• Clinical Research •

Refraction difference value variations in children and adolescents with different refractive errors

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Abstract

● **AIM:** To evaluate the refraction difference value (RDV) variations in children and adolescents with different refractive errors and analyze its correlation with refractive development.

● **METHODS:** Participants aged 4-16y with different refractive statuses (hyperopia, emmetropia, myopia) underwent comprehensive eye examinations, including spherical equivalent (SE) refraction, axial length (AL), total RDV (TRDV), and RDVs at various eccentricities (0°-15°, 15°-30°, 30°-45°) and quadrants (inferior, superior, nasal, temporal). Statistical analysis involved one-way ANOVA for group comparisons and Pearson correlation for examining relationships between SE/AL and RDVs. Paired *t*-tests compared quadrant-specific RDVs within groups.

● **RESULTS:** Significant difference was found in TRDV ($P<0.001$), RDV15°-30° ($P=0.033$), RDV30°-45° ($P<0.001$), RDV-inferior (RDV-I, $P<0.001$) and RDV-temporal (RDV-T, $P<0.001$) among hyperopia, emmetropia and myopia group. Pearson correlation analysis revealed a negative correlation of SE with TRDV ($P=0.001$), RDV30°-45° ($P=0.004$), RDV-I ($P=0.047$), and RDV-T ($P<0.001$). The differences between RDV-superior (RDV-S) and RDV-I were statistically significant in all groups ($P<0.001$ for all) and between RDV-T and RDV-nasal (RDV-N) were statistically significant in hyperopia group ($P<0.001$). Within the pre-myopic group, the analysis revealed a negative correlation of SE with RDV-I ($P=0.009$). Pearson correlation analysis revealed a positive correlation of AL with TRDV ($P=0.036$), RDV15°-30° ($P=0.004$), RDV30°-45° ($P<0.001$), RDV-S ($P=0.003$), RDV-I ($P<0.001$), RDV-T ($P<0.001$), RDV-N ($P=0.022$), while revealed a negative correlation of AL with RDV0-15° ($P=0.018$).

● **CONCLUSION:** Our study indicates TRDV, RDV30°-45°, RDV-I, RDV-T may relate to refractive development, and a negative correlation between SE and RDV-I in pre-myopic children.

● **KEYWORDS:** multispectral refractive topography; refraction difference value; degrees of myopia; children; adolescents

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INTRODUCTION

Myopia, the most prevalent refractive error, is a leading cause of visual impairment. Its incidence has been progressively rising globally, especially in Asian countries[1]. It is projected that by 2050, approximately 4.758 billion individuals will be affected by myopia, accounting for 49.8% of the world's population[2]. The pathogenesis of myopia, although not fully understood, is increasingly linked to the refractive status of the peripheral retina[3-4]. Research findings have demonstrated that the human visual system possesses the capacity to detect defocus and adjust its axial length (AL), resulting in the migration of the retina towards the defocused image[5-6]. Hence, peripheral defocus, particularly relative hyperopic defocus, significantly influences on ocular growth and the progression of refractive error[7-11]. In recent years, the relationship between peripheral retinal defocus in various quadrants and eccentricities and the progression of myopia has become a research hotspot. However, different studies[12-15] have produced conflicting results, and the relationship between defocus in different peripheral retinal regions and myopia development remains inconclusive, necessitating further exploration[16]. Multispectral refractive tomography (MRT), as a novel instrument for measuring the refractive status of the peripheral retina, primarily utilizes monochromatic

light and depth computer algorithms, providing precise and repeatable measurements within an eccentric range of 0° to 53° eccentricity[17-18].

In this study, we utilized MRT to measure refraction difference value (RDV) in different eccentricities and quadrants of retina in children and adolescents in the southwestern region of China. We aimed to assess the differences in RDV among patients with varying degrees of refractive error and explore the relationship between RDV and the onset and progression of myopia.

PARTICIPANTS AND METHODS

Ethical Approval This prospective, cross-sectional study was approved by the Ethics Committee of West China Hospital, Sichuan University, China (2023 Review No.1290). Before participating in this study, every child and their family provided written or verbal consent after being informed of the details.

Study Population Conducted between December 9, 2022, and August 4, 2023, at West China Hospital, Ophthalmology Outpatient Department, participants were selected based on the following inclusion criteria: 1) age 4-16y, 2) informed consent; 3) -10 D≤SE≤+7 D [only spherical equivalent (SE) within this range can be measured accurately by MRT]; 4) ability to fully cooperate during examinations; 5) best corrected visual acuity (BCVA)≥20/40 for age<6y, BCVA≥20/25 for age ≥6y. Exclusion criteria encompassed: 1) a history of strabismus, acute, chronic or congenital ocular pathologies; 2) a history of corneal contact lens usage in the past 1mo; and 3) a history of ocular surgeries potentially affecting refraction or AL.

Eye Examinations After enrollment, all the participants were examined by slit lamp microscope. ALs were measured using the IOL Master Biometry (Master 2000, Zeiss Co., Germany) under natural lighting conditions prior to pupil dilation. The mean of three measurements was taken as the final AL result. Refractive errors were assessed using an autorefractometer (AR-360A, NIDEK Co. Ltd., Japan), and the determined by a skilled optometrist under full cycloplegia. For achieving full cycloplegia[19]: 1) children under the age of 6y use 1.0% atropine eye ointment three times a day for three consecutive days; 2) children aged 6 to 12y use 1.0% cyclopentolate eye drops for at least 3 times; 3) children aged 12y and above use 0.5% tropicamide eye drops for at least 3 times. The final drop should be applied 30min before the refraction examination[19]. The refractive error was determined as the mean of three consecutive autorefraction measurements and SE was calculated for further statistical analysis. Then careful fundus examination was performed. Retinal defocus was assessed using MRT (version 1.0.5T05C; Thondar, Inc, China). Measurements were deemed valid and accurate when the machine-generated score was ≥90. If the score fell below 90, measurements were reiterated until a score of ≥90 was achieved. The results that initially met or surpassed the 90 were accepted. All examinations were conducted by the same highly trained and experienced optometrist.

Clinical Assessment The baseline demographic and clinical information of patients were collected, including age, AL, SE, total RDV (TRDV; TRDV within an eccentric range of 0° to 53°), RDVs in different eccentricities and quadrants. According to the SE values, we initially stratified participants into three groups: hyperopia group (>+0.50 D), emmetropia group (-0.5<SE≤+0.5 D) and myopia group (SE≤-0.5 D). Subsequently, we further subdivided the myopia group (SE≤ -0.5 D) into three groups: low myopia (-3.0<SE≤-0.5 D), moderate myopia (-6.0<SE≤-3.0 D), and high myopia (SE≤-6.0 D). Recently, the "Expert Consensus on Myopia Management White Paper (2022)"[20] in conjunction with the "Consensus on Myopia Management for Asia"[21], provides a definition for the concept of pre-myopia. It is defined as follows: SE in children aged 6y and above is less than or equal to the lower limit of hyperopic reserve for their age group, and their SE is greater than -0.50 D. Specifically, the lower limit of hyperopic reserve is +0.75 D for 6y, +0.50 D for 7-8y, +0.25 D for 9-10y, and 0.00 for 11y. To investigate the relationship between RDV and SE in pre-myopic children, some individuals were stratified into "pre-myopic stage" according to this definition[20-21].

Statistical Analysis Statistical evaluations were conducted using SPSS 26.0 (SPSS Inc., Chicago, IL, USA). Normal distribution data were presented as mean±standard deviation (SD), while non-normal data were depicted as median and interquartile range (IQR). Group comparisons involved one-way analysis of variance (ANOVA) for normally distributed variables, and the Kruskal-Wallis test for non-normally distributed ones. Post-hoc pairwise comparisons with Bonferroni correction were conducted following significant global test results. Additionally, paired *t*-tests were utilized to assess symmetry in peripheral refractive status, comparing nasal *vs* temporal and superior *vs* inferior refractions within each group. Pearson correlation analysis determined the relationships between SE and RDV, as well as AL and RDV. A significance level of $P<0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics of the Study Participants Total of 190 participants (378 eyes) were included in this study, but only 129 participants (256 eyes) provided complete refractive data and AL dates. Sixty-one participants (122 eyes) displayed uncooperative behavior during refractive errors testing. Among the 256 eyes with complete SE data, 102 exhibited hyperopia (>+0.50 D), 36 demonstrated emmetropia (-0.5<SE≤+0.5 D), 99 presented with low myopia (-3.0<SE≤-0.5 D), 15 had middle myopia (-6.0<SE≤-3.0 D),

Table 1 Baseline characteristics of the eyes

Characteristics	Hyperopia	Emmetropia	Myopia			No refractive data
			Low myopia	Middle myopia	High myopia	
Number	102	36	99	15	4	122
Age (y)	6.1±0.2	6.9±0.4	8.7±0.3	8.5±0.9	11.0±1.3	10.4±2.8
SE (D)	1.83±0.13	0.16±0.04	-1.46±0.06	-3.79±0.19	-8.31±0.79	Not available
AL (mm)	22.19±0.07	23.08±0.13	24.06±0.08	24.90±0.17	26.66±0.79	24.25±1.11

SE: Spherical equivalent; AL: Axial length.

Table 2 Comparison of mean differences in RDVs among hyperopia, emmetropia, and myopia groups mean±SD, D

Groups	Hyperopia (*n*=102)	Emmetropia (*n*=36)	Myopia (*n*=118)	*P*	P_{HE}	P_{HM}	P_{EM}
TRDV	-0.068±0.423	0.114±0.453	0.295±0.376	<0.001[a]	0.056	<0.001	0.054
RDV0°-15°	-0.016±0.157	-0.030±0.089	-0.048±0.075	0.131[b]	-	-	-
RDV15°-30°	-0.105±0.258	-0.094±0.241	-0.030±0.172	0.033[a]	0.972	0.037	0.307
RDV30°-45°	-0.081±0.377	0.074±0.407	0.189±0.313	<0.001[a]	0.063	<0.001	0.203
RDV-S	-0.489±0.693	-0.432±0.650	-0.368±0.570	0.366[b]	-	-	-
RDV-I	0.224±0.626	0.554±0.533	0.674±0.604	<0.001[a]	0.013	<0.001	0.549
RDV-T	-0.252±0.660	0.134±0.702	0.427±0.619	<0.001[a]	0.007	<0.001	0.047
RDV-N	0.257±0.697	0.303±0.682	0.473±0.704	0.061[b]	-	-	-

RDV: Refraction difference value; TRDV: Total RDV; RDV-S: RDV-superior; RDV-I: RDV-inferior; RDV-N: RDV-nasal; RDV-T: RDV-temporal; SD: Standard deviation; P_{HE}: Hyperopia group *vs* emmetropia group; P_{HM}: Hyperopia group *vs* myopia group; P_{EM}: Emmetropia group *vs* myopia group. [a]Statistically significant differences were found separately in TRDV, RDV0°-15°, RDV30°-45°, RDV-I, RDV-T among hyperopia, emmetropia and myopia groups; [b]The overall *P*-value is not significant, therefore post-hoc pairwise comparisons were not conducted.

and 4 had high myopia (SE≤-6.0 D). Thirty individuals were defined as "pre-myopic stage" (Table 1).

Inter-group Comparison of RDVs in TRDV (Within Total Eccentric Range of 0° to 53°) and Different Eccentricities Significant differences in TRDV were found among hyperopia (-0.068±0.423 D), emmetropia (0.114±0.453 D), and myopia (0.295±0.376 D) groups (*P*<0.001), with notable distinctions between hyperopia and myopia groups (*P*<0.001).

In RDV0°-15°, there is no significant difference among the three groups (hyperopia: -0.016±0.157 D, emmetropia: -0.030±0.089 D, myopia: -0.048±0.075 D, *P*=0.131). In RDV15°-30°, we found significant difference among three groups (hyperopia: -0.105±0.258 D, emmetropia: -0.094±0.241 D, myopia: -0.030±0.172 D, *P*=0.033), especially between hyperopia and myopia groups (*P*=0.037). In RDV30°-45°, the difference among the three groups was also significant (hyperopia: -0.081±0.377 D, emmetropia: 0.074±0.407 D, myopia: 0.189±0.313 D, *P*<0.001), again notably between hyperopia and myopia groups (*P*<0.001; Table 2).

Comparison of RDV0°-15°, RDV15°-30°, and RDV30°-45° Within Each Group Significant differences were found in RDV0°-15° (-0.033±0.177 D), RDV15°-30° (-0.069±0.222 D), and RDV30°-45° (0.065±0.374 D) across all participants (*P*<0.001), with increasing RDVs from 0°-15° to 30°-45° in emmetropia and myopia groups. Hyperopia groups showed consistent negative RDVs (RDV0°-15°: -0.016±0.157 D, RDV15°-30°: -0.105±0.258 D, RDV30°-45°: -0.081±0.377 D), while emmetropia and myopia groups exhibited hyperopic defocus in RDV30°-45° (emmetropia: 0.074±0.407 D, myopia: 0.189±0.313 D; Table 2).

Inter-group Comparison of RDV in Different Quadrants In RDV-S, all groups showed relative myopic defocus (hyperopia: -0.489±0.693 D, emmetropia: -0.432±0.650 D, myopia: -0.368±0.570 D), with no significant differences (*P*=0.366). RDV-N showed relative hyperopic defocus across all groups (hyperopia: 0.257±0.697 D, emmetropia: 0.303±0.682 D, myopia: 0.473±0.704 D), also without statistical significance (*P*=0.061).

However, RDV-I and RDV-T indicated increasing hyperopic defocus from hyperopia to myopia (both *P*<0.001). For example, RDV-I was getting greater from hyperopia to myopia groups (hyperopia: 0.224±0.626 D, emmetropia: 0.554±0.533D, myopia: 0.674±0.604 D), with notably different between hyperopia and emmetropia groups (*P*=0.013) but not between emmetropia and myopia groups (*P*=0.549). For the temporal quadrant part, RDV-T shifted from negative in hyperopia (-0.252±0.660 D) to increasingly hyperopic in emmetropia and myopia groups (emmetropia: 0.134±0.702 D, myopia: 0.427±0.619 D, *P*<0.001), with a significant difference between hyperopia and emmetropia groups (*P*=0.007; Table 2).

Comparison of RDV-S and RDV-I, as well as RDV-T and RDV-N in Each Group To investigate the asymmetry of superior and inferior, nasal and temporal quadrants, we

Table 3 Comparison of RDV-S and RDV-I, RDV-T and RDV-N in each group mean±SD, D

Groups	RDV-S *vs* RDV-I[a]	*P*	RDV-T *vs* RDV-N[b]	*P*
Hyperopia (*n*=102)	-0.710±0.954	<0.001	-0.506±1.072	<0.001
Emmetropia (*n*=36)	-0.986±0.685	<0.001	-0.169±1.025	0.330
Myopia (*n*=118)	-1.042±0.876	<0.001	-0.046±1.071	0.641

RDV: Refraction difference value; RDV-N: RDV-nasal; RDV-T: RDV-temporal; RDV-S: RDV-superior; RDV-I: RDV-inferior; SD: Standard deviation. [a]Significant differences between RDV-S and RDV-I in all groups, which means the defocus levels in the upper and lower regions exhibit asymmetry regardless of groups; [b]Hyperopic group showed significant asymmetry between the nasal and temporal side, while this asymmetry diminishes in myopic and emmetropic groups.

compared RDV-S and RDV-I, RDV-T and RDV-N in each group using a paired *t*-test. The differences between RDV-S and RDV-I are significant in all groups (P<0.001 for all; Table 3). Additionally, in each of these groups, the mean value of RDV-I is greater than 0, while the mean value of RDV-S is less than 0. The hyperopia group showed asymmetric relative defocus amount as the temporal quadrant (RDV-T= -0.252±0.660 D) showed relative myopic defocus compared to the nasal quadrant (RDV-N=0.257±0.697 D; P<0.001). However, this asymmetry was not present in emmetropia and myopia groups, with no significant differences between RDV-T and RDV-N. This can be attributed to the fact that the temporal quadrant exhibited relative myopic defocused in hyperopic group, and as myopia progressing, the temporal quadrant transitions to relative hyperopic defocus. The nasal side, on the other hand, consistently keeps in relative hyperopic defocus, resulting in the disappearance of this asymmetry.

Correlation Analysis of SE, AL, and RDVs As TRDV, RDV15°-30°, RDV30°-45°, RDV-I and RDV-T showed significant difference among the three groups, we performed Pearson correlation analysis to investigate the relation between SE, AL and these parameters. Among the 256 eyes with complete SE data, the Pearson correlation analysis revealed a negative correlation between SE and TRDV (r=-0.206, P=0.001), RDV30°-45° (r=-0.179, P=0.004), RDV-I (r= -0.124, P=0.047), and RDV-T (r=-0.338, P<0.001), while indicating no significant correlations between SE and RDV15°-30°. In the pre-myopic subgroup (30 eyes: 0.146±0.278 D), a significant negative correlation was observed between SE and RDV-I (r=-0.467, P=0.009).

Including an additional 61 participants (122 eyes) with missing SE data, linear correlation analysis between AL and retinal defocus showed a positive correlation of AL with TRDV (r=0.108, P=0.036), RDV15°-30° (r=0.148, P=0.004), RDV30°-45° (r=0.284, P<0.001), RDV-S (r=0.152, P=0.003), RDV-I (r=0.206, P<0.001), RDV-T (r=0.391, P<0.001), RDV-N (r=0.117, P=0.022), and a negative correlation with RDV0-15° (r=-0.121, P=0.018), involving all 190 participants (378 eyes).

DISCUSSION

Recent focus on peripheral retinal defocus in myopia development has brought forth two views: peripheral hyperopic defocus instigating axial myopia[12,22-23] and peripheral hyperopia resulting from ocular growth[24-26]. Our study utilized MRT to measure RDV in various eccentricities and regions of the retina for children and adolescents with different refractive status in southwestern region of China. The aim was to assess the differences in RDV among patients with varying degrees of refractive error and explore the relationship between RDV and the onset and progression of myopia.

Our study found statistically significant difference both in TRDV and RDV30°-45° among hyperopia, emmetropia and myopia groups. TRDV means total relative refractive error in the eccentric range of 0° to 53°. For hyperopic participants, TRDV was negative, indicating relative myopic defocus. But for emmetropic and myopic individuals, it becomes relative hyperopic defocus. Then we analyzed different eccentric range and found this change mainly comes from the peripheral range of 30°-45°. Because the difference of RDV30°-45° among hyperopic, emmetropic and myopic was significant. While the difference of RDV0°-15° was not significant, and RDV15°-30° only showed marginal difference. This aligns with Mutti *et al*'s[27] study, revealing greater relative peripheral hyperopic defocus in myopic children compared to those with emmetropia.

Pearson correlation analysis further confirmed the negative correlation of SE with TRDV (r=-0.206, P=0.001), RDV30°-45° (r=-0.179, P=0.004). The negative correlation between SE and TRDV has been extensively corroborated in numerous studies[12-15]. These consensus underscores the close association between the progression of myopia and the increment in peripheral relative defocus, like RDV30°-45°. Some scholars claimed that myopia onset due to hyperopic defocus, and posited that the underlying mechanism might be attributed to the fact that retinal defocus in the fovea or posterior region exerts less influence than peripheral defocus on the development of myopia[14]. But we think: as AL elongates, peripheral retinal changes become more prominent compared to changes in the central retina. The central region of the retina

relatively protrudes posteriorly, while this makes other areas of the retina, particularly the peripheral regions, shift relatively to the anterior space. This results in a reduction of RDV in the central region and an increase in RDV in other areas, especially the periphery. This potential mechanism could be further explored and validated that a positive correlation of AL with TRDV (r=0.108, P=0.036), RDV15°-30° (r=0.148, P=0.004), RDV30°-45° (r=0.284, P<0.001), while revealed a negative correlation of AL with RDV0°-15° (r=-0.121, P=0.018).

In the analysis of RDV in different quadrants, we observed a widespread asymmetry between the superior and inferior quadrants in all the participants. In the three groups (hyperopia, emmetropia, and myopia) the superior quadrant exhibited relative myopic defocus, while the inferior quadrant displayed relative hyperopic defocus (P<0.001 for all). Moreover, the difference of RDV-S and RDV-I was most prominent in myopia group (-1.042±0.876). And it was smallest in hyperopic group (-0.710±0.954). These results indicated that myopia progression exacerbated asymmetry between superior and inferior retinal quadrants, primarily due to changes in the inferior quadrant, as no significant RDV-S differences were found (P=0.366).

However, there was a significant difference in the RDV-I between three groups (P<0.001). The difference was identified between hyperopia group and emmetropia group (P=0.013), hyperopia group and myopia group (P<0.001). Adversely, the difference for RDV-I was not so remarkable between emmetropia and myopia group (P=0.549). Shen *et al*[15] compared peripheral refractive errors in the horizontal and vertical meridians, also revealing that the hyperopic shift was more pronounced in the inferior visual field compared to the superior visual field in the middle and high myopia groups[15]. Considering that the Pearson correlation analysis revealed a negative correlation of SE with RDV-I (r=-0.124, P=0.047) and a positive correlation of AL with RDV-I (r=0.206, P<0.001), increasing of RDV-I may serve as an indicative factor in the onset and progression of myopia. However, the precise role of RDV-I in different stages of myopia development remained to be further explored in future research.

The temporal quadrant transitioned from relative myopic defocus in the hyperopia group to relative hyperopic defocus in the emmetropia and myopia groups. Significant differences were also identified between each pair of groups: hyperopia and emmetropia group (P=0.007); hyperopia and myopia group (P<0.001); emmetropia and myopia group (P=0.047). In contrast, in each of the three groups, the nasal quadrant consistently exhibited relative hyperopic defocus, and all the participants in these groups (hyperopia, emmetropia and myopia) showed no significant difference (P=0.061). The refractive asymmetry of nasal and temporal retina was only observed in hyperopia group (P<0.001), and in the emmetropia and myopia groups, this asymmetry disappeared. Furthermore, our study marked the instance where we observed a negative correlation between SE and RDV-T (r=-0.338, P<0.001). The observed correlation between RDV-T and SE in myopia may relate to the retinal vascular anatomy and myopia pathophysiology. The temporal retina, receiving less blood supply and less resilient, may deform more during myopia progression, causing notable changes in RDV-T and its stronger correlation with SE. Furthermore, a study conducted by Ohno-Matsui[28], which employed three-dimensional magnetic resonance imaging and wide-field fundus imaging to analyze the pathologic myopic posterior staphyloma types, indicated that the change in curvature is notably more pronounced along the temporal margin of the staphyloma compared to the nasal margin[28]. This finding, to some extent, can offer additional insights supporting our hypothesis.

The “Expert Consensus on Myopia Management White Paper (2022)”[20] proposed the importance of managing children and adolescents at different myopia stages, especially in the pre-myopic stage, signifying that they are not yet myopic but exhibit risk factors for myopia[29]. Research by Zadnik *et al*[30] suggested that the amount of hyperopic reserve corresponding to a specific age was the most reliable predictor of myopia onset. This can be utilized for facilitating the early initiation of myopia prevention measures. Utilizing data from 30 pre-myopic children’s eyes, selected from 256 with complete SE data, we analyzed the relationship between SE and RDV, and the results revealed a negative correlation only between SE and RDV-I (r=-0.467, P=0.009). This finding aligned with our previous observations, suggesting that RDV-I may serve as a sensitive indicator of myopia development.

Subsequently, we conducted further subgroup analysis of RDVs within the myopia group, but no significant differences were found in RDVs among low, middle, and high myopia groups. This finding aligned with the results of a collaborative longitudinal evaluation of ethnicity and refractive error study[10], which reported a peripheral hyperopia acceleration prior to onset, followed by stable rates post-onset[10]. This implied varying influences on ocular expansion during different myopia stages.

In summary, this study examined the correlations between SE and AL with RDV in different eccentricities and quadrants on the retina. Our findings suggested that TRDV, RDV30°-45°, RDV-I, RDV-T may be closely related to the onset and progression of myopia, with the association between RDV-T and myopia progression being a novel contribution of this study. Furthermore, by incorporating the concept of pre-myopia[20-21], we conducted a secondary analysis on children and adolescents, revealing an innovative association between

the increase in RDV-I and the reduction in SE in pre-myopic children. This finding holds potential implications for myopia prevention in pre-myopic children. However, it's important to acknowledge certain limitations in terms of sample size and the distribution of study participants. Future research should build upon these conclusions by conducting larger-scale, longitudinal study to further explore the relationship between RDVs and myopia development. This will guide personalized myopia prevention and correction strategies for children and adolescents in clinical practice.

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