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Research Article

Accurate prediction of myopic progression and high myopia by machine learning

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Abstract

Background: Myopia is a leading cause of visual impairment in Asia and worldwide. However, accurately predicting the progression of myopia and the high risk of myopia remains a challenge. This study aims to develop a predictive model for the development of myopia.

Methods: We first retrospectively gathered 612 530 medical records from five independent cohorts, encompassing 227 543 patients ranging from infants to young adults. Subsequently, we developed a multivariate linear regression algorithm model to predict the progression of myopia and the risk of high myopia.

Result: The model to predict the progression of myopia achieved an R^2 value of 0.964 vs a mean absolute error (MAE) of 0.119D [95% confidence interval (CI): 0.119, 1.146] in the internal validation set. It demonstrated strong generalizability, maintaining consistent performance across external validation sets: $R^2 = 0.950$ vs MAE = 0.119D (95% CI: 0.119, 1.136) in validation study 1, $R^2 = 0.950$ vs MAE = 0.121D (95% CI: 0.121, 1.144) in validation study 2, and $R^2 = 0.806$ vs MAE = −0.066D (95% CI: −0.066, 0.569) in the Shanghai Children Myopia Study. In the Beijing Children Eye Study, the model achieved an R^2 of 0.749 vs a MAE of 0.178D (95% CI: 0.178, 1.557). The model to predict the risk of high myopia achieved an area under the curve (AUC) of 0.99 in the internal validation set and consistently high area under the curve values of 0.99, 0.99, 0.96 and 0.99 in the respective external validation sets.

Conclusion: Our study demonstrates accurate prediction of myopia progression and risk of high myopia providing valuable insights for tailoring strategies to personalize and optimize the clinical management of myopia in children.

Keywords: myopia; progression; machine learning; prevention; precision medicine

Introduction

Myopia is the leading cause of visual impairment worldwide. In 2016, the prevalence of myopia reached nearly 1.6 billion cases worldwide, a trend expected to surpass 5.6 billion cases within the next few decades [1]. In China alone, myopia affects nearly 400 million people, exceeding the entire population of the USA.

The distribution of myopia varies amongst different racial and environmental backgrounds. Typical onset occurs between 5–15 years of age; however, recent Chinese reports noted the development of myopia within the first 6 months of life [2]. Moreover, studies have shown that children from China and Singapore have drastically higher prevalence of myopia than their European counterparts, possibly due to more prolonged near work in a large majority of school-age children [3, 4]. In a review conducted by Pan *et al.*, only 3.4% of 10–11-year-old school children in the UK presented with myopia, compared to 30.1% of 10-year-old urban Chinese school children [3]. Moreover, the distribution of myopia among Chinese adults is shown to increase exponentially, further raising public health concern. By age 15, 78.4% of urban Chinese students have acquired myopia, and by age 18, this frequency reaches 80% [3, 5]. Similar trends have been noted in other Asian countries such as Republic of Korea, where the prevalence of myopia has been reported in 96.5% in 19-year-old male Seoul university students [6]. Alongside the growing prevalence of myopia, studies have also indicated increased prevalence of high myopia [≥−6.0 diopters (D)], which is associated with increased life-time risk of retinal detachment, myopic retinal degeneration and glaucoma [7].

This surge in myopia progression in Asian school children has led some to claim the emergence of a "myopic epidemic", as retinal damage due to high myopia can be irreversible and cause significant morbidity [6]. Meanwhile, myopia has gradually been

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Table 1. Cohorts of myopic patients used for training and validation of an AI system.

Cohort	Training	Internal validation	External validations			
	GMS	GMS	Validation study 1	Validation study 2	SCMS	BCES
Medical records (*n*)	273 307	29 445	203 462	100 213	4 148	1 955
Patients (*n*)	88 111	10 023	76 314	50 957	2 007	131
Male (*n*)	49 993	5 778	43 418	29 031	1 072	68
Female (*n*)	38 118	4 245	32 896	21 925	935	63
Mean interval between visits ± SD (years)	1.99 ± 1.32	1.93 ± 1.26	1.99 ± 1.33	1.99 ± 1.33	0.72 ± 0.21	2.47 ± 1.26
Mean age at first exam ± SD (years)	8.18 ± 3.54	8.14 ± 3.52	8.16 ± 3.54	8.19 ± 3.56	7.91 ± 3.19	7.71 ± 1.36
SE[a] at first exam ± SD (D)	−0.67 ± 3.45	−0.63 ± 3.44	−0.67 ± 3.45	−0.66 ± 3.45	−2.03 ± 1.81	−0.50 ± 1.37

[a]SE (spherical equivalent) calculated for both eyes combined.

recognized as a social problem due the high expenses associated with it. The average economic cost to stabilize myopia progression in Singapore equates to $709 USD per patient per year [8]. The price of refractive surgery in Europe varied between €3 075 to €3 123 (equivalent to US$4 046 to $4 109 when adjusted for 2021 inflation) [9]. A recent estimation indicates that the annual expenditure for the treatment and prevention of myopia in China is ∼US$10 billion [10]. The economic burden of correcting myopic visual impairment places a large population at risk of not seeking treatment; an estimated $121.4 billion international dollars are lost due to ongoing uncorrected visual impairment, as reduced visual acuity is correlated with reduced economic productivity [11], quality of life [12], and increased mortality (e.g. from increased risk of falls) [13,14]. Therefore, providing a predictive model for myopic progression could potentially help to identify those at high risk for developing high myopia, enable timely intervention, and mitigate the socio-economic burdens of visual impairment.

Due to new machine learning (ML) algorithms and their incorporation into the medical field, artificial intelligence (AI) is poised to revolutionize disease diagnosis and prediction, potentially leading to an overall higher standard of care. With the exponential increase in myopic cases within the last decade, large datasets can be assembled and serve as a tool for studies to predict if myopia cases will progress and predict the risk of high myopia at specific future time points. We investigated the prediction of myopic progression and development of high myopia in five independent cohorts of children with myopia. We demonstrate that ML-assisted evaluations can provide informed predictions regarding myopia progression and risk of high myopia.

Methods

Predicting myopia progression

Data collection

We collected data from the following five independent cohorts: Guangzhou Myopia Study (GMS) from the Zhongshan Ophthalmic Center of Sun Yat-sen University (302 752 medical records of 98 134 patients split 9:1 for training and internal validation; external validation study 1 was from Guangzhou Women and Children's Medical Center (203 462 medical records of 76 314 patients); external validation study 2 was from Guangzhou Medical University First Affiliated Hospital (100 213 medical records of 50 957 patients); the Shanghai Children Myopia Study (SCMS) was from the Eye and ENT Hospital of Fudan University (4 148 medical records of 2 007 pediatric patients); and the Beijing Children Eye Study was from Beijing Tongren Eye Center (BCES) (1 955 medical records of 131 pediatric patients). The institutional review boards of the EENT Hospital of Fudan University, Zhongshan Ophthalmic Center, Guangzhou Women and Children's Medical Center, Tongren Eye Center, and Guangzhou Medical University First Affiliated Hospital approved the study protocols. All participants were informed about the study objectives and signed written informed consent. All procedures adhered to the tenets of the Declaration of Helsinki. The characteristics of the cohorts are summarized in Table 1.

The GMS data used for training provided a plethora of information, consisting mainly of bilateral eye exams in both children and young adults. Right and left eyes were considered independent data. The mean age at the time of baseline was 8.18 years [standard deviation (SD): 3.54 years]. The mean spherical equivalent (SE) refraction at baseline was −0.67 D (SD: 3.54 D). The mean interval between visits was 1.99 years (SD: 1.32 years). For the internal validation set, the mean age at baseline, SE at baseline, and visit interval were 8.14 (SD: 3.52), −0.63 D (SD: 3.44 D), and 1.93 (SD: 1.26), respectively. The first external validation consisted mainly of bilateral eye exams in both children and young adults from validation study 1, with the mean age at the time of baseline being 8.16 years old (SD: 3.54 years). The mean SE refraction at baseline was −0.67 D (SD: 3.45 D) and the mean interval between visits was 1.99 years (SD: 1.33 years). The second external validation also consisted mainly of bilateral eye exams in both children and young adults from validation study 2, with the mean age at the time of baseline being 8.19 years (SD: 3.56 years). The mean SE refraction at baseline was −0.66 D (SD: 3.45 D) and the mean interval between visits was 1.99 years (SD: 1.33 years).

The SCMS data consisted of bilateral eye exams in children with mainly one follow-up visit, typically within 1 year after baseline. In this cohort, the mean age at baseline was 7.91 years (SD: 3.19 years). The mean SE refraction at baseline was −2.03 D (SD: 1.81 D). The mean interval between visits was 0.72 years (SD: 0.21 years). The BCES cohort was composed of primary school-aged children with six annual follow-ups between 2011 and 2016; refraction was measured only for the right eye at each visit. In this cohort, the mean age at baseline was 7.71 years (SD: 1.36 years). The mean SE refraction of the right eyes at baseline was −0.50 D (SD: 1. 37 D). The mean time period between visits was 2.47 years (SD: 1.26 years).

The SE was calculated from the refractive error, defined by the following equation:

$$Spherical\ Equivalent = Spherical\ Diopter + \frac{1}{2}(Cylindrical\ Diopter)$$

The annual progression of refractive error was calculated for each visit using the equation:

$$Progression = \frac{Spherical\ Equivalent_{baseline} - Spherical\ Equivalent}{t_{baseline} - t}$$

ML algorithms were used for myopia progression prediction

For training purposes, raw data were curated to include only patients meeting the following criteria: two or more visits; <20 years old at the baseline visit; follow-up periods at least 6 months apart; baseline SE between 6.00 and −20.00 D with presence of myopic progression, defined as endpoint SE < baseline SE. Myopia progression >3 D per year was considered atypical and excluded. We also excluded patients with strabismus or amblyopia in our study. The same inclusion criteria were applied to all five external validation data sets. Furthermore, we performed data preprocessing on the all datasets, with two senior ophthalmologists responsible for the removal or correction of missing values, outliers, and erroneous data from the original dataset. All participants' names and personal identifying information have been anonymized.

We used two distinct learning methods, regression and classification, to develop our ML models. We used multivariate linear regression to analyze the linear relationship between two or more explanatory variables. This model was applied to our data to predict annual myopia progression by exploring the linear relationship between the following features: age at baseline, SE at baseline, the time interval between baseline and follow-ups, and corresponding outputs: SE at subsequent follow-up sessions. We applied the same features to logistic regression, a form of classification, to determine if a patient would progress to high myopia, defined as SE ≤ −6.00 D.

GMS data were used for training and internal validation. Patients were split into a 9 : 1 training-to-testing ratio and simultaneously evaluated using 10-fold cross-validation. External validation was performed in four other independent cohorts to confirm the rate of progression.

The metrics used to evaluate the multivariate linear regression model with internal validation for the GMS cohort and external validation cohorts [the first external validation study (validation study 1), the second external validation study (validation study 2), SCES, BCMS] were mean absolute error (MAE) and R^2 value. MAE is calculated by taking of absolute errors, and is applied when needing to distribute equal weight across all errors. To evaluate the efficacy of logistic regression as a classification model of predicting high myopia cases, the following metrics were used: accuracy, sensitivity of predicting high myopia, specificity of identifying non-progressors, and area under the receiver operating characteristic (ROC) curve (AUC). The training and validation experiments utilized Python 3.6.9.

Analysis of factors affecting high myopia progression

To assess factors influencing the probability of progression to high myopia, we estimated survival curves by the nonparametric Kaplan–Meier method. The log-rank test was used for univariate analysis of categorical variables to determine differences between curves. $P < 0.05$ was considered significant. The study data were analyzed using R version 4.0.3.

Results

Patient characteristics

We collected 612 530 medical records of 227 543 patients from five Chinese cohorts retrospectively (Table 1). All cohorts were composed of a wide range of patients from infants to young adults who underwent complete eye exam, including cycloplegic refraction and visual acuity measurements, at various follow-up time points. A total of 273 307 clinical records of 88 111 patients (49 993 male, 38 118 female) with two or more visits from the GMS cohort were used to train the AI system. A total of 29 445 medical records of 10 023 patients (5 778 male, 4 245 female) were used as the internal validation set. Clinical demographics for each cohort are listed in Table 1. Four other patient cohorts were used to externally validate the ML model (see Methods).

We evaluated the myopic distribution data of the training cohort, and a noticeable correlation was observed between age and SE from age 2 to 20 years (supplementary Fig. 1, see online supplementary material). The younger children of the GMS cohort showed mainly hyperopic to plano refraction errors. At age 8 years, the median SE was + 0.07D [interquartile range (IQR): −1.74 to +1.28D]; at age 16 years, the median SE was −3.40D (IQR: −4.72 to −1.77D); at age 20 years, the median SE was −3.77D (IQR: −5.15 to −2.10D). These results indicate a progressive myopia shift over time. Furthermore, this progression trajectory is similar to other demographic population studies reported in the literature, supporting the representative nature of the cohort [2].

Myopia progression prediction

Multivariate linear regression was performed to analyze the progression of SE over time. Scatter plot graphs of actual and predicted SE for each instance in all cohorts and histograms of prediction error were generated to further evaluate the accuracy of the model for each cohort.

The model produced high accuracies across all cohorts while fitting the variability of each dataset. The internal validation of the GMS dataset produced an R^2 value of 0.964 (Fig. 1A) and MAE of 0.119D [95% CI: 0.119, 1.146], with predicted values within ± 1D of the actual SE 86% of the time (Fig. 1B).

We then tested the model on external independent cohorts from other parts of China. When tested in the first external validation dataset (validation study 1), the model produced an R^2 value of 0.950 (Fig. 1C) and a MAE of 0.119D [95% confidence interval (CI): 0.119, 1.136], with predicted values within ±1D 83% of the time (Fig. 1D); whereas in the external validation study 2 (validation study 2), the model produced an R^2 value of 0.950 (Fig. 1E) and a MAE of 0.121D [95% CI: 0.121, 1.144], with predicted values within ±1D 83% of the time (Fig. 1F). A third external independent validation using the SCES cohort was also performed, which produced an R^2 value of 0.806 (Fig. 1G) and a MAE of −0.066D [95% CI: −0.066, 0.569], with predicted values within ±1D 86% of the time (Fig. 1H). Furthermore, a fourth external independent validation using the BCES produced an R^2 value of 0.749 (Fig. 1I) with a MAE of 0.178D [95% CI: 0.178, 1.557] and predicted values within ±1D 74% of the time (Fig. 1J).

Prediction of progression to high myopia

High myopia (defined as SE ≤ −6.00 D) has been associated with a range of ocular comorbidities, including glaucoma, myopic maculopathy, and retinal detachment [15, 16]. In addition, the condition places significant financial and healthcare burdens on the working population, given the direct and indirect costs associated with vision loss. To predict the onset of high myopia, logistic regression classifiers were trained to detect cases likely to progress to high myopia, and ROC curves were built for all five cohorts. In the internal validation cohort, our AI algorithm produced an accuracy of 94.31%, sensitivity of 98.96%, and specificity

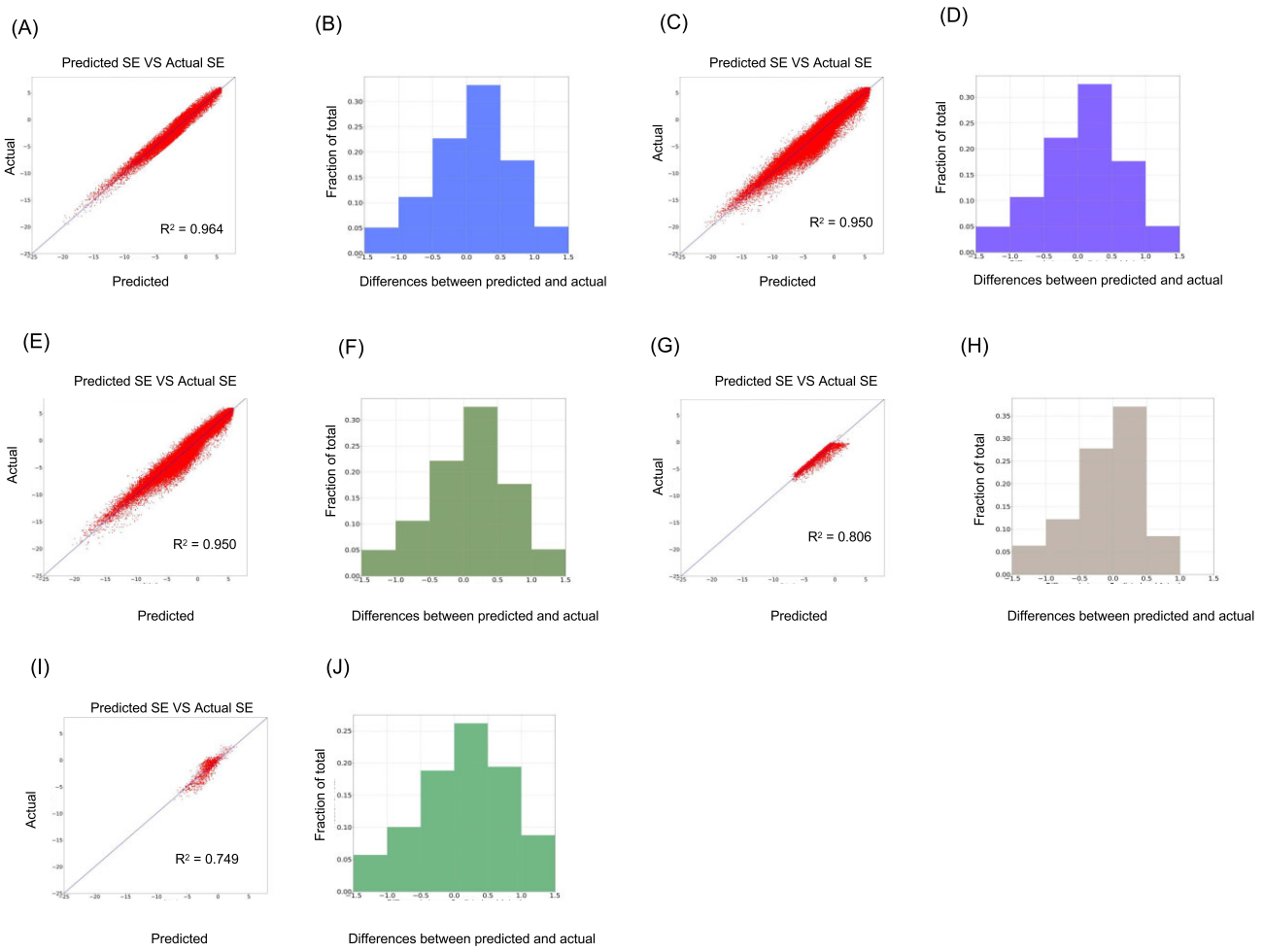


Figure 1. Training and validation of a ML model of myopia prediction. Scatter plots illustrating the linear regression model (**A**, **C**, **E**, **G**, **I**) and histograms displaying the prediction errors (**B**, **D**, **F**, **H**, **J**) for both internal and external validation cohorts. The corresponding cohorts are as follows: internal validation cohort in GMS (**A**, **B**), external validation study 1 (**C**, **D**), external validation study 2 (**E**, **F**), SCMS (**G**, **H**), and BCES (**I**, **J**).

of 93.70% (Fig. 2A) in detecting high myopia progressors, and AUC of 0.99, indicating high accuracy (Fig. 2B). Furthermore, external validation yielded comparable results. When evaluating the validation study 1 dataset, the model produced an accuracy of 93.95%, sensitivity of 96.28%, specificity of 93.62% (Fig. 2C), and AUC of 0.99 (Fig. 2D). Similar results were observed when classifying high myopia in the external validation study 2 dataset: logistic regression produced an accuracy of 93.93%, sensitivity of 96.29%, specificity of 93.59% (Fig. 2E), and AUC of 0.99 (Fig. 2F). When evaluating the SCES cohort, the model achieved an accuracy of 89.54%, sensitivity of 90.91%, specificity of 89.49% (Fig. 2G), and AUC of 0.96 (Fig. 2H). Similarly, an accuracy of 96.18%, sensitivity of 90.00%, specificity of 96.27% (Fig. 2I), and AUC of 0.99 (Fig. 2J) were produced when evaluating the BCES dataset. We further assessed factors influencing the probability of progression to high myopia. We found that an annual myopia progression rate > 1.00 D was associated with higher probability and shorter time frame for progression to high myopia. Specifically, the subgroup with annual progression rate > 1D had a median survival time of 3.39 years, which is faster than the survival time of 4.05 years for the subgroup with annual progression rate ≤ 1D for developing high myopia ($\chi^2 = 122$, $P < 0.001$, Fig. 3A). In addition, the subgroup of younger age of onset of myopia (between 3–7 years) was more likely to progress to high myopia (median survival time 3.13 years) than the subgroup with older age of onset (8–18 years, median survival time 4.01 years) ($\chi^2 = 178$, $P < 0.001$) (Fig. 3B).

Discussion

Myopia, commonly known as short-sightedness, has become a global epidemic. Already the leading cause of visual impairment globally, myopia continues to increase in prevalence, notably in children and young adults in urbanized environments. This prevalence is particularly concerning because myopia, and especially high myopia, is not only associated with the socio-economic burdens relating to spectacle- or contact lens-dependence, but also with increased life-time risks of irreversible vision loss from glaucoma, retinal detachment, and retinal degeneration.

In this study, we developed ML models to predict myopic progression and risk of high myopia in pediatric populations from China, where myopia is highly prevalent. We validated this model in several external validation cohorts from across urban areas in China (Guangzhou, Shanghai, and Beijing), the results of which suggest that the model can consistently predict myopia progression with a high degree of accuracy and is applicable to different

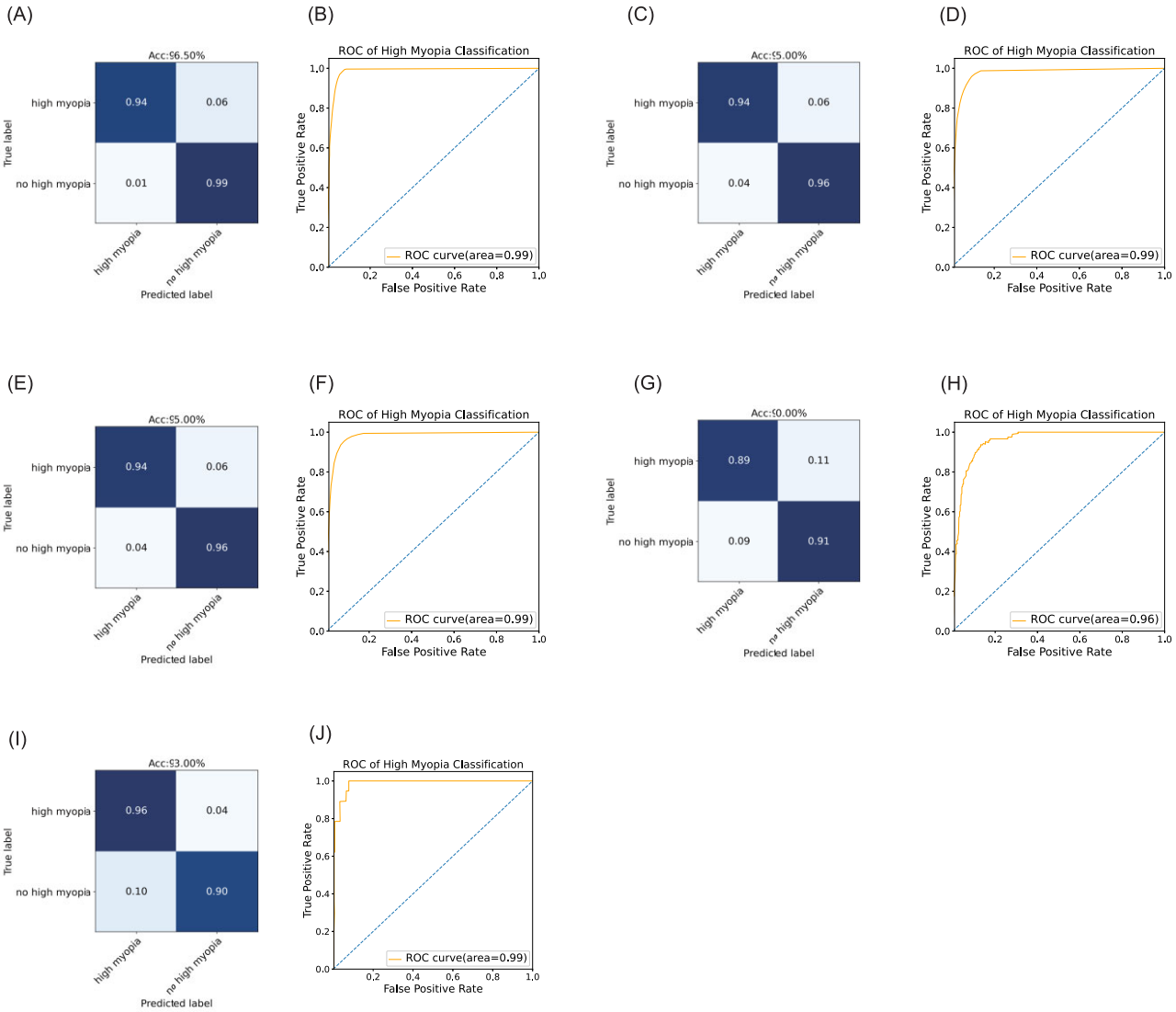
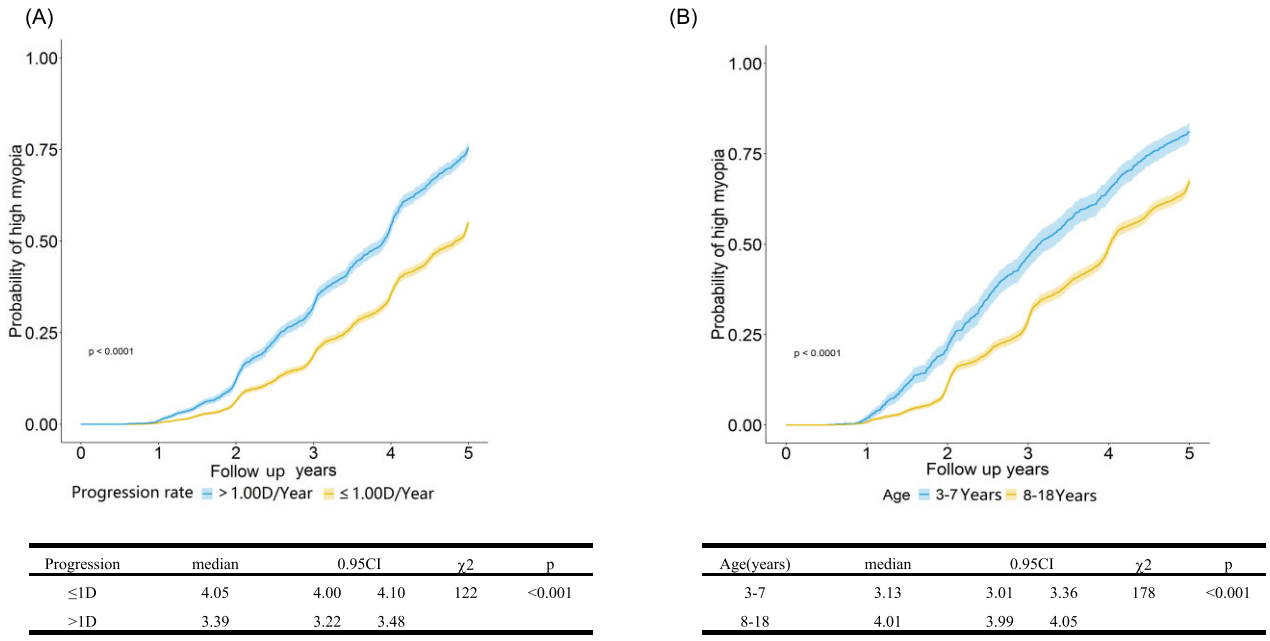


Figure 2. Prediction of progression to high myopia. Normalized confusion matrices (**A**, **C**, **E**, **G**, **I**) and ROC (**B**, **D**, **F**, **H**, **J**) of high myopia classification via a logistic regression model for internal validation and external validation. The corresponding cohorts are as follows: internal validation cohort in GMS (**A**, **B**), external validation study 1 (**C**, **D**), external validation study 2 (**E**, **F**), SCMS (**G**, **H**), and BCES (**I**, **J**).

urban geographic populations. Our study has some limitations, one of which is how it can be generalized and applied to other ethnic groups or in rural areas. A recent study investigated myopia progression in school-age children in China and observed similar findings, which support our conclusions [17]. In addition, their study included cohorts from rural and less-urbanized areas in China, suggesting this ML method may be generalizable in a wider range of populations in different geographic locations in China.

We developed a logistic regression model that demonstrated robust ability to predict children who were at a higher risk of developing high myopia among the general myopic population. Our analyses suggest that high myopia is associated with early age of onset of myopia (under the age of 8 years) and >1.0D myopia shift over 1 year. Stratifying myopic patients into early versus late/fast versus slow progressors will help to identifying inherent genetic risk and external environmental factors in myopia progression, as the exact pathogenic mechanism remains largely unclear. Current modalities for preventing myopia progression in children range from low-risk strategies such as lifestyle adjustments (e.g. increased outdoor activity time) and light therapy [18], to more invasive treatments such as orthokeratology lenses and daily administration of cycloplegic eye drops (e.g. atropine) [19]. Given the high prevalence of childhood myopia and the importance of parental participation and involvement in the administration of any potential therapy or intervention, tailoring the management of myopia in a child at the highest risk of progression is critical. Therefore, our ML algorithm can have an important clinical impact for identifying children at risk of developing high/pathologically high myopia for early intervention to reduce their risk of myopia-related morbidities.

In summary, in this study we developed a comprehensive ML framework for prediction of myopia progression and the risk of high myopia. Our ML models will aid in identifying high-risk patients and help guide developments in advancing therapeutic interventions for this common condition.



Progression	median	0.95CI		χ2	p
≤1D	4.05	4.00	4.10	122	<0.001
>1D	3.39	3.22	3.48		

Age(years)	median	0.95CI		χ2	p
3-7	3.13	3.01	3.36	178	<0.001
8-18	4.01	3.99	4.05		

Figure 3. Analysis of factors affecting high myopia progression. (**A**) Probability of progression to high myopia according to annual progression rate over time. Table reports median survival time of different progression rate groups. Probability of progression to high myopia (y-axis) was measured over time (x-axis) in two groups with an annual progression rate > or ≤ 1.00D. The group with >1.00 D annual progression rate (blue line) had a higher probability and a shorter time frame to progress to high myopia. Log-rank test was used to calculate *P* values. (**B**) Probability of progression to high myopia according to age of onset over time. Table reports median survival time of different age groups. Probability of progression to high myopia (y-axis) measured over time (x-axis) in two different age groups. The blue-line group (3 to 7 year-olds) was more likely to progress to high myopia than the yellow-line group (8 to 18 year-olds) ($P = 0.0001$). Log-rank test was used to calculate *P* values.

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Supplementary data

Supplementary data is available at *PCMEDI* online.

Conflict of interest

The authors declare no competing interests. Besides, as an Editor-in-Chief of Precision Clinical Medicine, the corresponding author Kang Zhang was blinded from reviewing and making decision on this manuscript.

Author contributions

Conceptualization and Supervision: X.-T.Z. and K.Z.; Data curation and Methodology: X.-T.Z., Y.Z., J.X., Z.Li, J.Zhao, M.L., J.L., S.Z., J.Zeng, W.X., I.Z., H.M., Z.Z., T.G., Z.Liu, Z.S., R.W., H.J., Y.G., and K.Z.; Writing-review & editing: X.-T.Z., and K.Z.; Funding acquisition: W.X., and K.Z. .

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