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Research Paper

Early changes in choroidal thickness and ocular biometry in predicting who will achieve full myopia control with repeated low-level red light therapy

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ABSTRACT

Purpose: To evaluate the early predictors for achieving full myopia control with repeated low-level red light (RLRL) therapy based on two independent randomized clinical trials (RCTs).
Methods: Myopic children undergoing RLRL therapy from a multi-center RCT (training set) and a single-center RCT (validation set) were included. Full myopia control was defined as axial elongation <0.1mm/year. Variables included age, sex, baseline refraction, ocular parameters at baseline, 1 and 3 months (axial length [AL] and subfoveal choroidal thickness [sChT]), as well as their rates of change over the first 3 months. Four random forest models to predict full myopia control after 1 year and a logistic regression was used to estimate 2-year outcome.
Results: A total of 148 children were analyzed. The proportions of 1-year full myopia control was 54.2 % of eyes in the training set and 55.0 % in the validation set. Random forest models incorporating the rate of change in AL and sChT showed high predictive accuracy (AUC: 0.97 to 0.98) in external validation. The rate of change in AL contributed the most for model accuracy. For 2-year control, the rate of AL change had an AUC of 0.99 while the rate of change in sChT achieved only 0.69.
Conclusions: The rate of change in AL during the first three months emerged as the most important predictor for treatment outcomes at both 1-year and 2-year, rather than the change in sChT. Early monitoring of AL changes could be a valuable tool for identifying children most likely to benefit from this intervention.

1. Introduction

With the increasing prevalence of myopia and the early onset of myopia, controlling the progression of myopia to prevent it from developing into high myopia and related complications has become a significant research topic over the past few decades [1–4]. Currently, there are various treatment methods available for myopia, including low-dose atropine eye drops, orthokeratology, and defocus spectacles. The reduction in myopic progression rate with these methods typically ranges around 42.0 % [5]. However, for younger individuals with higher degrees of myopia, the effectiveness of these treatments may be relatively limited, as these patients often progress more rapidly and require more potent control measures. Other behavior-related interventions, such as spending more time outdoors and reducing near-work activities or screen time, have not shown a significant impact on myopia progression [6], highlighting the need for more effective strategies and a deeper understanding of myopia management.

In recent years, Repeated Low-level Red Light (RLRL) therapy has emerged as a novel approach for myopia control. Multiple randomized controlled trials have demonstrated that RLRL achieves a control

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efficacy of around 80 % [7–10]. With this treatment, many patients can attain complete myopia control, with minimal or even reduced axial elongation, with a proportion of 20 % experiencing axial shortening [11, 12]. However, current RLRL therapy involves laser irradiation. Although most devices claim to meet Class 1 laser standards, research suggests that many devices may exceed safety limits [13]. In 2023, Liu H et al. reported a case of laser-induced retinal injury [14], which raised concerns and prompted stricter policies on the use of RLRL in China [15]. Early identification of whether myopic patients can benefit from RLRL therapy, reducing unnecessary adverse reactions, is therefore critical.

Nevertheless, the mechanism behind this treatment approach remains unclear. Studies utilizing RLRL have consistently observed a significant 10–20 % thickening of the posterior choroid in the eyes of myopic children following treatment with red light therapy [7,8,12,16]. The potential mechanism underlying its efficacy may be attributed to the photobiomodulation effect, where the wavelength of red-light irradiation is absorbed by cytochrome C oxidase in the mitochondrial respiratory chain. This absorption increases the activity of cytochrome C oxidase, which in turn helps activate complex V (ATP synthase), leading to the production of more ATP. The increased ATP in regions with injury or impaired blood perfusion can help reactivate injured cells and correct metabolic disorders [17,18]. However, whether choroidal thickening is a determinant for optimal myopia control has yet to be substantiated by research. In pre-myopic children, the 3-month change in choroidal thickness can predict AL progression of ≤0.15 mm/year after RLRL treatment [19]. However, there has been no external validation or long-term data to further confirm choroidal thickness as a reliable predictor of treatment efficacy.

Therefore, we aim to assess the role of choroidal thickness and ocular biometry in predicting individuals who will achieve complete myopia control using RLRL, and this will be validated using independent randomized controlled trial data. This investigation seeks to identify early predictors for the treatment outcomes of this innovative treatment and enhance our understanding of the underlying mechanisms, ultimately guiding personalized treatment strategies for myopia management.

2. Methods

2.1. Study populations

The RCT data were sourced from two studies. The first was a multicenter, randomized clinical trial conducted at five study centers across four tertiary hospitals in China. This study ran from July 2019 to August 2019, followed by a one-year real-world observation to assess the long-term efficacy and safety of the treatment. In the first year, the RCT included 264 myopic children aged 8–13, with spherical equivalent refraction (SER) ranging from −1.00 to −5.00 diopters, astigmatism of ≤ 2.50 D, anisometropia ≤1.50 D, and best-corrected visual acuity (BCVA) of 1.0 or better in either eye. Participants were randomly assigned to receive either RLRL + single-vision glasses or single-vision glasses for myopia treatment [12]. In the second year, 138 children continued with follow-up [20]. The second study was a single-center RCT conducted in Shenzhen, China, from June 2021 to July 2022, involving 72 myopic children aged 7–15, with SER ≤−1.0D, astigmatism ≤ 2.50D, anisometropia ≤1.50 D, and BCVA of 1.0 or better in both eyes. Participants were randomly assigned to receive either RLRL + single-vision glasses or 0.01 % atropine + single-vision glasses treatment [11]. The current analysis included myopic children treated with RLRL+ single-vision glasses, using data from the multicenter RCT to develop a predictive model and validating it with data from the single-center RCT. Both studies used the same device for RLRL therapy (Eyerising, Suzhou Xuanjia Optoelectronics Technology). This device emits red light at 650 ±10 nm from semiconductor laser diodes at an illuminance level of 1600 lx, directed from the pupil to the fundus for three minutes, twice daily, with at least a four-hour interval between sessions. The multicenter study followed a protocol of five days per week, while the single-center study instructed daily use, seven days a week.

2.2. Measures

In both RCTs, cycloplegic autorefraction was measured using autorefractors (multi-center RCT: Topcon KR8800; single-center RCT: Nidek ARK-1) for each participant at baseline and each follow-up visit. Cycloplegia was achieved using 3 drops of 1 % cyclopentolate (Alcon, Geneva, Switzerland). Ocular biometry was measured using IOLMaster (Carl Zeiss IOLMaster 500). Uncorrected visual acuity (UCVA) was assessed using ETDRS logMAR charts following standard procedures in both trials [21,22]. Choroidal thickness was obtained from OCT images (multi-center RCT: Topcon DRI-OCT Triton; single-center RCT: Carl Zeiss Cirrus OCT 500). The choroidal thickness was defined as the distance between outer choroid-scleral margin and retinal pigment epithelium-Bruch's complex. Sub-foveal choroidal thickness (sChT) was used in the analysis.

2.3. Statistical methods

Both eyes were included for analysis. The SER was defined as the sum of the sphere power and half the cylinder power. Myopia was defined as an SE of ≤ −0.50 diopters (D). Full myopia control was defined as an annual axial length (AL) progression of <0.1 mm. The rate of change in AL was calculated as the beta coefficient of the linear regression for the AL measurements at baseline, the first month, and the third month. Similarly, the rate of change in sChT was defined as the beta coefficient of the linear regression for the sChT values at baseline, the first month, and the third month.

The normality of our data was tested using the Shapiro-Wilk test. A logistic regression analysis was conducted to estimate univariate associations. A Random Forest algorithm was used to predict full myopia control, implemented using the randomForest package in R. The model was constructed using 500 trees to ensure stability of predictions. At each node in the trees, three predictor variables were randomly selected as candidates for splitting, which was appropriate given the total number of predictors in the model. Variable importance measures were calculated to assess the significance of each variable. Data from the multi-center RCT were used to build the model, and external validation was performed using data from the single-center RCT. Missing data at specific follow-up visits were imputed using the mean value at that time point. Early changes (1-month and 3-month visits) in axial length (AL), sChT, and UCVA were compared between the fully controlled and non-fully controlled groups using *t*-tests. P-values <0.05 were considered statistically significant. All analyses were conducted using Stata 16.0 (StataCorp) and R software (https://www.r-project.org/).

3. Results

A total of 119 children, with an average age of 10.44 ± 1.37 years, from a multi-center RCT, and 29 children, with an average age of 9.87 ± 1.51 years, from a single-center RCT, were included in the current study. As summarized in Table S1, the mean age at baseline between the model training set and the external validation set showed a slight difference ($P = 0.0402$). There were no significant differences in gender distribution, SER, and AL in the right eyes at baseline (all $P > 0.05$). In the training set, 129 eyes (54.2 %) achieved full myopia control after 1 year of treatment, and 14 eyes (58.3 %) achieved full control after 2 years of treatment. In the validation set, the rate of full myopia control for 1-year treatment was 55.0 %.

Table 1 presented the baseline characteristics of 1-year fully controlled and non-fully controlled group in training set. The baseline age and gender distribution were similar between the fully controlled and non-fully controlled groups in the training set, with no significant differences ($P > 0.05$ for both). The baseline SER was slightly more myopic in the fully controlled group compared to the non-fully

Table 1
Baseline characteristics of the fully controlled and non-fully controlled group.

Parameter	Fully Controlled (n = 119)	Non-fully Controlled (n = 29)	P
Baseline age, mean(SD), y	10.64(1.29)	10.16(1.43)	0.0599
Female, %	52.9 %	46.15 %	0.5430 *
Baseline SER, mean(SD), D	−2.28(0.87)†	−2.67(0.94)‡	0.0010
Baseline AL, mean(SD), mm	24.53(0.61)†	24.58(0.70) ‡	0.5280

* Chi-square test. †238 eyes. ‡ 62eyes.
SD: standard deviation. SER: spherical equivalent refraction. AL: axial length.

controlled group (−2.28 ± 0.87 D vs. −2.67 ± 0.94 D, P = 0.0089). However, there was no significant difference in baseline axial length (AL) between the two groups (24.53 ± 0.62 mm vs. 24.58 ± 0.70 mm, P = 0.5280).

Based on the previous analysis of the RCT data, AL and sChT were the two ocular parameters that showed the most significant changes [11, 12]. Additionally, 21.8 % of participants experienced an improvement in UCVA of >2 lines. Therefore, we selected AL, sChT, and UCVA for analysis to explore their early changes between the fully controlled myopia group and the non-fully controlled group.

As shown in Fig. 1A–C, for subjects undergoing 1-year treatment, AL decreased in both groups at the 1-month (fully controlled: −0.05±0.06 mm, non-fully controlled: −0.01±0.05 mm). However, in the non-fully controlled group, AL increased at 3 months (0.04±0.06 mm, P < 0.05), indicating a difference in early AL change trends between different treatment effects. Both the fully controlled and non-fully controlled groups showed an increase in sChT at 1 month, but by the 3-month, sChT began to decrease in the non-fully controlled group (−3.75±17.80 μm). Changes in UCVA at 1 and 3 months showed no significant differences between the two groups (P > 0.05 for all).

For subjects with 2-year treatment (Fig. 1D–F), there was a significant difference in AL change at 1 month between the two groups (fully controlled: −0.09±0.07 mm vs. non-fully controlled: −0.01±0.05 mm, P = 0.0109). However, no significant differences were observed in the changes of AL, sChT, and UCVA for the remaining time points.

We used logistic regression for univariate analysis to identify potential significant predictors. As shown in Table 2, the 1-month and 3-month changes in AL and sChT demonstrated statistical significance in the univariate logistic analysis (all P < 0.05), whereas UCVA did not. The rate of change in AL and sChT, defined as the linear regression coefficient over three time points, also showed a significant association with the 1-year full control outcome (both P < 0.05).

We used four different combinations of variables in a random forest model to predict 1-year full myopia control. The predictive performances are summarized in Table 3. All four models achieved a high AUC of 1.00 in the training set. However, Model 1, which included age, sex, 3-

Table 2
Univariate logistic regression in training sets.

Variable	OR	95 %CI	P
1-month change in AL	−12.01	−17.12, −6.89	<0.001
1-month change in sChT	1.03	1.01, 1.05	0.018
1-month change in UCVA	2.39	0.16, 36.25	0.531
3-month change in AL	0.00	0.00, 0.00	<0.001
3-month change in sChT	1.06	1.03, 1.08	<0.001
3-month change in UCVA	4.80	0.39, 59.02	0.221
Rate of change in AL (0 to 3 months)	0.00	0.00, 0.00	<0.001
Rate of change in sChT (0 to 3 months)	1.07	1.02, 1.12	0.008
Rate of change in UCVA (0 to 3 months)	117.79	0.08, 169,737.8	0.199

OR: odds ratio. CI: confidence interval. AL: axial length. sChT: sub-foveal choroidal thickness. UCVA: uncorrected visual acuity.

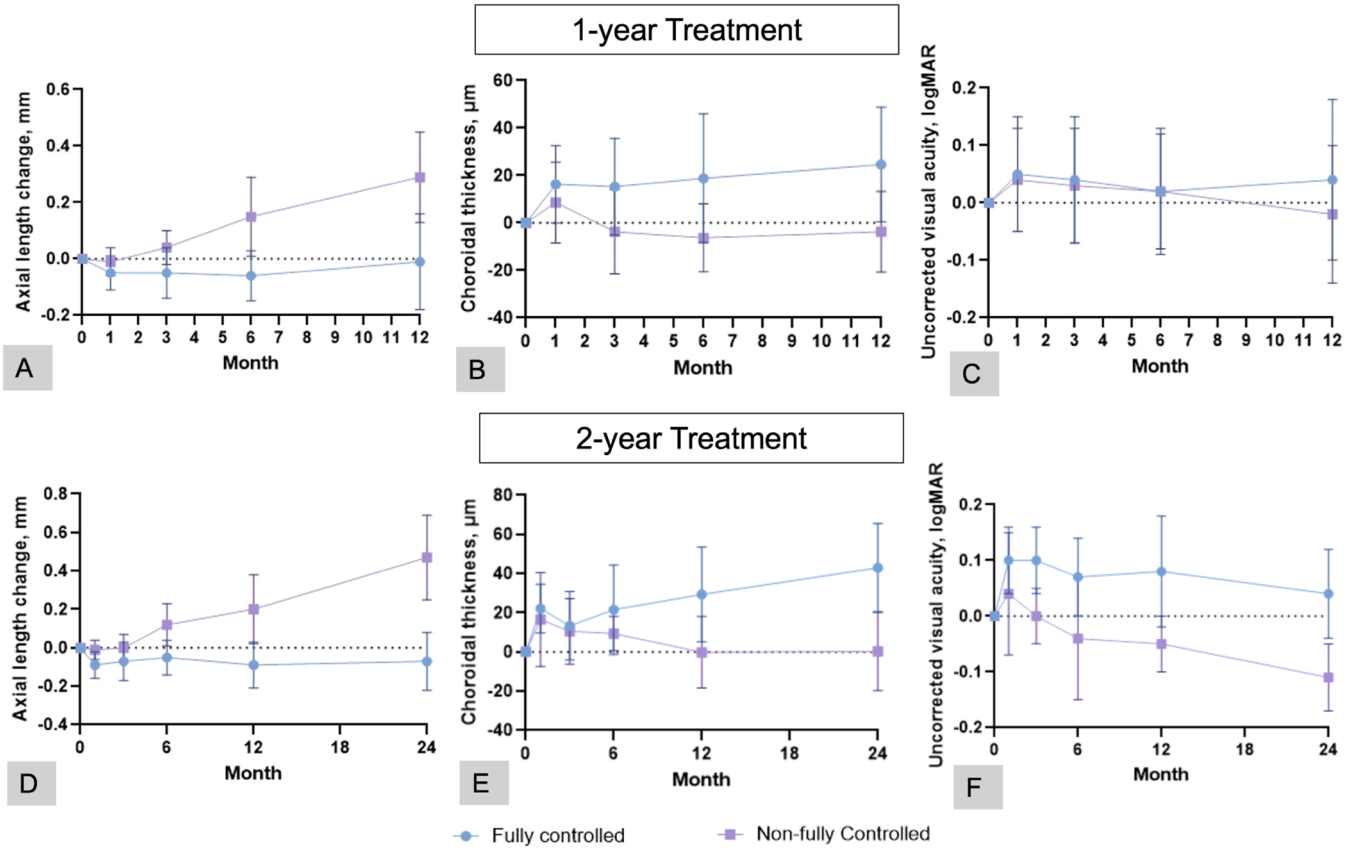

Fig. 1. The change of axial length, choroidal thickness and uncorrected visual acuity over time in children underwent red light therapy.

Table 3
Predictive performance of models for predicting 1-year full myopia control in internal and external validation data sets.

Model	Training set		External validation	
	AUC	95 %CI	AUC	95 %CI
1. Age, sex, 3-month change in AL, 3-month change in sChT	1.00	1.00, 1.00	0.74	0.61, 0.87
2. Age, sex, 3-month change in sChT, 3-month change in AL, rate of change in sChT, rate of change in AL	1.00	1.00, 1.00	0.98	0.96, 1.00
3. Age, sex, baseline sChT, baseline AL, baseline SER	1.00	1.00, 1.00	0.61	0.46, 0.76
4. Age, sex, baseline sChT, baseline AL, rate of change in sChT, rate of change in AL	1.00	1.00, 1.00	0.97	0.93, 1.00

AUC: area under curve. CI: confidence interval. sChT: sub-foveal choroidal thickness. AL: axial length. SER: spherical equivalent refraction.

month change in AL, and 3-month change in sChT, only showed an AUC of 0.74 (95 % CI: 0.61 to 0.87) in external validation. Model 3, which included age, sex, baseline sChT, baseline AL, and baseline SER, achieved an AUC of only 0.61 (95 % CI: 0.46 to 0.76) in external validation. In contrast, models that included the rate of change as predictors performed better in external validation, with Model 2 (Model 1+ rate of change in AL and sChT) achieving an AUC of 0.98 (95 % CI: 0.96 to 1.00), and Model 4 (Model 3 + rate of change in AL and sChT) achieving an AUC of 0.97 (95 % CI: 0.93 to 1.00).

The variable importance of the best performed model, Model 2, was plotted in Fig. 2. Rate of change in AL over the first 3 months showed the highest importance (59.83), indicating that it contributes thee most to the accuracy of the model. It followed by 3-month change in AL (41.00). The importance of age, rate of change in sChT, 3-month change in sChT and gender were <20 of mean decrease accuracy.

For the 2-year full myopia control analysis, due to the limited number of subjects and the absence of a 2-year follow-up in the validation dataset, we calculated the AUC using univariate logistic regression. As shown in Table S2, the rate of change in AL from 0 to 3 months demonstrated an excellent AUC of 0.99 (95 % CI: 0.91 to 1.00), followed by the 3-month change in UCVA, which had an AUC of 0.89 (95 % CI: 0.69 to 0.99). In contrast, the 3-month change in AL, as well as the 1-month and 3-month changes in sChT and UCVA, achieved lower AUCs.

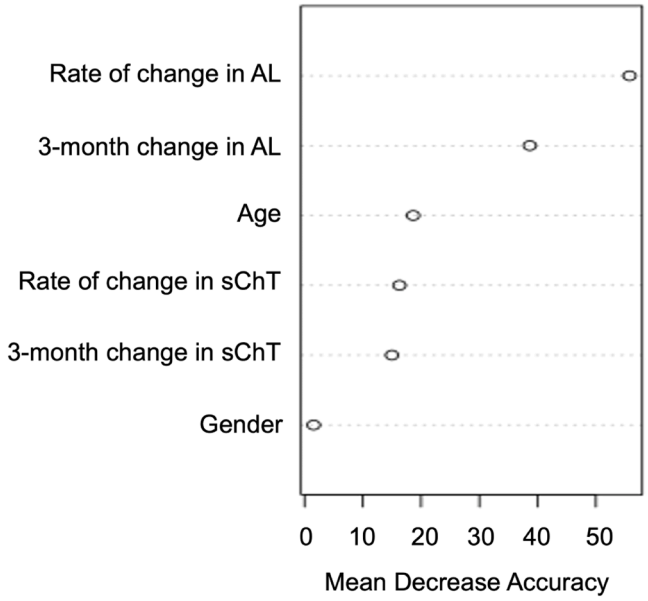

Fig. 2. Variable importance plot in random forest model 2.

4. Discussion

In this study, we identified early predictors of full myopia control using RLRL therapy by analyzing data from a multi-center and a single-center RCT. Our findings revealed that patterns of axial length and choroidal thickness change significantly differed between the fully controlled and non-fully controlled groups. Notably, the rate of change in AL during the first three months emerged as the most important predictor for treatment outcomes at both the 1-year and 2-year, rather than change in sChT. Models incorporating the rate of change in AL demonstrated high accuracy, with AUC values ranging from 0.97 to 0.98 in external validation. These results suggest that monitoring changes in AL at early phase of treatment could be a valuable tool for identifying patients who are most likely to benefit from this innovative myopia intervention.

Choroidal thickening is a notable feature of using red light therapy for myopia treatment. A study used the 3-month change in sChT or perifoveal temporal choroidal thickness to predict the 1-year AL change of <0.15 mm/year in pre-myopic children, achieving high AUC values. However, they did not perform external validation [19]. In our study, while we achieved high accuracy in the training set, the actual changes in AL or sChT did not yield high AUC values during external validation. Conversely, the rate of early changes in AL was a strong predictor of the therapy's effectiveness, whereas sChT was less significant. Notably, for the 2-year outcomes, there was minimal difference in sChT between the two groups, and the rate of change in sChT was not a strong predictor for the 2-year outcome. Therefore, there may be no significant linear relationship between choroidal thickening and AL control effectiveness. Our previous analysis demonstrated that changes in sChT could only explain 28.3 % of the AL changes in the treatment group [23]. In the current study, the correlation between sChT thickening and AL change was smaller in the fully controlled group compared to the non-fully controlled group (−0.5420 vs. −0.6338). This suggests that other mechanisms may contribute to the efficacy of red light in controlling myopia, such as a potential decrease in myopia progression through the reduction of scleral glycosaminoglycan synthesis resulting from increased choroidal permeability [24,25].

In subjects undergoing one year of treatment, both the fully controlled and non-fully controlled groups exhibited significant AL shortening and choroidal thickening in the first month. However, the non-fully controlled group experienced a shift by the third month. In the study by Liu et al., myopic children receiving RLRL therapy showed the most pronounced AL shortening in the first month, with the rate of shortening beginning to decrease by the third month [26]. Similarly, Wang et al. reported a significant increase in sChT during the first month, with the rate of increase slowing by the third month [27]. However, neither study reported a connection between these changes and the final control outcomes. Therefore, the mechanisms behind these changes remain unclear. In our study, the baseline characteristics of the fully controlled and non-fully controlled groups were very similar, suggesting that age, gender, and baseline myopia level have a minimal impact on long-term full control outcomes. Further research may be needed to explore potential mechanisms, such as whether increases in the choroidal luminal area and stromal area [28] exhibit a saturation effect.

The rates of full myopia control after 1 year and 2 years (54.2 % and 58.3 %, respectively) were similar in our data. Notably, 81.25 % of subjects responded well at the first year continue to have full control at the second year. This indicating a sustained effect but not a significantly accumulated effect over the 2-year period, and the impact of the therapy may plateau over time. Several factors could contribute to this observation, including individual variability in response to treatment, potential adaptation to the therapy, or the natural progression of myopia that might not be fully mitigated by the treatment alone. Continuing the therapy could still be beneficial for maintaining the achieved level of control, especially in patients who respond well to the treatment.

However, it may be beneficial to consider a personalized approach to determine the optimal duration of treatment for each patient, such as when myopia progression stabilizes (for example, around the age of 15) [29]. Regular monitoring and assessment of myopia progression can aid in making informed decisions about whether to continue or adjust the treatment.

The concept of full myopia control originates from the cutoff points of physiological eye growth. Our previous study indicates that the compensated AL progression for progressive myopia is approximately 0.10 mm per year for children under 11 years old [30]. This means that when evaluating the effectiveness of myopia control, we need to consider whether the AL progression at least reaches the threshold of physiological growth. If the treatment effect does not meet this standard, then due to concerns about the adverse effects of red light therapy, its benefits may not outweigh the potential damage to the retina. Therefore, full myopia control can serve as an optimal endpoint for assessing the best treatment outcomes for red light therapy and other treatments with potential ocular safety concerns, including low-dose atropine (associated with risks of allergic conjunctivitis) and orthokeratology (correlated with corneal infection risks). For individuals who are unlikely to achieve full myopia control, less aggressive treatments can be considered, such as Defocus Incorporated Multiple Segments (DIMS) spectacles [31] and diffusion optics spectacles [32], to balance treatment effectiveness and risk. In the training set, 129 eyes (54.2 %) achieved full myopia control after 1 year of treatment, and 14 eyes (58.3 %) achieved full control after 2 years of treatment.

For interventions using different wavelengths of light, a study by S. Thakur et al. [33] investigated the effects of short-term exposure to different wavelengths of light—red, green, and blue—on ocular biometry in humans. Their findings suggest that blue light exposure may inhibit axial elongation, while red and green light exposure may lead to axial elongation. However, it is important to note that this study was conducted over a very short duration, with changes in AL measured in micrometers. Such small changes make it challenging to determine whether they are due to alterations in choroidal thickness, accommodation, or other factors. In contrast, RLRL therapy has been shown not to cause significant changes in choroidal thickness with short-term exposure [34]. But multiple RCTs have already validated its effectiveness of RLRL in controlling axial elongation in myopic eyes. While blue light may show promise in short-term studies, for exploring clinically meaningful interventions for myopia control, we prefer to rely on red light, which has more substantial evidence supporting its efficacy.

A study has documented a significant rebound effect of RLRL, showing that AL progression was approximately 0.5 mm per year after treatment cessation [20]. This rate, although lower than the 0.64 mm per year observed in individuals wearing single vision spectacles, raises questions about the treatment effect may be diminished by the rebound effect after discontinuation of the therapy. In our study, even though we aim for full myopia control, it remains unclear whether a dose-dependent rebound effect exists, which could potentially offset the benefits of the therapy. Therefore, further research is necessary, and for participants who have shown a positive response to the treatment, we recommend gradually discontinuing red light therapy to minimize the rebound effect.

This study has several strengths, including the external validation of our prediction model using an independent RCT with a study design similar to that of the training set. The high accuracy observed in the external validation underscores the robustness of the predictors in evaluating treatment outcomes. Furthermore, the integration of machine learning techniques, such as random forest models, with dynamic biomarker trajectories—particularly the quantification of AL and sChT rate changes within the first three months—enables early indicators to predict long-term treatment outcomes.

Some limitations must also be acknowledged. First, the limited sample size in the 2-year intervention subgroup ($n = 12$) compromises the ability to derive statistically robust longitudinal inferences, necessitating cautious interpretation of long-term efficacy trends. Second, the cohort comprising only Chinese participants restricts assessment of ethnic variability in therapeutic response, which may obscure population-specific biological or environmental confounders. Third, mechanistic interpretations remain constrained by the absence of advanced choroidal microstructural profiling (e.g., optical coherence tomography angiography or histopathological correlation), precluding definitive conclusions about structural drivers underlying sChT dynamics and their relationship to myopia control efficacy. These gaps collectively underscore the need for larger multiethnic longitudinal studies augmented by multimodal imaging to validate and extend these findings.

5. Conclusion

In conclusion, this study proved the early change in axial length predicts the 1-year outcome of myopia control with validated efficacy. The early change in choroidal thickness may not be a sensitive predictor for RLRL treatment outcome. Monitoring changes in AL at early phase of treatment could be a valuable tool for identifying patients who are most likely to benefit from this myopia intervention.

Statement of ethics

All participants or their guardians provided written informed consent was obtained from all participants. Ethical approval was obtained from the ethics committees at the Zhongshan Ophthalmic Center, and Peking University Shenzhen Hospital. Both trials have been registered (multi-center RCT: NCT04073238 with ClinicalTrials.gov; single-center RCT: ChiCRT2100045834 with the Chinese Clinical Trial Registry). All procedures were conducted in accordance with the Tenets of the World Medical Association's declaration of Helsinki.

CRediT authorship contribution statement

Yanxian Chen: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Mingge Li:** Writing – review & editing, Writing – original draft, Data curation. **Xianwen Shang:** Writing – review & editing, Formal analysis. **Guangyu Li:** Writing – review & editing, Formal analysis. **Ziwei Zhao:** Writing – review & editing, Data curation. **Pengju Li:** Writing – review & editing, Data curation. **Yanjun Liu:** Writing – review & editing, Data curation. **Ruilin Xiong:** Writing – review & editing, Data curation. **Mengying Lai:** Writing – review & editing, Supervision. **Yueye Wang:** Writing – review & editing, Supervision. **Mingguang He:** Writing – review & editing, Funding acquisition, Conceptualization. **Zhuoting Zhu:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The author(s) have made the following disclosure(s): Z.Z.: Patent of red light therapy titled "Method for increasing blood flow and metabolic rate of eye fundus" (US11420072; CN201910490186.6; AU2020233703C1). M.H.: Patent of red light therapy titled "Method for increasing blood flow and metabolic rate of eye fundus" (US11420072; CN201910490186.6; AU2020233703C1). He is also the director and shareholder of Eyerising International Pty Ltd.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pdpdt.2025.104672.

Data availability

All data generated or analyzed during this study are included in this article. For any inquiry, please contact the corresponding author.

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