Clinical Ocular Diagnostic Model of Marfan Syndrome in Patients With Congenital Ectopia Lentis by Pentacam AXL System

Tianhui Chen¹,², Jiahui Chen¹,², Guangming Jin³, Min Zhang¹,², Zexu Chen¹,², Danying Zheng³, and Yongxiang Jiang¹,²

¹ Department of Ophthalmology and Vision Science, Eye and ENT Hospital of Fudan University, Shanghai, China
² Key Laboratory of Myopia of State Health Ministry, and Key Laboratory of Visual Impairment and Restoration of Shanghai, Shanghai, China
³ State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China

Purpose: To construct an ocular diagnostic model of Marfan syndrome (MFS) distinguishing MFS from congenital ectopia lentis by the Pentacam AXL system.

Methods: Multivariable logistic regression was performed for the MFS ocular model. Furthermore, discrimination and calibration were validated externally. Data for 96 patients with ectopia lentis were assigned to the training cohort. Eighty patients with ectopia lentis were assigned to the test cohort. Diagnosis of MFS was based on the Ghent-2 criteria and diagnosis of congenital ectopia lentis in the control did not comply with the Ghent-2 criteria.

Results: The clinical model was based on the axial length/total corneal refractive power ratio. In the training cohort, the area under the receiver operating characteristic curve was 0.816 (95% confidence interval, 0.754–0.878) in the final model, which showed better performance than the previous minor criteria for diagnosis MFS of myopia of more than 3 diopters. In the test cohort, the area under the receiver operating characteristic curve was 0.818 (95% confidence interval, 0.718–0.918). In decision curve analysis, the net benefit of the model was better between threshold probabilities of 40% to 80%.

Conclusions: We demonstrated the value of the axial length/total corneal refractive power ratio as a potential diagnostic marker of MFS and clinical performance of diagnostic models, which may assist ophthalmologists in rapid identification of the patients at high risk of MFS.

Translational Relevance: This clinical ocular diagnostic model can be easily applied using the Pentacam AXL system. This model aids in the early differential diagnosis of MFS from other forms of congenital ectopia lentis, which may decrease the risk of developing severe ocular symptoms.
ectopia lentis during an observation period of 20 years were re-diagnosed with MFS according to the revised Ghent criteria. Therefore, because of the severity of MFS, patients diagnosed as isolated ectopia lentis should be re-evaluated.

Although congenital ectopia lentis is insufficient as a diagnostic criterion for the ocular system of MFS, ectopia lentis was given more weight in the Revised Ghent Nosology.6 Three minor ocular features in the Ghent-1 criteria, namely an abnormally flattened cornea, increased axial length (AL) of the eye, and a hypoplastic iris or hypoplastic ciliary muscle caused by decreased miosis, were replaced with myopia of greater than −3 diopters (D) for simplicity and to reduce the cost associated with imaging tests.7 In recent research, Konradsen et al.8,9 observed that 19 of 31 eyes (61.29%) of patients with MFS classified as having ectopia lentis had myopia of less than −3 D, whereas 33 of 46 patients (71%) with MFS without ectopia lentis had myopia of less than −3 D, indicating that myopia of greater than −3 D may not be a good marker of MFS. Because myopia of greater than −3 D is relatively common in the general population and other diseases such as Weill–Marchesani syndrome and primary lens dislocation cause similar ocular manifestations that can be confused with MFS, ophthalmologists face a significant challenge in identifying MFS.10

In our previous study, we observed significant differences between patients with MFS and non-MFS groups in terms of AL, corneal curvature and corneal astigmatism. These ocular parameters can be measured simply and accurately using the Pentacam AXL system, which may help ophthalmologists to distinguish MFS from congenital ectopia lentis in a timely manner.11

In this study, we aimed to construct and evaluate models based on ocular parameters to distinguish MFS from other types of congenital ectopia lentis. Our primary objectives were to (1) compare ocular parameters measured using the Pentacam AXL system between MFS and non-MFS groups; (2) construct the models in the training cohort by logistic regression; (3) perform a receiver operating characteristic (ROC) analysis and a decision curve analysis to evaluate the clinical performance of MFS diagnostic models; and (4) explore the efficiency of the AL/total corneal refractive power ratio (AL/TCRP) ratio as a diagnostic marker for MFS based on multicenter data. The Guidelines for Transparent Reporting of a Multivariable Model for Individual Prognosis or Diagnosis (the TRIPOD statement) have been followed in this cross-sectional study.

Materials and Methods

Ethics Statement

To build a diagnostic model for MFS, we collected data from the Eye and Ear, Nose and Throat (ENT) Hospital of Fudan University as the training cohort. Data collected from the Zhongshan Ophthalmic Center of Sun Yat-sen University (China) and the Eye and ENT Hospital of Fudan University were used as the test cohort. The study was approved by the Human Research Ethics committee of the Eye and ENT Hospital of Fudan University. The study adhered to the tenets of the Declaration of Helsinki. All of the participants provided signed informed consent.

Participants

Training Cohort

From May 2017 to October 2019, a total of 95 patients with congenital ectopia lentis were treated at the Eye and ENT Hospital of Fudan University. Participants with keratoconus, retinal detachment, a history of ocular surgery, microspherophakia, uveitis, corneal disease, glaucoma, or use of contact lenses in the 2 weeks before the examinations were excluded from this study. All cases of MFS had been confirmed by genetics testing. In total, 41 patients with congenital ectopia lentis in whom the diagnosis of MFS was ruled out (non-MFS groups) were matched for age and sex to the MFS group. Twenty-seven participants (65.9%) without MFS were diagnosed with other hereditary diseases such as homocystinuria by genetic testing. The training samples were obtained from 55 patients with MFS (107 eyes) and 41 patients without MFS with congenital ectopia lentis (79 eyes). A flow chart summarizing the selection of the training cohort is shown in Figure 1.

Test Cohort

The test cohort consisted of two parts: 42 eyes from 42 patients (21 patients with MFS and 21 patients without MFS) from Zhongshan Ophthalmic Center of Sun Yat-sen University and 38 eyes from 38 patients (17 patients with MFS and 21 patients without MFS) from the Eye and ENT Hospital of Fudan University. The specific selection criteria were the same as those described for the training cohort.

Outcome

In this study, the outcome was the correct prediction of the diagnosis of MFS using ocular diagnostic...
model compared with the clinical diagnosis by Ghent-2 criteria. MFS was diagnosed based on the Ghent-2 criteria, while participants in the non-MFS group did not comply with the Ghent-2 criteria.

Predictors

Based on previously published reports and clinical findings, 38 parameters that can be easily measured using the Pentacam AXL system were chosen as potential predictors for development of the diagnostic model. The Cataract Pre OP pattern of the Pentacam AXL system (Oculus Inc., Wetzlar, Germany) with a rotating Scheimpflug camera was used to measure the AL, mean keratometry of the anterior corneal surface (Km F), mean total corneal refractive curvature (TCRP) and corneal astigmatism. The corneal aberration data included wave front aberration (WFA) in the 4-mm zone around the corneal apex (WFA 4-mm zone), total corneal spherical aberrations (Z4,0) in the 6-mm zone around the corneal apex (WFA Z40) and the root mean square of the total corneal high order aberrations calculated in the 4-mm zone around the corneal apex (WFA HO RMS). The corneal diameter and thickness were also recorded.

All participants were examined by experienced ophthalmologists who were well-acquainted with the Pentacam AXL system. The family and medical histories of all participants were recorded before examinations. All parameters in each eye were recorded as the means of five repeated measurements obtained using the equipment. The right and left eyes were analyzed individually.

Statistical Analyses

The Kolmogorov–Smirnov test was used to confirm normal distribution of the variables. All variables were described as the mean ± standard deviation and categorical variables were expressed as number and proportion as appropriate. The χ² test, Student t test, and Wilcoxon rank-sum test (Mann–Whitney U test) were used to compare data between the MFS and non-MFS groups in the training and test cohorts.

Univariable logistic regression analysis was used to describe the relationship between each individual predictor variable and the diagnosis of MFS. Multiple logistic regression (forward stepwise selection and exclusion criteria of type I error = 0.1 based on likelihood ratio tests) was then performed to build the risk prediction model. All predictor variables were described as odds ratios (ORs) with 95% confidence intervals (CI) and P values were calculated.

To assess the validity of the diagnostic models, we measured calibration and discrimination. To assess the calibration, we compared C-statistics and calibration ability using Hosmer–Lemeshow χ² statistics. We also chose the minimal Akaike’s information criterion (AIC), net reclassification improvement and integrated
Table 1. Baseline Characteristics of the Training and Test Cohorts

<table>
<thead>
<tr>
<th></th>
<th>Training Cohort</th>
<th>Test Cohort</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects/eyes</td>
<td>96/186</td>
<td>80/80</td>
<td></td>
</tr>
<tr>
<td>Sex (female: male)</td>
<td>47:49</td>
<td>42:38</td>
<td>0.839</td>
</tr>
<tr>
<td>Eyes (right: left)</td>
<td>93:93</td>
<td>51:29</td>
<td>0.03</td>
</tr>
<tr>
<td>Myopia &gt; −3D (%)</td>
<td>134 (72.04%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>19.16 ± 17.04</td>
<td>14.09 ± 8.35</td>
<td>0.87</td>
</tr>
<tr>
<td>AL (mm)</td>
<td>24.72 ± 2.51</td>
<td>24.87 ± 2.36</td>
<td>0.598</td>
</tr>
<tr>
<td>AL/TCRP (mm/D)</td>
<td>61.29 ± 7.49</td>
<td>60.96 ± 7.54</td>
<td>0.85</td>
</tr>
<tr>
<td>Km F (D)</td>
<td>40.93 ± 2.25</td>
<td>40.73 ± 1.81</td>
<td>0.68</td>
</tr>
<tr>
<td>Astig F (D)</td>
<td>1.65 ± 0.91</td>
<td>1.72 ± 0.93</td>
<td>0.619</td>
</tr>
<tr>
<td>Km TCRP (D)</td>
<td>40.51 ± 2.08</td>
<td>40.99 ± 2.11</td>
<td>0.096</td>
</tr>
<tr>
<td>Astig TCRP (D)</td>
<td>1.79 ± 1.07</td>
<td>1.88 ± 0.93</td>
<td>0.362</td>
</tr>
<tr>
<td>WFA 4-mm zone (D)</td>
<td>−1.27 ± 3.18</td>
<td>−1.71 ± 0.92</td>
<td>0.33</td>
</tr>
<tr>
<td>WFA Z40 (D)</td>
<td>0.12 ± 0.14</td>
<td>0.11 ± 0.09</td>
<td>0.461</td>
</tr>
<tr>
<td>WFA HO RMS (D)</td>
<td>0.19 ± 0.13</td>
<td>0.19 ± 0.12</td>
<td>0.804</td>
</tr>
<tr>
<td>ACD int (mm)</td>
<td>4.1 ± 18.22</td>
<td>3.08 ± 0.76</td>
<td>0.023</td>
</tr>
<tr>
<td>B/F ratio</td>
<td>82.2 ± 6.6</td>
<td>82.77 ± 2.19</td>
<td>0.936</td>
</tr>
<tr>
<td>ACD ext (mm)</td>
<td>5.51 ± 27.18</td>
<td>3.63 ± 0.77</td>
<td>0.016</td>
</tr>
<tr>
<td>Cornea dia (mm)</td>
<td>11.7 ± 0.5</td>
<td>11.5 ± 1.27</td>
<td>0.819</td>
</tr>
<tr>
<td>Pupil dia (mm)</td>
<td>4.34 ± 1.57</td>
<td>4.01 ± 1.84</td>
<td>0.122</td>
</tr>
<tr>
<td>Pachy apex (μm)</td>
<td>538.33 ± 45.36</td>
<td>540.11 ± 93.77</td>
<td>0.083</td>
</tr>
<tr>
<td>Pachy thickness (μm)</td>
<td>529.98 ± 40.95</td>
<td>545.07 ± 40.24</td>
<td>0.04</td>
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ACD, anterior chamber depth; Astig, astigmatism; B/F ratio, mean radius of the posterior corneal surface/mean radius of the anterior corneal surface ratio; Cornea, corneal diameter (horizontal); F, front (anterior corneal surface); Km, mean keratometry; Pupil dia, pupil diameter; Pachy (apex), corneal thickness at the apex; Pachy (pupil), corneal thickness at the pupil’s center; TCRP, total corneal refractive power; WFA HO RMS, root mean square of the total corneal high order aberrations calculated in the 4-mm zone around the corneal apex.

discrimination improvement to improve the goodness of fit between the new model and the myopia of greater than −3 D model. To assess discrimination, we compared the area under the ROC curve (AUC) between our model and the myopia of greater than −3 D model to distinguish MFS from other types of ectopia lentis. The ROC analysis was performed to calculate the AUC in evaluating the diagnostic performance of the models. The AUC was presented with a 95% CI using 1000 bootstrap resampling. We also examined the net benefit using a decision curve analysis with regard to clinical usefulness. Finally, the training cohort was used to build the clinical ocular diagnostic model of MFS in patients with congenital ectopia lentis. Then, we verified our model in the test cohort.

P values of less than 0.05 were considered statistically significant. SPSS software version 23.0 (IBM Corp, Armonk, NY) was used for all statistical analyses. We use the R software to generate the nomogram, ROC curves, calibration plots, decision curve analysis and the decision curve analysis program was provided by Vickers.

Sensitivity Analyses

The log ORs, corresponding CIs, AUCs, minimal AIC, and decision curve analysis of the new model were compared with those of myopia of greater than −3 D model.

Results

Patient Characteristics

The training cohort contained 96 patients with congenital ectopia lentis and the test cohort consisted of 80 cases. Baseline ocular characteristics of the participants are shown in Table 1. There were no significant differences in baseline characteristics between the training and test cohorts.

Model Development

The ocular characteristics of the MFS and non-MFS groups in the training and test cohorts are...
summarized in Table 2. There were significant differences in the AL and mean TCRP between the MFS and non-MFS groups in both the training and test cohorts. The cut-off values were 24.6 mm for the AL (AUC, 0.76; 95% CI, 0.691–0.829) and 36.35 D for the mean TCRP (AUC, 0.72; 95% CI, 0.645–0.794). Because the Pearson correlation coefficient revealed a negative correlation between AL and TCRP of −0.44, we selected the AL/TCRP ratio as a new potential predictor (ROC, 0.816; 95% CI, 0.754–0.878), which showed better diagnostic ability than AL and TCRP. In addition, the AL/TCRP ratio also combined the flattened cornea and increased AL of the eye, which are two minor ocular characteristics of the Ghent-1 criteria.

The ocular data showing obvious differences were selected as potential predictors for the ocular model of MFS. WFA Z40 and TCRP pupil center were also chosen as possible predictors, even though there were no significant differences in the test cohort. Following univariable analysis, the predictor variables showing significant associations with standard outcomes (P < 0.001) were collected for further multivariate logistic regression analysis. Finally, only the AL/TCRP ratio remained to build the model. The OR of the AL/TCRP ratio was 1.22 (95% CI, 1.143–1.302). The results are shown in Table 3.

Based on these results, we developed a diagnostic model and a nomogram to determine the probability of MFS as shown in Figure 2. For patients with congenital ectopia lentis with relatively limited data, the AL/TCRP would be a supplemental diagnosis factor. For example, if a patient’s AL/TCRP ratio is 65, their probability of MFS is 78%; therefore, a comprehensive examination should be recommended to obtain a definitive diagnosis.

### Model Performance

The calibration plots and ROC curves of the model for the training and test cohorts were well-calibrated (Fig. 3). The Hosmer–Lemeshow statistical test of the
Table 3. Univariate and Multivariate Logistic Regression Models

<table>
<thead>
<tr>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
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<tbody>
<tr>
<td>OR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>AL (mm)</td>
<td>1.626 (1.361–1.942)</td>
</tr>
<tr>
<td>AL/TCRP (mm/D)</td>
<td>1.227 (1.149–1.309)</td>
</tr>
<tr>
<td>Km F (D)</td>
<td>0.695 (0.586–0.825)</td>
</tr>
<tr>
<td>Km TCRP (D)</td>
<td>0.68 (0.574–0.805)</td>
</tr>
<tr>
<td>WFA Z40 (D)</td>
<td>0.036 (0.003–0.399)</td>
</tr>
</tbody>
</table>

F, front (anterior corneal surface); Km, mean keratometry.

Figure 2. Nomogram to predict the probability of MFS in a patient with congenital ectopia lentis. By drawing a line straight downward from the AL/TCRP ratio axis to the diagnostic possibility axis, the corresponding point on the diagnostic possibility axis represents the probability risk of MFS. For example, if a patient’s AL/TCRP ratio is 65, the straight line drawn downwards to the axis of the diagnostic possibility shows their probability of MFS is 78% and a thorough examination is recommended for a definitive diagnosis.

The decision curve analysis curves, which are used to predict the correct diagnosis of MFS, of the new model and the myopia of greater than −3 D model in training and test cohorts are shown in Figure 4. In terms of the net benefit of the models between threshold probabilities of 40% to 80%, the new model is obviously better than the myopia of greater than −3 D model, because its curve was significantly lower than that of the new model.

Discussion

As a progressive disease, the symptoms and signs of MFS can be highly variable with advancing age.12–14 Although young patients affected by cardiovascular and skeletal abnormalities are often relatively severe, some patients were identified only by the ocular disorder commonly observed by ophthalmologists as an earliest sign in childhood.15

In terms of the history of the diagnostic criteria for MFS, the Ghent criteria (Ghent-1 criteria) were released in 1996 as a revision of the criteria of the first international nosology.16 The major criterion in the ocular system was ectopia lentis of any degree. Retinal detachment and myopia were deleted because an increased AL of the eyes causes myopia and contributes to retinal detachment, which cannot be considered as separate manifestations.17 However, the revised Ghent criteria, adapted in 2010, gave more weight to aortic root aneurysm and ectopia lentis, and myopia of greater than −3 D was added, canceling the previous ocular minor criteria.
Figure 3. Calibration curve and ROC curve. (A) Calibration curve of the training cohort. The solid curve represents the relationship between the predicted and observed probabilities of MFS diagnosis. The ideal calibration is the represented by the solid curve that fits the gray line exactly. (B) Calibration curve of the test cohort. The black curve of the new model is above the red curve of the myopia $>-3$ D model. The AUC of the new model is 0.816 (95% CI, 0.754–0.878), whereas the AUC of the myopia $>-3$ D is 0.567 (95% CI, 0.484–0.65). (C) ROC curve of the training cohort. The AUC of the new model in the test cohort is 0.818 (95% CI, 0.718–0.98). An AUC equal to 0.5 indicates no discrimination, whereas an AUC equal to 1.0 shows perfect discrimination.

Figure 4. Decision curve analysis. (A) Training cohort. The net benefit of the new model between the threshold probabilities of 40% to 80% is obviously better than that of the myopia $>-3$ D, because its curve is significantly lower than that of the new model. (B) Test cohort.

to allow for early diagnosis and simplicity of criteria application.\textsuperscript{6,18} Although myopia of greater than $-3$ D is representative of an increase in AL and corneal curvature abnormalities, it is also influenced by many other factors. Similarly, the equivalent spherical lens degree is affected by corneal astigmatism and crystalline lens astigmatism. Once ectopia lentis occurs, it is difficult for the ophthalmologist to make an accurate assessment of the patient’s refraction state. Gehle et al.\textsuperscript{14} reported that myopia of greater than $-0.75$ D had higher frequencies and OR as a diagnostic criterion
for MFS than myopia of greater than $-3\, \text{D}$, indicating that myopia of greater than $-3\, \text{D}$ is not a good biometric marker of MFS. In our study, the AUC of the myopia of greater than $-3\, \text{D}$ group (0.567; 95% CI, 0.484–0.65) was also unsatisfactory. In addition, myopia is also becoming common, especially in Asian countries. For example, in some studies in Asia, myopia is reported in 31.1% of the overall population and 80% to 90% of children who completed high school were myopic, of which 10% to 20% had high level myopia.\(^{19}\)

Congenital ectopia lentis is caused by different inherent diseases. In a retrospective study of 366 patients with congenital ectopia lentis conducted in Denmark, 68.2% of the participants were diagnosed as MFS and 21.2% were classified as ectopia lentis et pupillae, whereas patients with simple lens ectopic accounted for 8.0%.\(^{10}\) To distinguish patients with MFS from those with other diseases, especially the patients without any other previous clinical data or with other unclear clinical manifestations, an ocular model for predicting the probability of MFS is needed by ophthalmologists.

Previous studies showed that the AL/corneal radius of the curvature ratio was significantly greater in myopic eyes than in nonmyopic eyes.\(^{20,21}\) Thus, He et al.\(^{22}\) proposed that the AL/corneal radius of the curvature ratio was a more sensitive and specific measurement for the diagnosis of myopia. In addition, there were differences in the AL and TCRP between patients with MFS and non-MFS groups. As potential predictors, AL and TCRP showed high discrimination with high AUC. By combining the corneal curvature of the anterior and posterior surfaces, TCRP may be a better parameter than CR in patients with MFS with flattened cornea. With confirmation of the inverse correlation between AL and TCRP, we selected AL/TCRP ratio as one of predictors for the new MFS model.

Diagnostic models were constructed for MFS with ocular biometrics and AL/TCRP ratio based on the Cataract Pre OP pattern of the Pentacam AXL system. In addition, patients with congenital ectopia lentis defined as simple lens ectopic were enrolled in the study. Significant differences in the AL, corneal curvature of the anterior surface, and TCRP in the center and different zones related to the corneal apex or the pupil center were observed between the MFS and non-MFS groups in both training and test cohorts, although there were no significant differences in corneal astigmatism and aberrations between the two groups.

After strict evaluation, the AL/TCRP ratio was selected as the only index in the ocular model of MFS by multiple logistic regression. As shown in Figure 2, a nomogram was created to determine the probability of MFS and the performance of the new model was compared with that of the myopia of greater than $-3\, \text{D}$ model in the training cohort. The AIC of the new model was decreased, while the integrated discrimination improvement and net reclassification improvement were both greater than zero, indicating that the AL/TCRP ratio is an ideal predictor for MFS. As shown in Figure 3 and Figure 4, the new model showed good performance in the external multicenter test cohort.

In patients with ocular abnormalities, regular assessment of the AL/TCRP ratio might help to distinguish MFS from simple ectopia lentis and support the diagnosis of MFS for prompt and appropriate treatment. Clinical ophthalmologists can easily obtain the value of AL/TCRP ratio because the data generated by the Cataract Pre OP pattern of the Pentacam AXL system are necessary for cataract and ectopia lentis surgery. By comparing the AL/TCRP ratio using the nomogram, the probability of MFS can be obtained easily and used to advise patients on the importance of seeking further medical advice. To the best of our knowledge, we are the first to use AL/TCRP ratio to provide an objective assessment of AL and corneal curvature as a biometric marker of the ocular system.

There are three limitations of this study. First, only 176 patients (93 patients with MFS and 83 patients without MFS) were enrolled in this study, so larger cohort studies might be necessary in the future. Second, owing to differences in database management of two ophthalmic centers, some ocular characteristics were not documented in the same way; therefore, we excluded patients with missing data. We did not compare the new model with the myopia of greater than $-3\, \text{D}$ in the test cohort and only showed the performance of the model in the test cohort. Moreover, this study was retrospective in design. AL, which is a crucial parameter for eyeball development, can be influenced by age. Chen et al.\(^{12}\) also reported that the proportion of AL values of greater than 23.5 mm and the mean AL were significantly increased with age in the young patients with MFS, whereas there was no correlation between age and TCRP, which indicated that the AL/TCRP ratio increases with age. Therefore, a longitudinal study is needed to determine whether the AL/TCRP ratio changes over time.

In conclusion, the AL/TCRP ratio was investigated as a potential diagnostic factor for MFS. A new model was built for MFS and showed good performance in the external multicenter test cohort and comparison with the myopia of greater than $-3\, \text{D}$ model. Therefore, we suggest that the AL/TCRP ratio should be evaluated as a promising clinical criterion for the diagnosis of MFS.
Acknowledgments

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