RESEARCH ARTICLE

Validation of the predictive value of corneal hysteresis volume biomechanical parameters in cardiovascular risk stratification in FBN1 mutation patients

Shouyang Hu*

School of Medical Engineering, Xinxiang Medical University, Xinxiang, Henan, China.

Received: August 5, 2025; **accepted:** November 19, 2025.

Recent studies indicate that corneal biomechanical indices especially corneal hysteresis (CH) and stress–strain index (SP-A1) correlate with systemic arterial stiffness and aortic structural changes, suggesting that the cornea may act as a noninvasive "mechanical window" of connective tissue status. This research investigated whether corneal biomechanical parameters could independently predict postoperative cardiovascular events and thus serve as complementary early-warning markers to conventional anatomical measures by validating the predictive value of corneal hysteresis volume biomechanical parameters in cardiovascular risk stratification among patients with pathogenic FBN1 variants. Sixty-one patients with FBN1 mutations were included with 60 healthy volunteers as the controls. Corneal biomechanical parameters were measured using the Corvis ST device and analyzed in conjunction with cardiovascular imaging data. The association between corneal parameters and postoperative cardiovascular events was assessed by multifactorial Cox regression analysis, and a novel biomechanical model was constructed to compare with the traditional anatomical model. The results showed that the corneal hysteresis was significantly lower, and the stress-strain index was significantly higher in patients with FBN1 mutation than in controls. Corneal parameters correlated with aortic structural changes and independently predicted postoperative cardiovascular events. Risk models based on corneal biomechanical parameters were superior to traditional anatomical models. Corneal biomechanical parameters could be used as an early warning indicator of cardiovascular risk in patients with FBN1 mutations, and the novel biomechanical model was superior to the traditional indicators in risk assessment, which was of important clinical application value.

Keywords: corneal hysteresis volume; biomechanics; FBN1 mutation; cardiovascular risk; prediction model.

***Corresponding author:** Shouyang Hu, School of Medical Engineering, Xinxiang Medical University, Xinxiang, Henan 453003, China. Email: 17525939906@163.com.

Introduction

FBN1 gene mutation is one of the central pathogenic factors of connective tissue genetic diseases, which encodes fibrillin-1, an important component of extracellular matrix microfibrils and widely distributed in aortic wall, lens suspensory ligament, corneal stroma, and other tissues [1, 2]. Pathogenic variants in FBN1 gene can trigger systemic connective tissue disease represented by Marfan syndrome (MFS) with its typical cardiovascular manifestations including aortic root dilatation and related complications as one of the main causes of disability and death of patients [3, 4]. At present, cardiovascular risk management for people carrying FBN1 variants mainly relies on imaging monitoring and genotype phenotype correlation analysis to take

intervention measures when anatomical changes occur [5-7]. Although the traditional strategy based on imaging and genotype has important value in clinical practice, there are still several key limitations that need to be remedied. Aortic dilatation reflected by imaging is often the result of structural changes, and this morphological performance often lags the early degenerative changes in the biomechanical properties of the vascular wall, so it is difficult to achieve sufficient early warning of acute events [6]. The difference in pathogenicity of a single gene locus makes the accuracy of risk stratification based on a single anatomical index insufficient [7]. Therefore, finding new markers that can reflect the early mechanical degeneration of connective tissue to complement the blind spots of imaging and genetics has important clinical significance for optimizing the cardiovascular early warning system of patients carrying FBN1 mutations [5].

In recent years, the cornea as the "mechanical window of systemic connective tissue" has received more and more attention because of the correlation between its biomechanical characteristics and systemic connective tissue lesions [8]. The fibrin-1 and elastic fiber network in the corneal stroma endows the cornea with unique viscoelastic properties [9]. The dynamic corneal deformation analyzer (Corvis ST) captures the deformation response of the cornea under transient pressure in real time through non-contact gas pulse technology and can quantitatively measure a series of biomechanical parameters such as corneal hysteresis (CH) and stress–strain index (SP-A1) [10]. Several existing studies have shown that, under the pathological conditions represented by systemic elastic fiber diseases such as Marfan syndrome, the biomechanical parameters of the cornea may be abnormal before the morphological changes of the aorta, thus suggesting its potential value as a surrogate index reflecting the mechanical state of connective tissue throughout the body [11]. However, to date, most studies still focus on the association between ophthalmic phenotype and genotype. Whether corneal biomechanical parameters can be used for cardiovascular risk stratification in patients carrying FBN1 mutations, especially the early warning efficacy in predicting postoperative/clinical events, is still lack of sufficient and systematic validation and clinical accessibility evaluation [12]. In this context, systematic research based on corneal biomechanical parameters to verify its correlation with the progression of aortic disease and postoperative adverse events and to evaluate its incremental value to traditional indicators in clinical risk stratification model has become a key problem that needs to be solved urgently in this field.

This research compared corneal biomechanical indices measured by Corvis ST between FBN1 mutation carriers and matched healthy controls through a retrospective cohort study and assessed the predictive value of these indices for postoperative cardiovascular events using multivariable Cox regression and discrimination/reclassification metrics to investigate whether corneal biomechanical parameters could serve as independent early-warning markers for cardiovascular risk in patients harboring pathogenic FBN1 variants. This study provided a non-invasive, dynamic, and reproducible risk assessment tool for patients with FBN1 gene mutations to promote the transformation of cardiovascular disease management from "anatomy-driven" to "biomechanical-driven" approaches. It also provided a practical tool for precision medicine in the field of connective tissue diseases and a theoretical basis for precision medicine practices in this field.

Materials and methods

Patient recruitment and grouping

By using the electronic medical record (EMR) system, this retrospective study recruited 61 patients with pathogenic/likely-pathogenic FBN1 variants confirmed by genetic testing and 60 age- and sex-matched healthy controls from the Department of cardiovascular medicine, Shengjing Hospital, China Medical University and

the Department of cardiovascular medicine, the First Affiliated Hospital of China Medical University, Shenyang, Liaoning, China from January 2018 to June 2023 with the screening keywords of "FBN1 mutation", "Marfan syndrome", and "aortic root dilatation" [13]. The FBN1 group had a mean age of 38.5 ± 12.3 years old and comprised 33 males and 28 females, while the control group had a mean age of 38.2 ± 11.8 years old and comprised 32 males and 28 females. The subject population was predominantly Han Chinese with 58/61 in FBN1 group and 57/60 in control group. Key baseline physiological and ocular measures were comparable between groups (e.g., BMI, resting heart rate, central corneal thickness), consistent with the pre-specified matching procedure. The patient inclusion criteria for FBN1 group were (1) diagnosis of pathogenic or possibly pathogenic FBN1 mutations *via* clinically validated next-generation sequencing (NGS) with mutation classification strictly following American College of Medical Genetics and Genomics (ACMG) guidelines and confirmed through double-blind reviewing by two independent medical geneticists; (2) aged 18 – 65 years old to avoid biomechanical parameter interference from minor growth and development [14]; (3) completion of standardized Corvis ST measurements at Shengjing Hospital of China Medical University or the Ophthalmology Department of the First Affiliated Hospital of China Medical University within 1 month before aortic root surgery/intervention with ≥ 3 valid measurements per eye and data including core parameters CH, SP-A1, and corneal biomechanical index (CBI) [15]; (4) completion of preoperative and postoperative cardiovascular imaging follow-up; (5) no other inherited connective tissue disorders, end-stage organ failure, or active systemic inflammatory diseases [16]. The control group inclusion criteria were (1) 1:1 age matching (± 3 years) and identical sex ratio with the FBN1 group and recruited from the same region to control geographic effects on biomechanical parameters; (2) no cardiovascular disease, metabolic syndrome, or chronic inflammation with aortic root diameter < 40 mm, resting blood pressure < 140/90 mmHg, body mass index (BMI) 18.5 – 24.9 kg/m², and three-generation family history excluding connective tissue disease, aortic disease, or first-degree relative sudden death; (3) no corneal disease or refractive surgery history with normal corneal morphology and central corneal thickness (CCT) 450 – 600 μm [17]; (4) completion of three corneal biomechanical measurements using the same Corvis ST device and protocol as the FBN1 group at the same hospital. All procedures of this research were approved by the Ethics Committee of Shengjing Hospital of China Medical University (Shenyang, Liaoning, China) (Approval No. 2018PS743K).

Measurement of corneal biomechanical parameters

Corneal biomechanics were measured using OCULUS Corvis ST (software version v.2.3.1) (Optikgeräte GmbH, Wetzlar, Germany), while corneal topography was obtained using Pentacam (Optikgeräte GmbH, Wetzlar, Germany). The device was equipped with a high-speed Scheimpflug camera and a precise air pressure pulse control system that allowed real-time recording of the dynamic deformation of the cornea under transient air pressure stimulation [18]. The laboratory environment was strictly controlled at 22 ± 1°C and a humidity level of 50 ± 5%. Subjects were required to stop using corneal contact lenses for ≥ 72 hours before measurement and enter the testing room 30 minutes in advance to adapt to the ambient light. CCT was measured using a non-contact ultrasonic corneal thickness gauge (DGH Technology, Exton, PA, USA) with CCT < 450 μm or > 650 μm to be excluded [19]. 0.1% sodium hyaluronate drops were injected to improve the lubrication of the ocular surface. After 5 minutes, OCULUS Keratograph 5M (Optikgeräte GmbH, Wetzlar, Germany) was used to measure the tear film breakup time (BUT) for ≥ 10 seconds. Then, the height of the mandibular and frontal rests were adjusted to make the corneal apex coincide with the laser localization spot, and the infrared pupil tracking system monitored the stability of fixation in real time. The measurements were

automatically interrupted when the excursion amounted > 0.5 mm. A triple quality control mechanism was used for data collection, which included that the device automatically generated a quality score (Q-score) after each measurement, excluding data with a Q-score < 8/10; the morphology of the deformation curves was manually reviewed to exclude abnormal waveforms due to microtransients; the difference in CH values between the three valid measurements had to be ≤ 1.0 mmHg and the difference in SP-A1 ≤ 0.15. The final data were calculated by the Corvis ST built-in algorithm for CH, SP-A1, and Corvis Biomechanical Index (CBI). The raw data were exported in encrypted format to EpiData 4.6 (https://www.epidata.dk/) for double-blind entry verification.

Cardiovascular imaging data collection

The aortic root diameter in FBN1 group was measured by a combination of transthoracic echocardiography (TTE) using Philips EPIQ CVx cardiac ultrasound system (Koninklijke Philips N.V., Amsterdam, Netherlands) and cardiac MRI (CMR) using a GE Discovery MR750w 3.0T scanner (GE Healthcare, Chicago, IL, USA) [20]. TTE measurements were performed in a biplane imaging mode with end-diastolic imaging enabled in parasternal long-axis view. The AutoMeasure algorithm was used to automatically identify the intima-media border of the aortic sinus and to synchronize the recording of aortic wall strain parameters. The CMR scan included a bSSFP cine sequence, 4D flow imaging, and a delayed enhancement sequence with the image clarity being ensured by respiratory navigation gating. Image analysis was performed independently by two senior physicians under 3mensio Vascular software (3mensio Medical Imaging BV/Pie Medical Imaging, Bilthoven, The Netherlands) using semiautomated 3D reconstruction to accurately localize the maximal diameter of the aortic sinus, dynamic multiplanar reorganization (MPR) to assist manual review, and a finite element analysis module to integrate real-time blood pressure and elastic modulus data to calculate wall stress. Postoperative follow-up was assessed every 6 months by combined TTE + CMR, longitudinally aligned imaging data using the 3mensio Follow-up module to quantify the annual growth rate of the aortic diameter and the rate of false lumen expansion. The acute events were verified by low-dose CTA using Siemens Force dual-source CT (Siemens Healthineers, Erlangen, Germany). All data were stored in Siemens Syngo *via* PACS system with a structured reporting format to ensure traceability of measured parameters.

Genotyping and clinical data integration

A systematic gene-clinical data integration system was constructed based on the complete whole-exon sequencing of the FBN1 gene using Illumina NovaSeq 6000 second-generation sequencing platform and the TruSight Cardio Panel (Illumina, San Diego, CA, USA) to capture the target region. The sequencing library was constructed using KAPA HyperPlus kit (Roche, Basel, Switzerland) following manufacturer's instructions [21]. Raw data were bioinformatically analyzed using Illumina DRAGEN Bio-IT platform (version 4.2). The automatic classification of variants was completed by applying the InterVar system (http://wintervar.wglab.org/) in conjunction with the ACMG/ClinGen guidelines and was reviewed by two ABMGG-certified geneticists under double-blind conditions. The controversial variants were sequenced using Applied Biosystems 3500xL Genetic Analyzer (Thermo Fisher Scientific, Waltham, MA, USA) to validate and submit to Molecular Tumor Board arbitration. Clinical data were integrated with structured entry of phenotypic features and family lineage information using Progeny Clinical (v9.3) (Progeny Genetics, Aliso Viejo, CA, USA), and spatiotemporal alignment of data from multiple sources was achieved through the REDCap platform (version 13.4.2) (Vanderbilt University, Nashville, TN, USA), in which genotypic data were aligned with corneal biomechanical parameters and imaging metrics using the LOINC/SNOMED CT coding (https://loincsnomed.org/) for semantic mapping. Data security was ensured by double-

blind hash encryption and ISO 27001 certified servers with Python scripts (version 3.10) (https://www.python.org/).

Observation of indicators

CH recorded the corneal ability to recover from deformation under transient pressure by means of a non-contact air-pulse technique measured in mm Hg. Three valid measurements were taken in each eye for the average with a required CV of ≤ 10%. In addition, the SP-A1 quantified the nonlinear stress-strain relationship during corneal deformation, reflecting the rigidity of the corneal tissue, and was also calculated simultaneously with the Corvis ST device with the average of the three measurements required for data collection. Cardiovascular parameters included aortic root diameter and aortic root dilatation rate. Aortic root diameter was measured by TTE and CMR at end-diastole, and the maximum internal diameter of the aortic sinus was measured in millimeters. Measurements were analyzed double-blind by two cardiovascular imaging physicians with an ICC > 0.90 to ensure reliability of the results. The rate of aortic root dilatation was based on preoperative and ≥ 3 years of postoperative imaging follow-up data. The average annual growth rate was calculated and used to assess the rate of pathological progression. In addition, postoperative cardiovascular events were assessed including aortic coarctation recurrence, aneurysm rupture, and secondary surgery, which were blindly adjudicated by an independent endpoints committee according to the European Society of Cardiology (ESC) (https://www.escardio.org) guidelines. The novel biomechanical model categorized patients into low, intermediate, and high risk using a high-risk threshold of CH ≤ 7.0 mmHg and SP-A1 ≥ 1.5, while the conventional anatomical model used aortic root diameter ≥ 50 mm as the criterion for the high-risk group. To assess the predictive efficacy of the model, this study used the C-index to assess the discriminatory ability of the model, quantified the overall accuracy of the model by the area under the receiver operating characteristic (ROC) curve (AUC), and assessed the improvement of the model using the net reclassification index (NRI) and the integrated discriminant improvement index (IDI). Survival analysis was performed using Kaplan-Meier curves to compare the event-free survival rates of different risk-stratified groups, and the Log-rank test was used to test the differences between groups and calculate the median survival time to further validate the clinical prognostic value of the model.

Statistical analysis

R 4.2.0 and SPSS 26.0 (IBM, Armonk, New York, USA) were employed for the statistical analysis of this research. All continuous variables were assessed for normality by the Shapiro-Wilk test. Normally distributed data were described by mean ± standard deviation, and comparisons between groups were made using the independent samples t-test. Non-normal data were expressed as median (interquartile range), and differences between groups were tested using the Mann-Whitney U test. Pearson coefficient was selected for correlation analysis based on data distribution characteristics. For the prediction of postoperative cardiovascular events, the study constructed a multifactorial Cox proportional risk regression model by incorporating covariates such as age, sex, baseline aortic diameter, and β-blocker utilization rate to adjust for confounding effects and calculated the hazard ratio (HR) and 95% confidence interval (CI). Optimization of the risk stratification model was based on the Youden index to determine the optimal cutoff value of CH versus SP-A1, and the model discriminatory ability was verified by the C index and Kaplan-Meier survival curves. Net reclassification index and combined discriminant improvement were further used to quantify the degree of model improvement. For quality control, imaging data were analyzed in a double-blind manner, and intragroup correlation coefficients ensured measurement consistency. The coefficient of variation of Corvis ST measurements guaranteed data stability. All tests were two-sided with P value less than 0.05 as statistically significant difference.

Results and discussion

Between-group differences in corneal biomechanical parameters

The results demonstrated significant differences in corneal biomechanical parameters between FBN1 mutant patients and healthy controls, while the correlation between these parameters and aortic-related indexes provided a mathematical and logical basis for subsequent studies. CH exhibited a significant difference between the FBN1 mutation group and the control group with a mean CH of 7.2 ± 1.1 mmHg in FBN1 mutation group and 9.8 ± 1.3 mmHg in the control group (P < 0.001), which indicated that the corneal hysteresis in the FBN1 mutation patients was significantly lower than that in the healthy population, suggesting that the FBN1 mutation might cause a systemic biomechanical degradation of connective tissue and therefore affected corneal biomechanics. Low CH values are usually associated with decreased elasticity and increased rigidity of tissues, which may reflect early biomechanical changes in connective tissue lesions, especially the elastic degradation of large vessels such as the aorta. The SP-A1 also showed significant difference between the FBN1 mutation group and the control group with 1.4 ± 0.3 in the FBN1 mutation group and 0.9 ± 0.2 in the control group (P < 0.001), which suggested that FBN1 mutations might lead to increased corneal tissue stiffness and further supported the use of corneal biomechanical properties as a potential biomarker reflecting pathological changes in connective tissue (Figure 1). Meanwhile, Corvis ST intra-session coefficient of variation was ≤ 10% and imaging intraclass correlation coefficient exceeded 0.90, ensuring measurement reliability. Correlation analysis revealed CH was significantly negatively correlated with aortic root diameter (r = −0.62, P < 0.01), indicating that the lower the CH in patients with FBN1 mutations, the larger the aortic root diameter. The results suggested corneal biomechanical parameters might be associated with aortic structural degeneration and further validated the cornea's potential as a "mechanical window" for systemic connective tissue pathologies as corneal biomechanical characteristics could reflect early pathological changes in vessels like the aorta. Additionally, SP-A1 was significantly positively correlated with aortic root dilatation rate (r = 0.58, P < 0.01), implying increased corneal rigidity might be linked to aortic dilatation rate and that SP-A1 could serve as a useful biomarker for evaluating aortic pathological progression. Collectively, the significant correlation between corneal biomechanical parameters and aortic pathological indicators in patients with FBN1 mutations further demonstrated the potential of corneal biomechanical measurements in cardiovascular risk assessment.

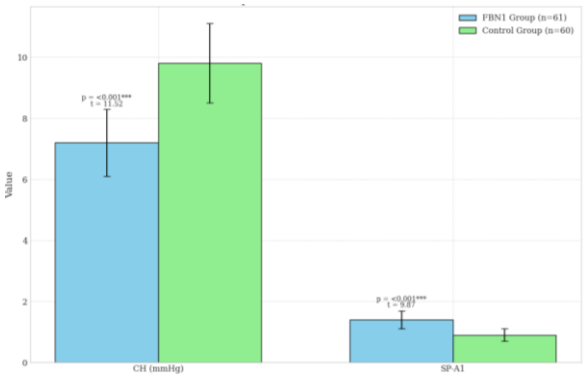

Figure 1. Intergroup differences in corneal biomechanical parameters.

Predictive efficacy of postoperative cardiovascular events

The results demonstrated that FBN1 group showed lower CH and higher SP-A1 values, suggesting that FBN1 mutations might lead to biomechanical degradation of connective tissue, which in turn affected the mechanical properties of the cornea. In addition, correlation analysis of corneal biomechanical parameters with aortic structure further validated the potential of corneal biomechanical measurements as a predictor of cardiovascular risk. Those results laid the foundation for further exploration of corneal biomechanical parameters in the prediction of postoperative cardiovascular events in patients

Table 1. Analysis of multifactor Cox regression.

Variable type	Variable name	HR (95% CI)	*P* value
Biomechanical parameters	CH ≤ 8.0 mmHg	2.80 (1.42 - 5.52)	0.003**
Biomechanical parameters	SP-A1 ≥ 1.2	2.45 (1.28 - 4.70)	0.007**
Traditional anatomical indicators	Aortic diameter ≥ 50 mm	1.15 (0.70 - 1.90)	0.58
Covariates	Age (per 10-year increase)	1.10 (0.88 - 1.37)	0.39
Covariates	Male	1.05 (0.62 - 1.78)	0.86
Covariates	Baseline aortic diameter (per 1 mm)	1.02 (0.96 - 1.08)	0.53
Covariates	Beta-blocker use	0.90 (0.52 - 1.56)	0.71

Note: **: $P < 0.01$.

with FBN1 mutations. Subsequently, this study explored the effectiveness of corneal biomechanical parameters in predicting postoperative cardiovascular events in patients with FBN1 gene mutations. With a median follow-up of 4.2 years, this study evaluated the value of corneal biomechanical parameters in predicting postoperative cardiovascular events such as recurrent aortic coarctation, aneurysm rupture, and reoperation to verify whether corneal biomechanical parameters could be combined with traditional imaging and clinical data as an independent early warning tool, thus providing a new perspective for predicting cardiovascular events in patients with FBN1 gene mutations. This study further explored the practical application of corneal biomechanical characteristics in the management of cardiovascular disease, especially their efficacy in long-term postoperative follow-up. Among patients with FBN1 mutations, 61 cases had postoperative cardiovascular events with an overall event rate of 22.9% with 14 specific events including recurrent aortic dissection as the most common type, accounting for 64.3% (9 cases), mainly involving the incompletely replaced remnant ascending aorta or distal aorta, which suggested that the biomechanically weak region of the remnant aortic wall remained a major risk source after surgery. Aneurysm rupture accounted for 21.4% (3 cases), which mostly occurred in the surgically unrepaired aortic arch and associated with persistent connective tissue degeneration. Secondary surgery accounted for 14.3% (2 cases), reflecting the risk of long-term failure of prosthetic vessels or valves. This event distribution highlighted that systemic connective tissue mechanical failure caused by FBN1 mutations was not limited to surgically repaired sites and further supported the value of corneal biomechanical parameters as a monitoring tool for systemic lesions. After correcting confounding factors such as age and gender, CH ≤ 8.0 mmHg and SP-A1 ≥ 1.2 were independent predictors of postoperative events with significantly higher risk ratios than traditional anatomic indicators (Table 1). Every 1 mmHg decrease in CH was associated with an approximate 40% increase in the risk of an event, whereas a 0.1 unit increase in SP-A1 corresponded to an 18% increase in risk. This result confirmed that corneal biomechanical parameters captured early signals of micromechanical degradation of the aortic wall, and their predictive efficacy was independent of anatomical repair, providing a new dimension for dynamic postoperative monitoring. The combined CH and SP-A1 prediction model significantly improved the sensitivity and specificity balance by 12% over the conventional aortic diameter model, suggesting that biomechanical parameters could accurately identify high-risk patients. At the optimal cutoff value, the model correctly warned 78.6% of those with events, while avoiding over intervention in 46.4% of low-risk patients. The combined CH and SP-A1 prediction model showed a significant improvement in efficacy over the traditional aortic diameter model, which was critical for clinical decision making, especially in resource-limited settings that prioritized enhanced follow-up of high-risk patients (Figure 2).

Table 2. Stratification criteria.

Proposed biomechanical model	Traditional anatomical model
Low-risk group: CH > 7.0 and SP-A1 < 1.5	High-risk group: aortic root diameter ≥ 50 mm
Intermediate-risk group: CH ≤ 7.0 or SP-A1 ≥1.5	Non-high-risk group: aortic root diameter < 50 mm
High-risk group: CH ≤ 7.0 and SP-A1 ≥ 1.5	

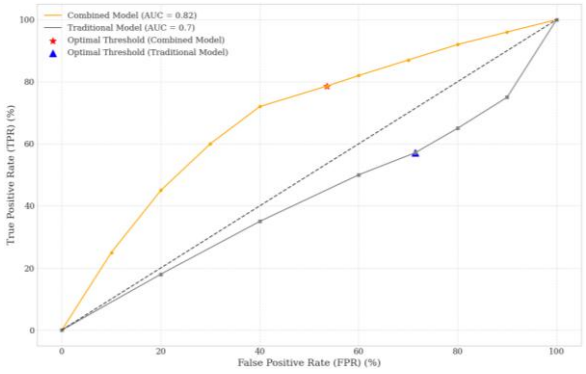

Figure 2. ROC curves of combined model and traditional model.

The survival curves showed that the 4-year event-free survival rate was significantly lower in the CH ≤ 8.0 mmHg group than that in the CH > 8.0 mmHg group, and it was also significantly lower in the SP-A1 ≥ 1.2 group than in the SP-A1 < 1.2 group (Figure 3). The risk of events in the biomechanical abnormality group accumulated rapidly at 2 - 3 years postoperatively, suggesting that 1 - 3 years postoperatively was a critical window for mechanical intervention. Biomechanical stratification allows earlier identification of subgroups requiring close monitoring than traditional anatomical metrics.

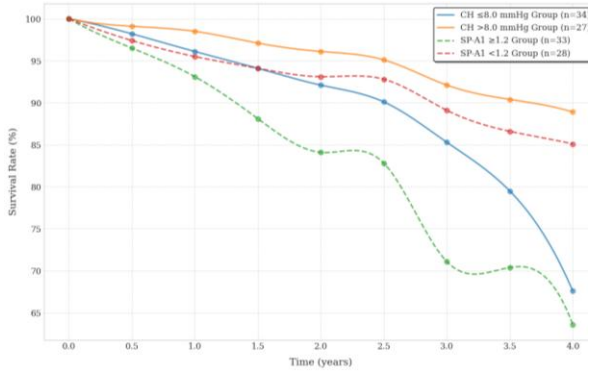

Figure 3. Kaplan-Meier survival curve.

Risk stratification model and its optimization analysis

Two risk stratification models including a novel biomechanical model and a traditional anatomical model were constructed to evaluate the predictive efficacy and clinical application value of the models by several statistical indicators. The proposed model utilized CH and SP-A1 as the primary biomarkers to comprehensively reflect the biomechanical degradation of connective tissue and thus effectively predict the risk of cardiovascular events. In contrast, the traditional model relied only on anatomical indicators such as aortic root diameter ≥ 50 mm to define high-risk and non-high-risk groups (Table 2). The three-level stratification system based on CH ≤ 7.0 mmHg and SP-A1 ≥ 1.5 demonstrated excellent clinical predictive value. The postoperative cardiovascular event rate in the high-risk group of the proposed model was 57.1%, which was twice as high as that in the high-risk group of the traditional anatomical model. Its C-index and AUC were significantly better than those of the traditional model, indicating that the biomechanical parameters could more accurately capture the early mechanical degradation signals of the aortic wall. Survival analysis further validated the clinical significance of the stratified model with the 3-year event-free survival rate in the high-risk group of the proposed model being only 35.7%, and the median survival time being shortened to 2.3 years that was significantly shorter than 4.1 years of the high-risk group of the traditional model. Notably, the event rate in the low-risk group was only 3.7%, reflecting superior risk exclusion compared with the traditional model non-high-risk group. The model improvement metrics showed NRI = 0.36, indicating that 36% of event

Table 3. Summary of specific results.

Observation metrics	Proposed biomechanical model	Traditional anatomical model	Statistical analysis
Model discrimination			
C-index (95% CI)	0.81 (0.73 - 0.89)	0.65 (0.55 - 0.75)	$P < 0.001$
AUC (95% CI)	0.82 (0.73 - 0.91)	0.70 (0.62 - 0.78)	$P < 0.001$
Event incidence			
High-risk group cumulative rate	57.1% (8/14)	28.6% (4/14)	$P = 0.003$
Medium-risk group cumulative rate	25.0% (5/20)	—	—
Low-risk group cumulative rate	3.7% (1/27)	—	—
Survival analysis			
3-year event-free survival rate	High-risk: 35.7% Medium-risk: 75.0% Low-risk: 92.3%	High-risk: 71.4% Non-high-risk: 85.7%	Log-rank $P < 0.001$ (proposed model groups) Log-rank $P = 0.004$ (*vs*. traditional high-risk)
Median event-free survival time (95% CI)	High-risk: 2.3 years (1.5-3.1) Medium-risk: 4.8 years (3.9-5.7) Low-risk: Not reached	High-risk: 4.1 years (3.2-4.9) Non-high-risk: Not reached	$P = 0.004$ (high-risk comparison)
Clinical utility			
Net Reclassification Index (NRI)	0.36	—	$P = 0.02$
Integrated Discrimination Index (IDI)	0.15	—	$P = 0.01$
Subgroup analysis			
Mutation type (truncating *vs*. missense)	HR consistency: 0.85-1.12 ($P > 0.05$)	—	Interaction $P > 0.05$
Gender (male *vs*. female)	HR consistency: 0.92-1.08 ($P > 0.05$)	—	Interaction $P > 0.05$

patients were correctly reclassified to the high-risk group, and IDI = 0.15 suggesting a 15% improvement in the overall risk discrimination ability of the proposed model, which was valuable for optimizing the frequency of postoperative monitoring and timing of intervention (Table 3). Subgroup analyses confirmed that the proposed model maintained stable predictive efficacy in both mutation types and gender groupings, highlighting the generalizability of its biological mechanisms. Together, these results supported the conclusion that corneal biomechanical parameters, by quantifying systemic connective tissue mechanical failure caused by FBN1 mutations, could break through the lagging limitations of traditional anatomical indicators and provide dynamic early warning of the critical risk window of 2 - 3 years postoperatively, thus facilitating cardiovascular risk management to move from "passive monitoring of morphologic changes" to "proactive intervention of mechanical abnormalities". This study validated the clinical value of corneal biomechanical parameters, particularly CH and SP-A1, in patients with FBN1 mutations. The results showed that connective tissue biomechanical degeneration due to FBN1 mutation preceded aortic morphological changes, and this change could be noninvasively quantified by corneal biomechanical parameters. CH showed a significant negative correlation with aortic root diameter, while SP-A1 showed a significant positive correlation with aortic dilatation rate, which suggested that corneal biomechanical characteristics could reflect early degeneration of aorta and other large vessels. The risk stratification model based on corneal biomechanical parameters demonstrated higher predictive accuracy than that in the traditional anatomical model and could better identify high-risk patients, which was especially of high clinical value for early warning of cardiovascular events during long-term postoperative follow-up. Based on the findings of this study, corneal biomechanical parameters were recommended as a complementary tool for cardiovascular risk assessment in patients with FBN1 mutations, especially in the early stages, to help identify potentially at-risk populations. Specifically, CH and SP-A1 should be emphasized as important biomechanical markers in the routine examination of patients and combined with

imaging data for comprehensive assessment. In addition, it was recommended that clinical risk stratification models based on corneal biomechanical parameters should be gradually introduced into cardiovascular risk management as a reference for early intervention with a view to increasing the frequency of monitoring high-risk patients and optimizing the treatment protocols in resource-limited settings.

Although this study provided important evidence for the use of corneal biomechanical parameters in the assessment of cardiovascular risk in patients with FBN1 mutations, there were some limitations, which included that this research was a single-center retrospective cohort study with a relatively small sample size and included only patients from specific regions that might have regional bias. Therefore, the broad applicability and generalizability of the study results need to be further verified by multicenter, large-sample prospective studies. The measurement of corneal biomechanical parameters in the study relied on the Corvis ST device, and the degree of standardization of its operation and data collection process might have an impact on the results. The control of device calibration and data consistency should be strengthened in future studies. Future studies should focus on the multicenter, international, large-sample prospective study to further validate the predictive efficacy of corneal biomechanical parameters across different races, mutation types, and cardiovascular disease spectrums, which would help confirm the applicability of these parameters as a tool for cardiovascular risk assessment in patients with FBN1 mutations on a global scale. Mechanistic studies of corneal biomechanical parameters need to be further investigated, and the relationship between corneal biomechanical changes and systemic connective tissue degeneration should be explored through experiments at the cellular and molecular levels to provide a more solid theoretical basis for their clinical application. Future research should also explore how to combine corneal biomechanical parameters with other biomarkers to construct a more comprehensive and accurate cardiovascular risk assessment model, which will provide more support for individualized treatment and prevention. With the development of precision medicine, how to optimize the clinical application of corneal biomechanical parameters by using artificial intelligence and big data technology to improve the efficiency of early diagnosis and treatment decision-making is also an important direction for future research.

References

1. Li L, Huang J, Liu Y. 2024. The extracellular matrix glycoprotein fibrillin-1 in health and disease. Front Cell Dev Biol. 11:1302285.
2. Curry T, Barrameda ME, Thomas TC, Esfandiarei M. 2024. *In vivo* phenotypic vascular dysfunction extends beyond the aorta in a mouse model for fibrillin-1 (Fbn1) mutation. Sci Rep. 14(1):5779.
3. Pugnaloni F, De Rose DU, Digilio MC, Magliozzi M, Braguglia A, Valfrè L, *et al*. 2024. Neonatal Marfan syndrome: A case report of a novel fibrillin 1 mutation, with genotype-phenotype correlation and brief review of the literature. Ital J Pediatr. 50(1):183.
4. Gupta SD, Chanda PK. 2024. Aortic root enlargement by "Y" technique—our experience. Cardiovasc J. 16(2):98-101.
5. Muiño-Mosquera L, Cervi E, De Groote K, Dewals W, Fejzic Z, Kazamia K, *et al*. 2024. Management of aortic disease in children with FBN1-related Marfan syndrome: A joint statement from the pediatric subgroup of the European Reference Network of Vascular Diseases (VASCERN, Heritable Thoracic Aortic Disease working group) and the Association for European Pediatric and Congenital Cardiology (AEPC). Eur Heart J. 45(39):4156-4169.
6. Wang X, Huang X. 2024. Risk factors and predictive indicators of rupture in cerebral aneurysms. Front Physiol. 15:1454016.
7. Di Bari L, Bisardi M, Cotogno S, Weigt M, Zamponi F. 2024. Emergent time scales of epistasis in protein evolution. Proc Natl Acad Sci. 121(40):e2406807121.
8. Komninou MA, Seiler TG, Enzmann V. 2024. Corneal biomechanics and diagnostics: A review. Int Ophthalmol. 44(1):132.
9. Yang Q, Wang S, He Y, Zhang Y. 2023. The research progress on the molecular mechanism of corneal cross-linking in keratoconus treatment. Contact Lens Anterior Eye. 46(2):101795.
10. Liu MX, Zhu KY, Li DL, Dong XX. Liang G, Grzybowski A, *et al*. 2024. Corneal biomechanical characteristics in myopes and emmetropes measured by Corvis ST: A meta-analysis. Am J Ophthalmol. 264:154-161.
11. Asif MI, Kalra N, Sharma N, Jain N, Sharma M, Sinha R. 2023. Connective tissue disorders and eye: A review and recent updates. Indian J Ophthalmol. 71(6):2385-2398.

12. Mascolini MV, Toniolo I, Carniel EL, Fontanella CG. 2024. *Ex vivo*, *in vivo* and *in silico* studies of corneal biomechanics: A systematic review. Phys Eng Sci Med. 47(2):403-441.
13. Yu S, Huang L, Ren J, Zhang X. 2024. Association of polymorphisms in FBN1, MYH11, and TGF-β signaling-related genes with susceptibility of sporadic thoracic aortic aneurysm and dissection in the Zhejiang Han population. Open Med. 19(1):20241025.
14. Xiang K, Chen J, Zhao W, Zhu Z, Ding L, Bulloch G, *et al*. 2023. Changes of corneal biomechanics in children using orthokeratology and their roles in predicting axial length progression—a prospective 2-year study. Acta Ophthalmol. 101(7):755-765.
15. Jalilibal Z, Amiri A, Castagliola P, Khoo MB. 2021. Monitoring the coefficient of variation: A literature review. Comput Ind Eng. 161:107600.
16. Gouda P, Kay R, Habib M, Aziz A, Aziza E, Welsh R. 2022. Clinical features and complications of Loeys-Dietz syndrome: A systematic review. Int J Cardiol. 362:158-167.
17. Arruda HA, Pereira JM, Neves A, Vieira MJ, Martins J, Sousa JC. 2021. Lenstar LS 900 versus Pentacam-AXL: Analysis of refractive outcomes and predicted refraction. Sci Rep. 11(1):1449.
18. Abdelmotaal H, Abdou AA, Omar AF. 2021. Pix2pix conditional generative adversarial networks for scheimpflug camera color-coded corneal tomography image generation. Transl Vis Sci Technol. 10(7):21-21.
19. Soulantzou K, Plakitsi A, Chalkiadaki E, Anastasopoulou M, Karmiris E. 2023. Comparison of central corneal thickness in healthy eyes using ultrasound pachymetry, non-contact specular microscopy and a high-resolution Scheimpflug camera. Int Ophthalmol. 43(2):363-370.
20. Hofbauer T, Heber S, Schoeny H, Ritter H, Wessner B, Neidenbach R, *et al*. 2024. Sex-specific reference values for automated three-dimensional echocardiography across healthy and physically active individuals with different fitness levels. Eur J Prev Cardiol. 31(Suppl 1):zwae175.260.
21. Jeon SA, Park JL, Park SJ, Kim JH, Goh SH, Han JY, *et al*. 2021. Comparison between MGI and Illumina sequencing platforms for whole genome sequencing. Genes Genomics. 43:713-724.