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Preliminary Application of a Continuous Functional Contrast Visual Acuity System in the Assessment of Visual Function in Dry Eye Patients

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Purpose: To investigate the feasibility and efficacy of a continuous functional contrast visual acuity (CFCVA) system in the assessment of visual function in dry eye disease (DED).

Methods: Twenty patients with DED and 15 normal controls were recruited. Subjective symptoms were evaluated using the Ocular Surface Disease Index (OSDI) questionnaire, and tear film stability was assessed by a noninvasive corneal topographer. Under natural blinking conditions, the custom-built CFCVA system was used to take serial visual acuity measurements at 100%, 25%, 10%, and 5% contrast for 60 seconds. A 5-minute measurement at a 100% contrast level was defined as the stress test (ST). Mean CFCVA was defined, and visual maintenance ratio (VMR) was the ratio of mean CFCVA divided by baseline visual acuity.

Results: In both groups, VMR decreased and mean CFCVA (logarithm of the minimum angle of resolution) increased with decreasing optotype contrast (from 100% to 5%). In ST, the ST VMR at the fourth and fifth minutes (VMR54 and VMR55) showed the strongest correlations with OSDI total, ocular symptoms, and vision-related function (−0.646 and −0.598, −0.688 and −0.693, and −0.599 and −0.555, respectively, $P < 0.05$). VMR54 and VMR55 also demonstrated the best discriminating ability for detecting DED, with areas under the curve of 0.903 and 0.867, respectively.

Conclusions: Extending the continuous measuring time was more effective for detecting vision-related functional abnormalities in patients with DED than simply decreasing the optotype contrast level.

Translational Relevance: The proposed CFCVA system and associated parameters offer a potential method for quantifying and interpreting the visual symptoms of DED in clinical care.

Introduction

The Second International Dry Eye Workshop (DEWS II) in 2017 updated the definition of dry eye disease (DED), and the loss of tear film homeostasis was emphasized as the pathophysiologic basis.[1] In patients with DED, the reduction in tear film stability leads to changes or interruptions in tear film morphology shortly after blinking, resulting in a change in tear film optical quality and further affecting retinal imaging quality.[2,3] As the first refractive surface, a stable tear film is essential for maintaining clear vision.[4–7] Currently, most tests used to diagnose and monitor DED focus on detecting morphologic changes,[8–10] production or wettability,[11,12] and biophysical and biochemical aspects of the tear film.[13] The optical quality of the tear film and its impact

on retinal imaging quality can be analyzed by serial measurements of higher-order aberrations or double-pass objective scatters.[14–16] Although several tests, such as contrast sensitivity,[4,17,18] functional visual acuity (FVA),[19–21] and interblink interval visual acuity decay,[22] have been validated to assess various aspects of visual performance in patients with DED, a sensitive, easily administered, and time-efficient test for directly measuring and quantifying visual function decline in DED is not currently available.[23]

FVA is a continuous measurement for a specific time interval (10 to 60 seconds) to evaluate visual acuity in daily working and living conditions.[20,24] It was first used by Goto et al.[25] to assess visual impairment in patients with dry eyes. Patients with dry eyes were more prone to ocular surface irregularities in a short period due to decreased tear film stability, and their FVA decreased significantly with prolonged gaze time.[26] Therefore, FVA measurements can be used to detect and quantify the visual disturbances associated with tear film instability in patients with dry eyes. However, the effectiveness of discriminating between patients with DED and normal individuals using the currently established FVA system has been reported to be low and not functional for DED screening with a single parameter.[26] It has been reported that patients with dry eyes with visual impairment or symptoms in daily life have reduced contrast sensitivity.[27–29] Low-contrast vision tests are more sensitive and have a higher detection rate for some diseases than high-contrast vision tests. Therefore, measuring visual acuity at different contrast levels may provide a more comprehensive understanding of visual function in healthy and diseased individuals.

In this study, we developed a new continuous function contrast visual acuity (CFCVA) measurement system to investigate the difference in CFCVA-related parameters between patients with DED and normal controls. The purpose of this study was to preliminarily investigate the clinical feasibility and efficacy of the CFCVA system in assessing visual function in patients with DED.

Methods

Participants

For this prospective case-control study, 35 participants were consecutively recruited at the Eye Hospital and School of Ophthalmology and Optometry, Wenzhou Medical University. Inclusion criteria were as follows: age ≥18 years and best-corrected visual acuity (BCVA) of 0.0 (logarithm of the minimum angle of resolution [logMAR]) or better in both eyes. Participants with cataracts, corneal opacities, and any other ocular conditions that could increase ocular scatter were excluded. Other exclusion criteria were as follows: a history of ocular surgery or trauma, a recent history of contact lens wearing (within 1 week for soft contact lenses, 3 weeks for rigid contact lenses, and 3 months for orthokeratology lenses), and the usage of any medication that affects the tear system within 24 hours of the examination (such as artificial tears). Ethics approval was obtained from the institutional review board of the Eye Hospital and School of Ophthalmology and Optometry, Wenzhou Medical University (approval number 2022-187-K-146), and the study was conducted in accordance with the tenets of the Declaration of Helsinki. All volunteers agreed to participate in this study and provided written informed consent.

Tear Function Diagnosis and Ocular Surface Assessment

All participants underwent a complete dry eye examination, including (1) the Ocular Surface Disease Index (OSDI) questionnaire, which is divided into three subscales: ocular symptoms, vision-related function, and environmental triggers and (2) measurement of tear meniscus height (TMH) and noninvasive tear breakup time (NIBUT) by Keratograph 5M (K5M; Oculus Optikgerate GmbH, Wetzlar, Germany), with the mean of the three measurements taken. According to the DEWS II Diagnostic Methodology Report,[30] the diagnostic criteria for DED were as follows: OSDI score ≥13 and NIBUT <10 seconds, and the participants were divided into the dry eye group (DED group) and normal control group (NC group).

Continuous Functional Contrast Visual Acuity Measurement System

The reaction time–based CFCVA measurement system was proposed based on the previously established FVA measurement system.[21,24] The specific modifications made to the custom-developed FVA software have been documented in our previous study,[31] with the major differences being the introduction of reaction time and the feature of setting different contrast levels of the optotypes. The display algorithm of optotypes in the CFCVA measurement system is shown in Figure 1. The contrast level was preset and remained constant throughout each test.

The measurement procedure of each participant consisted of two steps: (1) four CFCVA tests performed at 100%, 25%, 10%, and 5% contrast, with each test

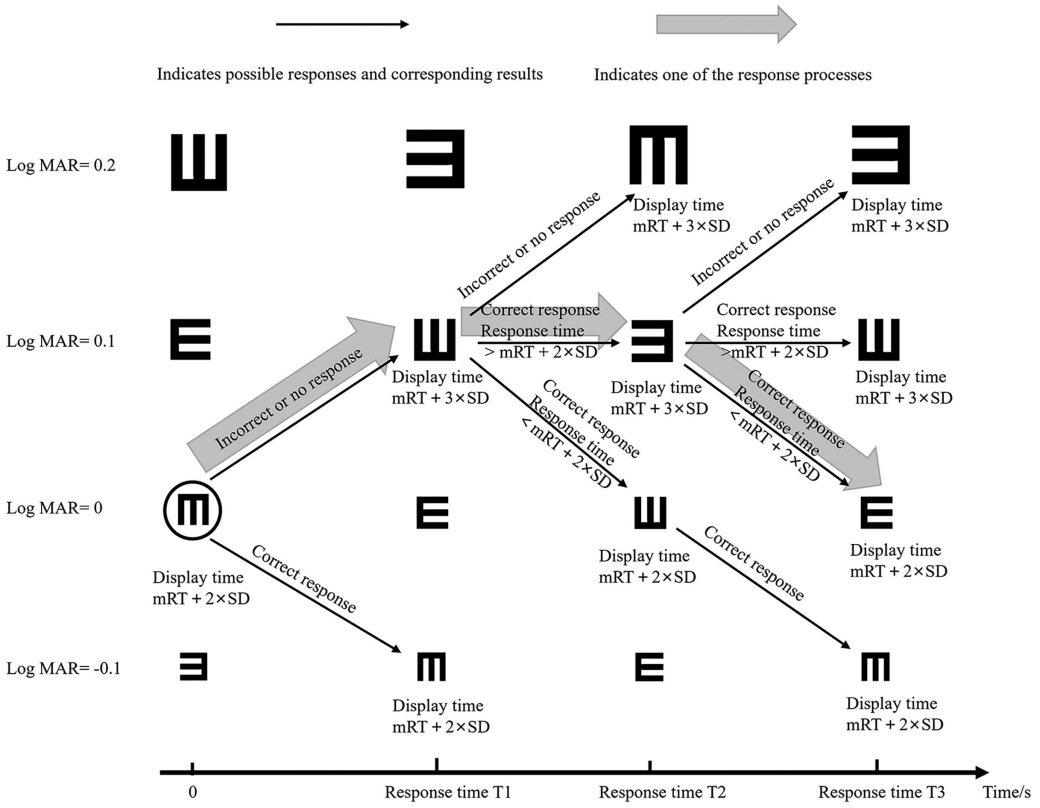

Figure 1. The display algorithm of optotypes in the CFCVA measurement system. The mean reaction time (mRT) and standard deviation (SD) were first measured and calculated for each participant, and the optotype display time was initially set to mRT + 2 × SD. The display time and size of each optotype were determined according to the following rules: (1) The optotype decreased by one size (0.1 logMAR unit) automatically when the response was correct and within an mRT + 2 × SD; (2) The optotype increased by one size, and the display time for next optotype was set to an mRT + 3 × SD when the answer was incorrect or when there was no response within the set display time; and (3) the optotype size remained unchanged and the display time for next optotype was set to an mRT + 3 × SD when the response was correct and the response time was longer than an mRT + 2 × SD.

lasting 60 seconds with an interval break of 1 minute between tests, and (2) the stress test (ST), in which a 5-minute CFCVA test at 100% contrast was used to simulate the fatigue state of vision that may be encountered in daily life, such as when reading or driving for a long period. Both steps were performed under natural blinking conditions.

The parameters related to the CFCVA test were defined as follows: (1) mean CFCVA was defined as the average of all visual acuity values measured over time in a single CFCVA test, representing the timewise change in visual acuity over time during the entire test (Fig. 2). For the ST, the mean CFCVA was calculated separately for each minute (Fig. 3) and for the total 5 minutes. (2) The visual maintenance ratio (VMR) was calculated as (lowest logMAR visual acuity – mean CFCVA) / (lowest logMAR visual acuity – baseline BCVA), and it was proposed to assess the difference between continuous visual acuity variation and baseline visual acuity by calculating the ratio of mean CFCVA divided by the value of baseline BCVA.[20,21,24,31] Meanwhile, the lowest logMAR visual acuity was a constant set to 2.7,[20,21,24] which allowed comparison of VMR between participants with different baseline BCVA (Fig. 2). (3) VMR5n (VMR51 to VMR55) and mean CFCVA5n (mean CFCVA51 to mean CFCVA55) referred to the VMR and mean CFCVA of the nth minute, respectively (Fig. 3).

Statistical Analysis

The data obtained in this study were analyzed using SPSS 25.0 (SPSS, Inc., Chicago, IL, USA). Each variable was tested for normal distribution using the Shapiro–Wilk test. Results for all continuous variables were expressed as mean ± SD. Independent samples *t*-test or Mann-Whitney *U* test was used to compare related parameters between the DED and NC groups. Repeated-measures analysis of variance with Bonfer-

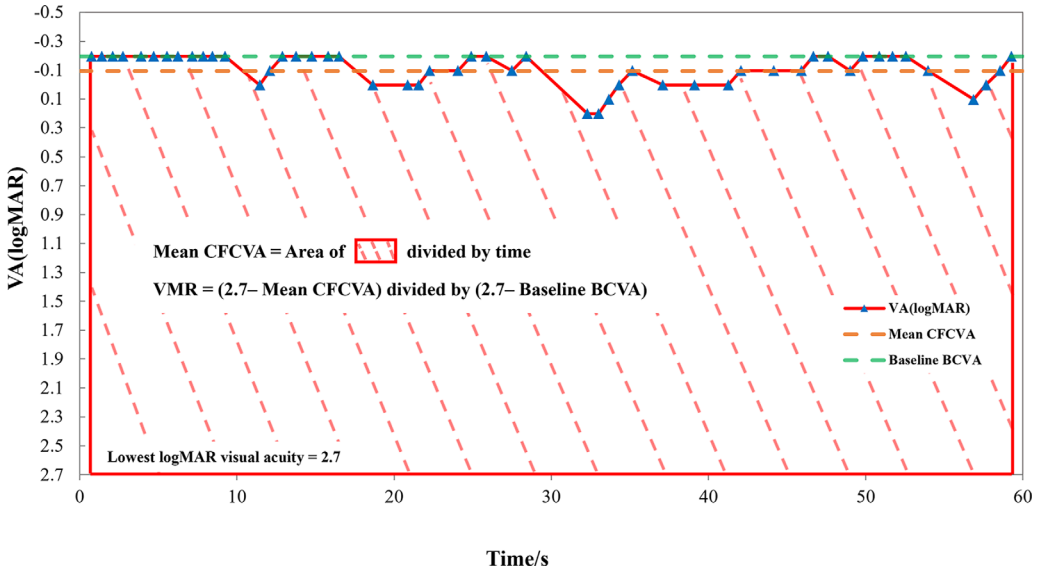

Figure 2. The schematic diagram shows the definition of mean CFCVA and VMR. Continuous visual acuity values (*blue triangles*) measured over the entire test are denoted by a *red line*, and a *green dotted line* denotes the baseline BCVA. The mean CFCVA was calculated as the ratio of the *red-dashed area* to the time and is indicated by an *orange dotted line*. The VMR was the ratio of the mean CFCVA divided by the value of baseline BCVA and was calculated as (2.7 – mean CFCVA) / (2.7 – baseline BCVA). The lowest logMAR visual acuity was a constant set to 2.7. In this case, the baseline BCVA was –0.196, while the area of the *red-dashed region* was 163.45. The time taken from the first to the last response was 58.5 seconds. The mean CFCVA was determined by the formula 2.7 – 163.45 / 58.5, giving a value of −0.094. Finally, the VMR = [2.7 − (−0.094)] / [2.7 − (−0.196)] = 0.965.

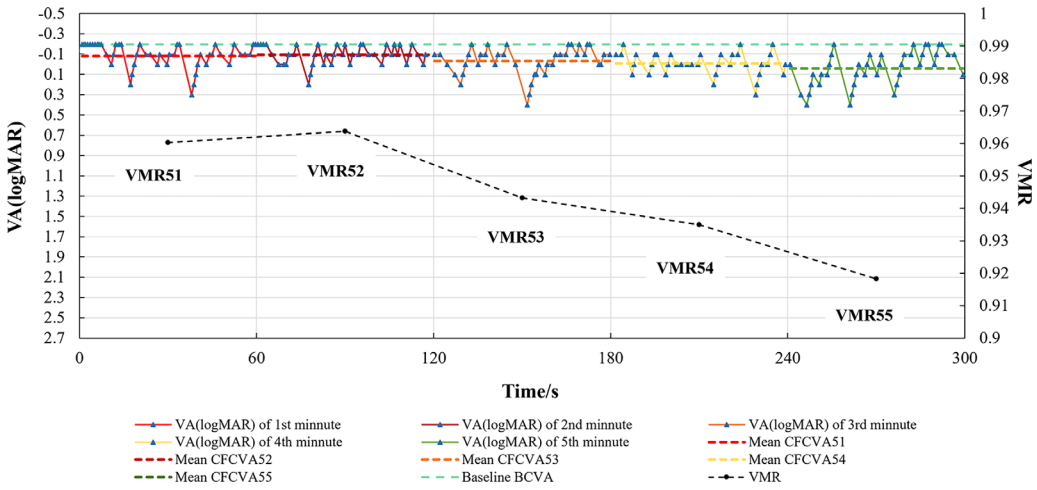

Figure 3. A dual y-axis graph of one participant in the dry eye group shows the continuous change in mean CFCVA and VMR during the ST. Continuous visual acuity values (*blue triangles*) measured throughout the test are denoted by *solid lines* of different colors. Mean CFCVA and VMR were calculated separately for each minute. VMR5n (VMR51 to VMR55) and mean CFCVA5n (mean CFCVA51 to mean CFCVA55) refer to the VMR and mean CFCVA of the nth minute, respectively.

roni correction was used to assess differences in CFCVA-related parameters between groups and to determine the interaction and main effects. Receiver operating characteristic (ROC) curve analysis was used to determine the area under the curve (AUC) to assess and compare the diagnostic efficacy of CFCVA-related parameters. The optimal diagnostic cutoff for the ROC curve was determined using the Youden index (sensitivity + specificity – 1). Correlations between OSDI and CFCVA-related parameters were described using either Pearson's or Spearman's rank correlation coefficients, as appropriate. Correlation coefficients (absolute value) between 0.70 and 0.90, 0.50 and 0.70, and 0.25 and 0.50 were classified as high, moderate, and low correla-

tion, respectively. $P < 0.05$ was considered statistically significant.

Results

A total of 35 participants (35 eyes) were included in this study. According to the diagnostic criteria for dry eye, the participants were divided into the DED group (20 eyes) and the NC group (15 eyes). The clinical characteristics of the two groups are shown in Table 1, and the differences in NIBUT, TMH, and OSDI scores between the two groups were statistically significant.

Comparison of CFCVA-Related Parameters Between the DED and NC Groups

In the ST, the VMR values (VMR51 to VMR55) at every minute were significantly lower in the DED group than in the NC group, while only mean CFCVA54 and mean CFCVA55 were significantly higher than in the NC group (Table 2). The 5-minute average of VMR and mean CFCVA during ST (mean ST VMR, mean ST CFCVA) were 0.952 ± 0.014 and 0.074 ± 0.056 in the DED group and 0.969 ± 0.012 and 0.031 ± 0.055 in the NC group, respectively, with both differences being statistically significant between groups ($P < 0.001$, $P = 0.033$). Comparison of VMR and mean CFCVA at 100%, 25%, 10%,

Table 1. Clinical Characteristics of the DED and NC Groups

Characteristic	DED Group	NC Group	*P* Value
Number of eyes	20	15	—
Gender (male/female)	3/17	9/6	**0.006**
Age	25.10 ± 1.59[a]	25.27 ± 1.16[a]	0.734
NIBUT (s)	5.86 ± 1.43[a]	14.34 ± 4.24	**<0.001**
TMH (mm)	0.18 ± 0.08[a]	0.20 ± 0.05[a]	0.577
OSDI total	30.27 ± 10.35[a]	4.15 ± 3.73[a]	**<0.001**
OSDI ocular symptoms	34.17 ± 12.94[a]	3.33 ± 4.22	**<0.001**
OSDI vision-related function	27.94 ± 11.71[a]	3.17 ± 4.74	**<0.001**
OSDI environmental triggers	30.42 ± 11.95	7.22 ± 8.25	**<0.001**

Significant *P* values ($P < 0.05$) are bolded.
[a]Normally distributed.

Table 2. Comparison of CFCVA-Related Parameters of the 5-Minute ST Between the DED and NC Groups

Parameter	NC Group	DED Group	*F*	*P* Value
VMR51	0.975 ± 0.013	0.963 ± 0.011	9.494	**0.004**
VMR52	0.970 ± 0.015	0.953 ± 0.019	7.970	**0.008**
VMR53	0.966 ± 0.015	0.953 ± 0.018	4.822	**0.035**
VMR54	0.969 ± 0.010	0.946 ± 0.018	19.424	**<0.001**
VMR55	0.968 ± 0.013	0.943 ± 0.020	17.584	**<0.001**
Mean CFCVA51	0.013 ± 0.055	0.041 ± 0.055	2.238	0.144
Mean CFCVA52	0.028 ± 0.067	0.068 ± 0.071	2.867	0.100
Mean CFCVA53	0.040 ± 0.058	0.068 ± 0.064	1.824	0.186
Mean CFCVA54	0.031 ± 0.052	0.088 ± 0.071	6.875	**0.013**
Mean CFCVA55	0.034 ± 0.062	0.096 ± 0.053	10.499	**0.003**

Interaction and Main Effects

VMR		Mean CFCVA	
Group (*F*, *P*)	15.568, **<0.001**	Group (*F*, *P*)	5.016, **0.032**
Time (*F*, *P*)	11.417, **<0.001**	Time (*F*, *P*)	11.379, **<0.001**
Time × group (*F*, *P*)	2.428, 0.070	Time × group (*F*, *P*)	2.494, 0.064

VMR and mean CFCVA were calculated separately for each minute. VMR5n and mean CFCVA5n refer to the VMR and mean CFCVA of the nth minute, respectively. Significant *P* values ($P < 0.05$) are bolded.

Table 3. Comparison of CFCVA-Related Parameters Between the DED and NC Groups at Different Contrast Levels

Parameter	NC Group	DED Group	*F*	*P* Value
100% VMR	0.973 ± 0.011	0.959 ± 0.010	15.555	**<0.001**
25% VMR	0.971 ± 0.011	0.959 ± 0.010	12.013	**0.001**
10% VMR	0.965 ± 0.015	0.953 ± 0.012	7.474	**0.010**
5% VMR	0.957 ± 0.014	0.944 ± 0.013	7.560	**0.010**
100% mean CFCVA	0.018 ± 0.054	0.051 ± 0.059	2.801	0.104
25% mean CFCVA	0.133 ± 0.070	0.142 ± 0.051	0.190	0.665
10% mean CFCVA	0.254 ± 0.090	0.264 ± 0.075	0.119	0.733
5% mean CFCVA	0.374 ± 0.093	0.406 ± 0.069	1.361	0.252

Interaction and Main Effects

VMR		Mean CFCVA	
Group (*F*, *P*)	17.557, **<0.001**	Group (*F*, *P*)	0.986, 0.328
Contrast (*F*, *P*)	21.428, **<0.001**	Contrast (*F*, *P*)	302.435, **<0.001**
Contrast × Group (*F*, *P*)	0.072, 0.975	Contrast × Group (*F*, *P*)	1.616, 0.206

The 100% VMR/mean CFCVA, 25% VMR/mean CFCVA, 10% VMR/mean CFCVA, and 5% VMR/mean CFCVA refer to the VMR/mean CFCVA values at 100%, 25%, 10%, and 5% contrast levels, respectively. Significant *P* values ($P < 0.05$) are bolded.

and 5% contrast between the two groups is shown in Table 3, and significant differences were found for VMR values at each contrast level but not for mean CFCVA.

Trend and Interaction Analysis of Relevant Parameters in the DED and NC Groups

In the ST, significant main effects of time and group were found for both VMR and mean CFCVA, and the time × group interaction effect achieved a borderline level of significance (Table 2, $P = 0.070$, $P = 0.064$, respectively). The trends and magnitude of changes in VMR and mean CFCVA values over 5 minutes were compared between the DED and NC groups, as shown in Figures 4 and 5. There was an overall decline in VMR values for both groups, but the DED group demonstrated a more rapid decrease after 3 minutes. Similarly, CFCVA values increased overall in both groups, but the DED group showed a quicker increase after 3 minutes.

Figures 6 and 7 demonstrate a decrease in VMR values and an increase in mean CFCVA values (logMAR) with decreasing contrast levels of the optotype (both $P < 0.001$). No interaction effect of contrast × group was found for either VMR or mean CFCVA (Table 3, $P = 0.975$ and $P = 0.206$, respectively), indicating that VMR and mean CFCVA in both groups had the same tendency to change with varying contrast.

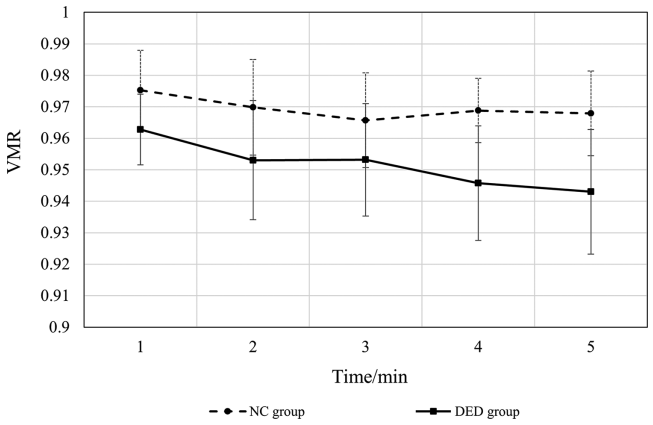

Figure 4. Trends and magnitude of changes in VMR values over 5 minutes in the ST for the DED and NC groups.

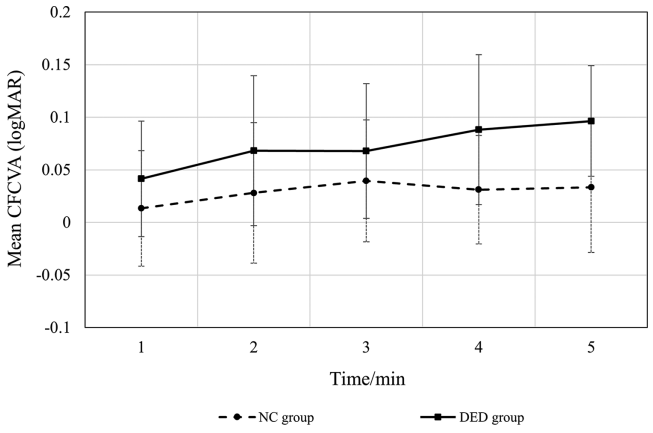

Figure 5. Trends and magnitude of changes in mean CFCVA values over 5 minutes in the ST for the DED and NC groups.

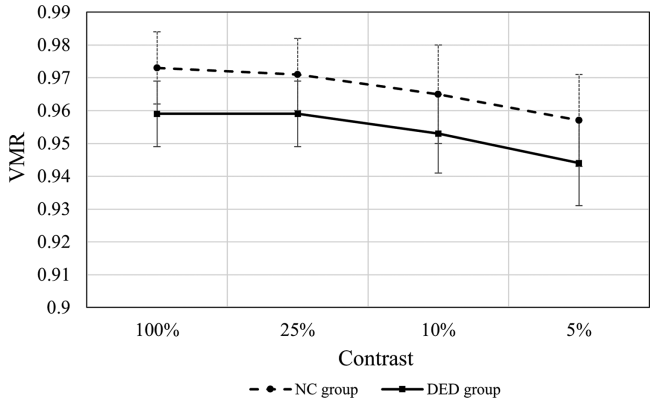

Figure 6. Trends and magnitude of changes in VMR values at different contrast levels for the DED and NC groups.

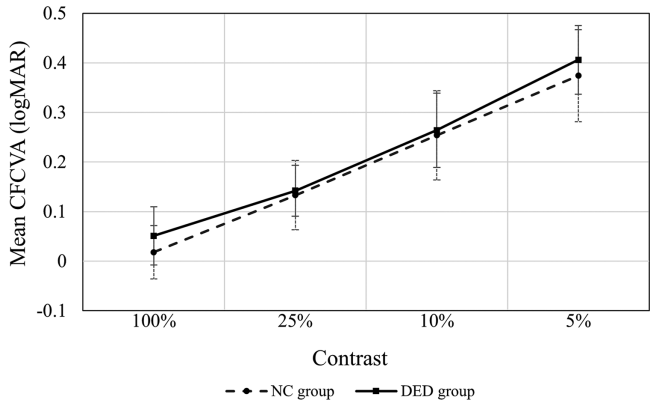

Figure 7. Trends and magnitude of changes in mean CFCVA values at different contrast levels for the DED and NC groups.

Correlation Analysis of CFCVA-Related Parameters and OSDI Scores

The study investigated the correlations between CFCVA-related parameters and OSDI scores, and statistically significant correlations ($P < 0.05$) were identified and presented in Table 4. For the ST, there were low to moderate correlations between VMR values and OSDI scores, while most CFCVA values had only low correlations (if statistically significant) with OSDI scores. The VMR and CFCVA values at the fourth and fifth minutes had a stronger correlation with OSDI scores than those at the first 3 minutes (if statistically significant). Figure 8 shows the moderate negative correlation of VMR54 and VMR55 with OSDI scores (total and two subscales). Of the four contrast levels, if statistically significant, the strongest correlation with OSDI scores was found for VMR at a 25% contrast (25% VMR, Table 4). Among these parameters, VMR54 and VMR55 had the highest correlation coefficients (absolute value) with OSDI total, OSDI ocular symptoms, and OSDI vision-related function (–0.646 and –0.598, –0.688 and –0.693, –0.599 and –0.555, respectively, $P < 0.05$).

Discrimination Performance of CFCVA-Related Parameters

Table 5 showed the AUCs, cutoff values, and corresponding sensitivity and specificity of the CFCVA-related parameters used to discriminate between DED and NC groups. Of the four contrast levels, only VMR values had statistically significant discriminative ability ($P < 0.05$), while CFCVA values did not. Furthermore, there was no improvement in the discriminative ability (increase in AUCs) of the different VMR values with decreasing contrast. In the ST, the VMR values showed superior discriminative ability compared to the CFCVA values. Specifically, VMR54, VMR55, and mean CFCVA55 had the highest AUCs among the parameters in the other minutes, respectively. A combined index was generated by merging VMR54, VMR55, and mean CFCVA55 with a logistic regression model. This resulted in a significant improvement in discriminative ability, increasing the AUC to 0.923 (with a sensitivity of 0.900 and specificity of 0.867). ROC curves of CFCVA-related parameters for discriminating eyes with DED from normal controls are shown in Figure 9.

Discussion

To the best of our knowledge, this is the first study to investigate continuous functional visual acuity at different contrast levels. This may provide additional information about the visual performance of patients with dry eyes when compared with the established FVA system,[32,33] which only used the default 100% high contrast level of the optotype.

The brightness and contrast of the visual environments of the human eye are variable in daily life,[34–36] and instantaneous high-contrast visual acuity measurements are insufficient to fully reflect the visual function of patients with dry eyes who frequently have vision fluctuations.[36–38] In this study, we assessed the CFCVA-related parameters at four contrast levels and observed a direct effect of contrast level on the continuous functional visual acuity performance of the participants. In both the DED and NC groups, there was a consistent trend of change observed in the VMR and mean CFCVA values as contrast varied. Specifically, the VMR value decreased and the mean CFCVA value increased as the contrast level decreased. This was illustrated in Figures 6 and 7, with the NC group demon-

Table 4. Significant Correlations Between CFCVA-Related Parameters and OSDI Scores

OSDI Scores	CFCVA-Related Parameters	Correlation Coefficient (*r*)	*P* Value
OSDI total	100% VMR	−0.411	0.014
	25% VMR	−0.586	<0.001
	10% VMR	−0.381	0.024
	5% VMR	−0.349	0.040
	VMR51	−0.408	0.015
	VMR52	−0.430	0.010
	VMR54	−0.646	<0.001
	VMR55	−0.598	0.002
	Mean ST VMR	−0.580	<0.001
	Mean CFCVA54	0.394	0.019
	Mean CFCVA55	0.387	0.022
OSDI ocular symptoms	100% VMR	−0.523	0.001
	25% VMR	−0.589	<0.001
	10% VMR	−0.501	0.002
	5% VMR	−0.411	0.014
	VMR51	−0.419	0.012
	VMR52	−0.427	0.011
	VMR53	−0.352	0.038
	VMR54	−0.688	<0.001
	VMR55	−0.693	<0.001
	Mean ST VMR	−0.619	<0.001
	Mean CFCVA54	0.427	0.011
	Mean CFCVA55	0.462	0.005
	Mean ST CFCVA	0.366	0.031
OSDI vision-related function	100% VMR	−0.360	0.034
	25% VMR	−0.484	0.003
	VMR51	−0.368	0.030
	VMR52	−0.355	0.036
	VMR54	−0.599	<0.001
	VMR55	−0.555	0.001
	Mean ST VMR	−0.522	0.001
OSDI environmental triggers	100% VMR	−0.454	0.006
	25% VMR	−0.652	<0.001
	10% VMR	−0.396	0.019
	5% VMR	−0.450	0.007
	VMR51	−0.461	0.005
	VMR52	−0.535	0.001
	VMR53	−0.366	0.031
	VMR54	−0.670	<0.001
	VMR55	−0.606	<0.001
	Mean ST VMR	−0.638	<0.001
	100% mean CFCVA	0.361	0.033
	Mean CFCVA51	0.350	0.040
	Mean CFCVA52	0.422	0.012
	Mean CFCVA53	0.349	0.040
	Mean CFCVA54	0.519	0.001
	Mean CFCVA55	0.463	0.005
	Mean ST CFCVA	0.448	0.007

The 100% VMR/mean CFCVA, 25% VMR/mean CFCVA, 10% VMR/mean CFCVA, and 5% VMR/mean CFCVA refer to the VMR/mean CFCVA values at 100%, 25%, 10%, and 5% contrast levels, respectively. VMR5n and mean CFCVA5n refer to the VMR and mean CFCVA of the nth minute, respectively. Mean ST VMR and mean ST CFCVA refer to the 5-minute average of VMR and mean CFCVA during the ST.

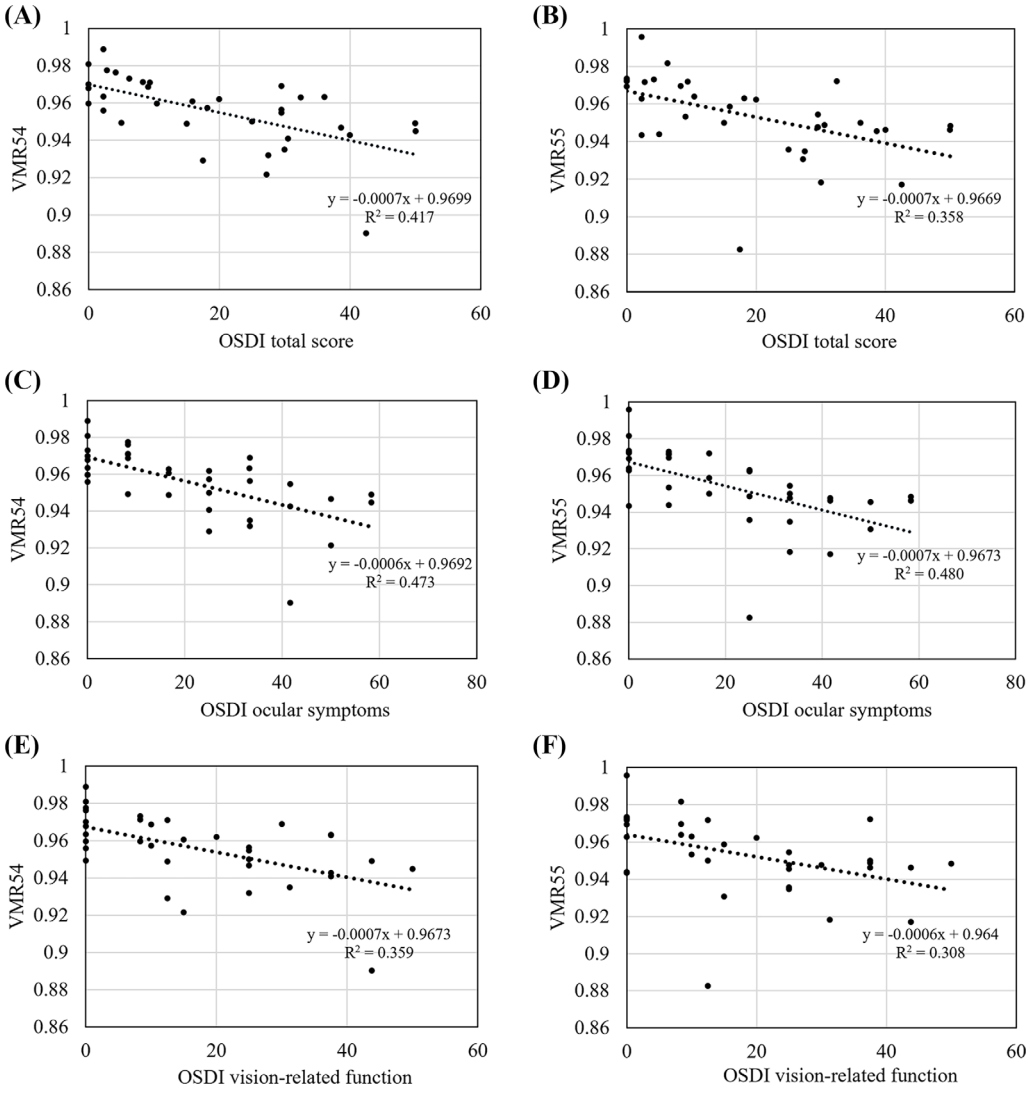

Figure 8. Scatterplots of correlations between VMR values at the fourth and fifth minutes of the ST and OSDI scores. (**A**) The OSDI total score had a moderate negative correlation with the VMR54 ($r = -0.646$, $P < 0.001$). (**B**) The OSDI total score had a moderate negative correlation with the VMR55 ($r = -0.598$, $P = 0.002$). (**C**) The OSDI ocular symptoms score had a moderate negative correlation with the VMR54 ($r = -0.688$, $P < 0.001$). (**D**) The OSDI ocular symptoms score had a moderate negative correlation with the VMR55 ($r = -0.693$, $P < 0.001$). (**E**) The OSDI vision-related function score had a moderate negative correlation with the VMR54 ($r = -0.599$, $P < 0.001$). (**F**) The OSDI vision-related function score had a moderate negative correlation with the VMR55 ($r = -0.555$, $P = 0.001$).

strating superior results than the DED group at different contrast levels. In previous studies,[20,31] the VMR at 100% contrast level, equivalent to the 100% VMR used in this study, was found to be effective in assessing the dynamic changes in visual acuity in patients with dry eyes. In our study, the statistically significant differences between the DED group and the NC group were also found for VMR values at lower contrast levels (25%, 10%, and 5%). Studies have demonstrated that low-contrast visual acuity assessments may be more sensitive than high-contrast visual acuity assessments in detecting diseases such as glaucoma,[39] multiple sclerosis,[40] and Parkinson disease.[41] However, our study did not find that the low-contrast level had a more favorable result than the high-contrast level (Table 3, Figs. 6 and 7), despite the significant difference noted between the two groups of VMR values at each contrast level. Although 25% VMR showed the highest correlations with OSDI scores among the four contrast levels (Table 4), there was no significant tendency toward an improvement in the ability of VMR values to detect dry eye with decreasing contrast (Table 5). Therefore, we were unable to determine the most sensitive contrast level for DED assessment, possibly due to the short test duration and the limited sample size. Further study of the specific contrast level is required to determine

Table 5. Discrimination Performance of CFCVA-Related Parameters in Discriminating Eyes With DED From Normal Controls

Parameter	Sensitivity	Specificity	AUC	Cutoff Value	*P* Value
100% VMR	0.550	1.000	0.830	0.961	**0.001**
25% VMR	0.950	0.600	0.787	0.969	**0.004**
10% VMR	1.000	0.533	0.762	0.969	**0.009**
5% VMR	0.650	0.933	0.740	0.947	**0.016**
100% mean CFCVA	0.500	0.800	0.667	0.067	0.096
25% mean CFCVA	0.450	0.800	0.570	0.174	0.484
10% mean CFCVA	0.950	0.333	0.550	0.182	0.617
5% mean CFCVA	0.900	0.400	0.630	0.338	0.194
VMR51	0.900	0.667	0.757	0.970	**0.010**
VMR52	0.900	0.600	0.767	0.967	**0.008**
VMR53	1.000	0.400	0.677	0.975	0.077
VMR54	0.950	0.733	0.903	0.963	**<0.001**
VMR55	0.900	0.800	0.867	0.963	**<0.001**
Mean CFCVA51	0.500	0.800	0.637	0.064	0.172
Mean CFCVA52	0.750	0.667	0.667	0.042	0.096
Mean CFCVA53	0.650	0.733	0.627	0.059	0.205
Mean CFCVA54	0.550	0.933	0.750	0.091	**0.012**
Mean CFCVA55	1.000	0.533	0.763	0.030	**0.008**
VMR54, 55, mean CFCVA55	0.900	0.867	0.923	0.524	**<0.001**

The 100% VMR/mean CFCVA, 25% VMR/mean CFCVA, 10% VMR/mean CFCVA, and 5% VMR/mean CFCVA refer to the VMR/mean CFCVA values at 100%, 25%, 10%, and 5% contrast levels, respectively. VMR5n and mean CFCVA5n refer to the VMR and mean CFCVA of the nth minute, respectively, during the ST. Significant *P* values ($P < 0.05$) are bolded.

the lowest specific contrast level that best detects subtle changes in visual acuity for DED.

The original concept of the FVA was to simulate changes in visual acuity during daily life in a state of unconscious transient blink suppression.[25] During early FVA testing, participants were asked to keep their eyes open for 10 to 30 seconds under topical anesthesia.[19,20,42] However, the use of topical anesthesia was considered a potential source of new variables and therefore raised concerns about whether the test results reflected what would happen in natural conditions.[21] Attempts have also been made to assess the visual function of patients with dry eyes under natural blinking conditions.[22,26,32,43] Kaido et al.[43] conducted a study to measure FVA parameters under both natural blinking and blink suppression with topical anesthesia conditions. The results of the two conditions were compared, and more favorable results were found for the FVA parameters measured under natural blinking without topical anesthesia for 60 seconds, which was a more accurate reflection of tear function and ocular surface status.[43] The test methodology of this study was comparable to that of Kaido et al.[43] by extending the test time to 60 seconds and allowing participants to blink naturally. An additional 5-minute ST was added to the test to simulate eye fatigue in daily life and to assess the difference in the visual fluctuation between patients with dry eyes and normal controls during a more prolonged visual task. In the ST, there were tendencies toward statistical significance ($P = 0.070$, $P = 0.064$, respectively) for the trend of changes in VMR and mean CFCVA over 5 minutes between two groups, and more remarkable changes were observed at the fourth and fifth minutes in the DED group (Figs. 4 and 5). At a significance level of $\alpha = 0.05$, it was only at the fourth and fifth minutes that both VMR and the mean CFCVA were simultaneously statistically significantly different between the DED and NC groups (Table 2). These results indicate that extending the continuous measuring time, such as that during the ST, to simulate the fatigued state of vision was more effective in detecting vision-related functional abnormalities in patients with DED.

Currently, the diagnosis of DED consists of symptoms (i.e., OSDI questionnaire) and positive results of homeostasis tests (i.e., NIBUT), and subjective symptoms are an essential part of a DED diagnosis.[44] As a potential DED screening tool,[26,31,32,45] the recommended methodology and screening parameters for FVA testing have yet to be established,

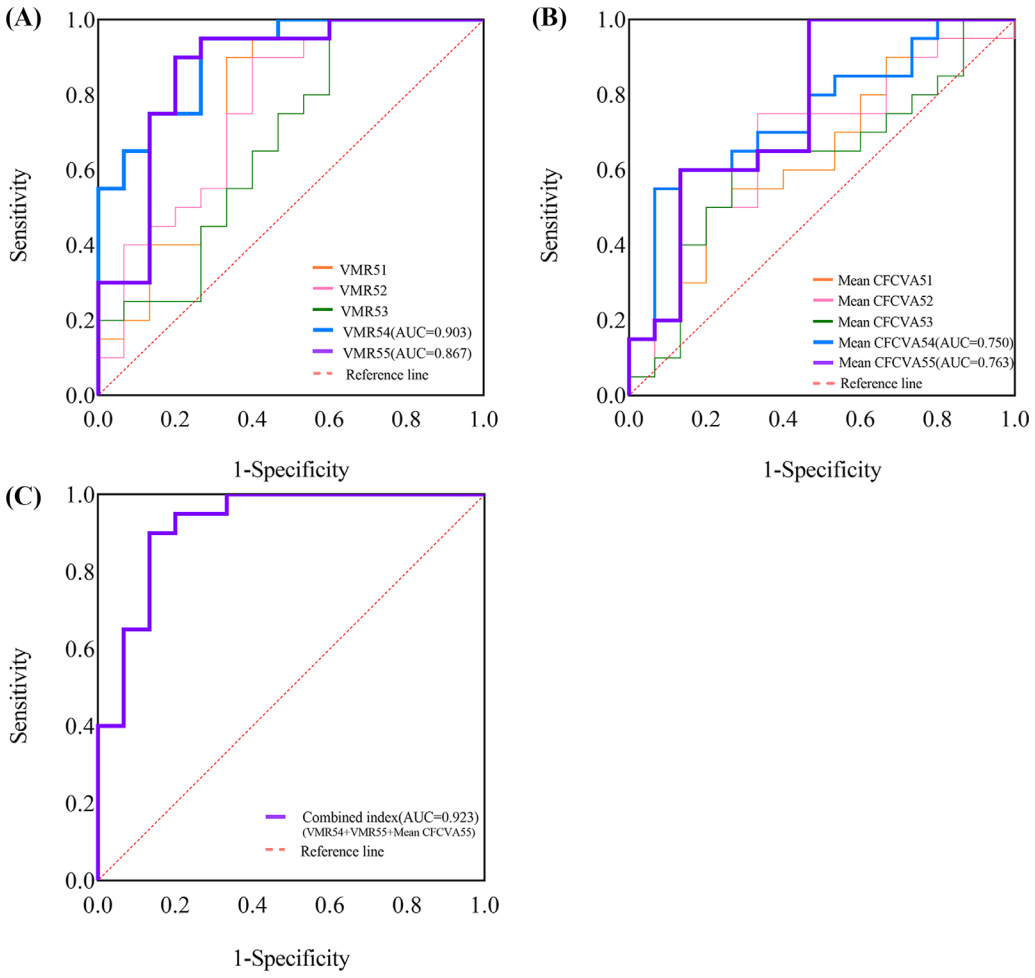

Figure 9. The ROC curves of CFCVA-related parameters for discriminating eyes with DED from normal controls. (**A**) The ROC curves of VMR values in the ST, with the ROC curves of VMR54 and VMR55 bolded. (**B**) The ROC curves of mean CFCVA values in the ST, with the ROC curves of mean CFCVA54 and mean CFCVA55 bolded. (**C**) The ROC curves of the combined index of VMR54, VMR55, and mean CFCVA55 are bolded.

and few studies have described the direct relationship between FVA results and tear film assessment parameters. In this study, the OSDI total score and subscale scores were moderately correlated with the VMR54 and VMR55 (Table 4), which were considered the most representative of all CFCVA-related parameters (including the parameters at four contrast levels) for quantifying ocular symptoms. The significant correlations of VMR and mean CFCVA at the fourth and fifth minutes with OSDI scores suggest that CFCVA-related parameters of the last two minutes of the ST can provide adequate information regarding dry eye symptoms and can therefore be used to confirm the ocular discomfort and visual disturbance in patients with DED. ROC curve analysis was used to investigate the discrimination performance of the CFCVA-related parameters in differentiating DED from normal controls. VMR54 and VMR55 were the two parameters that demonstrated the best performance among the CFCVA-related parameters for the detection of DED, achieving AUCs of 0.903 and 0.867 with sensitivities of 0.950 and 0.900 and specificities of 0.733 and 0.800, respectively. Furthermore, the combination of VMR and mean CFCVA (VMR54, VMR55, and mean CFCVA55) was considered valid as it increased the discriminatory capacity of CFCVA-related parameters with the highest AUC value of 0.923 (Table 5, Fig. 9), where the sensitivity and specificity were 0.900 and 0.867, respectively. In the study by Kaido et al.,[26] the FVA parameters needed to be combined with a dry eye questionnaire to achieve a clinically acceptable level of screening for DED, and the single parameter (VMR) measured with the currently established FVA system in 60 seconds showed relatively low diagnostic capabilities with an AUC of 0.553. In the present study, a single parameter (VMR51) with comparable setups (a 60-second duration under natural blinking conditions) exhibited superior diagnostic capabilities compared to

the study by Kadio et al., with an AUC of 0.757. The discrepancy in results could be attributed to the different study populations recruited, known as potential sampling bias, and the different testing methodologies used (specifically, the introduction of reaction time in the CFCVA measurement system) between the studies. As shown in Table 4, the diagnostic capabilities of VMR values were further improved by extending the continuous measuring time in the ST, but there was no improvement in the discriminative ability of the different VMR values with decreasing contrast. This suggested that extending the continuous measuring time was more effective in detecting vision-related functional abnormalities in patients with DED than simply decreasing the optotype contrast level.

In this study, the CFCVA system was used to directly analyze and quantify the decline of visual function in patients with DED at different contrast levels and test durations. New parameters have been proposed for the diagnosis of DED and for the assessment and interpretation of subjective symptoms. However, several limitations in this study need to be further explored: the optimal contrast level for the CFCVA system remains unclear and requires further study with a larger sample size, and the participants recruited in this study consisted of only young adults and, as suggested in the report by Uchino et al.,[46] the level of attentional concentration in different age groups may also affect the test results, and therefore further studies in different age groups are needed to determine the general performance of the CFCVA system. Patients with dry eyes have been found to have higher blinking rates than normal participants,[47,48] but a study by Himebaugh et al.[49] showed that the increased blinking rate in patients with dry eyes was not sufficient to compensate for the unstable tear film, as patients with dry eyes had more aggressive tear breakup even with a higher blinking rate during various visual tasks. Therefore, blinking quality, such as the completeness of the blink, may be more critical in affecting tear film stability[47,48] and should be further investigated in future research.

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