainly include the following 7 categories: mixing parameters, thickness progression parameters, surface morphological parameters, corneal volume parameters, height parameters, typical thickness parameters and dynamic response parameters. Among them, the diagnostic value of SPA1, which represents the biomechanical properties of cornea, is worthy of further attention in the diagnosis of keratoconus in forme fruste keratoconus. Moreover, the morphological parameters based on the typical position of the thinnest point of corneal thickness have potential special significance for the diagnosis of disease.

Declarations

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Consent for publication

All authors have agreed to the submission for the article

Availability of data and material

Data can be shared upon request.

Code availability

Code can be shared upon request.

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Figures

Figure 1

Flow chart of study identification, exclusion, and inclusion

Figure 2

A Pie distribution of parameters meeting the diagnostic AUC value of clinical keratoconus greater than or equal to 0.99 (A1: Pentacam output parameters; A2: Corvis ST output parameters and combined parameter). B Pie distribution of parameters meeting the diagnostic AUC value of forme fruste keratoconus greater than or equal to 0.80 (B1: Pentacam output parameters; B2: Corvis ST output parameters and combined parameter).

Figure 3

Screening results of sensitive parameters of clinical keratoconus (A: CKC-MSE; CKC-NP) and forme fruste keratoconus (B: FFKC-MSE; FFKC-NP) based on %IncMSE and IncNodePurity. (The length of each blue and orange bar was the final importance values of each parameter in different importance evaluation methods. The "⊕" sign on the right side of the bar indicated the corresponding parameter was sensitive diagnostic parameter. SPA1, indicated by the "red four-pointed star" symbol, was the only Corvis ST output parameter that was sensitive to forme fruste keratoconus besides the Combined parameter TBI and Corvis ST output parameter CBI)

Figure 4

A The summary receiver operator characteristic (SROC) curve of SPA1 for the diagnosis of FFKC. The numerical value in each circle represents the number of the included studies in the meta-analysis. B The evaluation of the publication bias ($p = 0.28$).

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