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ORIGINAL PAPER

Evaluation of tear film function by Oculus Keratograph 5M and IDRA ocular surface analyser

Jiajia Wang · Yan Shen · Xingtao Zhou · Zhiqiang Yu · Jiaxu Hong · Qihua Le

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Abstract

Purpose The aim of this study was to evaluate the function of tear film with Oculus Keratograph 5M (Oculus K5M) and IDRA ocular surface analyser (IDRA), analyse their consistency and explore the potential of IDRA in the diagnosis of dry eye disease (DED).

Methods This cross-sectional study enrolled 36 participants (DED group, 14 eyes; non-DED group, 22 eyes). The parameters of tear film function, including the first noninvasive breakup time (fNIBUT), average NIBUT (aNIBUT), tear meniscus height (TMH), lipid layer thickness (LLT), lipid layer colour (LLC), lipid layer uniformity (LLU), morphology of meibomian glands (MGs) and MG loss, were obtained with Oculus K5M and IDRA. The consistency of parameter measurements between the two devices was evaluated.

Results All the parameters except LLT, which can be measured only by IDRA, were not significantly different between the two instruments in DED eyes. However, IDRA reported lower values of fNIBUT, aNIBUT and TMH as well as higher MG loss scores in non-DED eyes than Oculus K5M did ($p < 0.001, < 0.001, = 0.002,$ and $= 0.002$, respectively). Further regression analysis revealed that aNIBUT and LLT measured by IDRA were the optimal parameters for diagnosing DED (OR = 0.567 and 0.845, $p = 0.057$ and 0.043, respectively), and their combination had the strongest diagnostic potential (AUC = 0.841, sensitivity = 85.7%, and specificity = 77.3%).

Conclusion As a user-friendly noninvasive device, the tear film function parameters measured by IDRA

Jiaxu Hong, Qihua Le have contributed equally to this work and are co-corresponding authors.

J. Wang · Y. Shen · X. Zhou · Z. Yu · Q. Le (✉)
Department of Ophthalmology, Eye & ENT Hospital Fudan University, Shanghai, China
e-mail: qihuale_eent@163.com

X. Zhou · Z. Yu · Q. Le
Research Center, Eye & ENT Hospital Fudan University, Shanghai, China

X. Zhou · Z. Yu · J. Hong · Q. Le
Key Laboratory of Myopia and Related Eye Diseases, NHC, Shanghai, China

J. Hong (✉)
Department of Ophthalmology, Eye & ENT Hospital, State Key Laboratory of Molecular Engineering of Polymers, Fudan University, Shanghai, China
e-mail: jiaxu.hong@fdeent.org

J. Hong
Shanghai Engineering Research Center of Synthetic Immunology, Shanghai, China

J. Hong
Department of Ophthalmology, Children's Hospital of Fudan University, National Pediatric Medical Center of China, Shanghai, China

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were highly consistent with those measured by Oculus K5M in DED patients. The combination of aNIBUT and LLT measured by IDRA had the best diagnostic accuracy for DED.

Keywords Diagnosis · Dry eye disease · IDRA ocular surface analyser · Oculus Keratograph 5M · Tear film

Introduction

Dry eye disease (DED), a multifactorial ocular surface disease, is characterized by the loss of tear film homeostasis, ocular surface inflammation and neurosensory abnormalities [1]. DED patients exhibit symptoms of ocular discomfort, and the clinical signs include reduced tear volume, an unstable tear film and ocular surface damage. With a prevalence ranging from 5 to 50%, DED has been one of the most common diseases in ophthalmological clinics in recent decades and affects millions of individuals globally [2].

In addition to ocular symptoms, abnormal tear film function and ocular surface damage are crucial signs for the diagnosis of DED. Traditional diagnostic examinations for DED include fluorescein tear film break-up time (FBUT), Schirmer I test (SIT) and corneal fluorescein staining (CFS). However, these methods have limitations. The FBUT might be affected by varying volumes and concentrations of fluorescein instilled into the conjunctival sac and depends on subjective assessment by the observer [3, 4]. Noninvasive breakup time (NIBUT) avoids the disturbance of fluorescein to tear film and offers an automated output. Its application in the diagnosis of DED has been considered in the past decade, and it is also recommended in the TFOS DEWS II [5]. SIT not only causes ocular discomfort but also might cause biases due to irritative tearing. The tear meniscus height (TMH), which accounts for 75% ~ 90% of the total tear volume [6], is highly consistent with SIT results and is considered a sensitive indicator of aqueous deficient DED [7, 8]. More importantly, the measurement procedure is noncontact, yielding a more accurate outcome.

Recently, several noninvasive devices have been developed to objectively evaluate tear film function using DED-related parameters such as the NIBUT and TMH [9]. Among them, Oculus Keratograph 5M (Oculus K5M, Wetzlar, Germany) is one of the most widely used devices; it can be used to measure the first NIBUT (fNIBUT), average NIBUT (aNIBUT), and TMH and to perform meibography [10–12]. However, the patients are required to keep their eyes wide open for as long as possible when the images of tear film break-up are captured, which is difficult for moderate-to-severe DED patients.

Equipped with three imaging techniques, including interferometry, Placido rings and infrared imaging, the IDRA ocular surface analyser (IDRA) (SBM Sistemi, Torino, Italy), a new device for evaluating tear film function, provides an upgraded comprehensive dry eye diagnostic platform and enables the measurement of fNIBUT, aNIBUT, TMH, and lipid layer thickness (LLT); blinking analysis; 2D and 3D meibography; and anterior segment imaging. The testing procedure is noncontact and rapid, and the outcomes are easily understood by offering visible images of tear films and MG as well as corresponding colourful indicators [13]. However, its consistency with other well-recognized devices and its diagnostic potential have not been investigated. Therefore, we performed this cross-sectional study to evaluate the function of tear film using IDRA, explore the consistency of its results with those of Oculus K5M, and assess its potential in the diagnosis of DED.

Methods

Study population

This study was conducted in accordance with the tenets of the Declaration of Helsinki for medical research and approved by the Institutional Review Board of Eye & ENT Hospital, Fudan University (protocol code EENTIRB-20190301). Written informed consent was obtained from all participants after providing a detailed explanation. Subjects who visited the Eye & ENT Hospital of Fudan University for refractive surgery screening from July to September 2022 were enrolled. The participants were classified into the DED group if they reported an Ocular Surface Disease Index (OSDI) score ≥ 13 and had any two of the following DED signs: (1) FBUT < 10 s, (2) SIT < 10 mm/5 min, and (3) corneal fluorescein staining (CFS) score ≥ 1 [14, 15]. For patients with bilateral DED, more severe eye was

included. The subjects who did not meet these criteria were assigned to the non-DED control group.

The exclusion criteria were as follows: (1) < 18 years of age; (2) inability to cooperate with the examinations; (3) uncontrolled systemic diseases; (4) current pregnancy or lactation; (5) history of ocular surgery or trauma; (6) history of ocular diseases other than DED and ametropia; (7) history of lacrimal punctual occlusion or medication usage affecting tear production within 4 weeks before enrolment; and (8) eye drop usage or contact lens wearing within 24 hours before enrolment.

Ocular examinations

Order of ocular examinations

With the assistance of trained research staff, demographic data, medical history and OSDI questionnaires were collected prior to ocular examinations to avoid disturbances from clinical encounters. All the participants subsequently underwent slit-lamp examination, FBUT measurement and CFS score evaluation. After that, the Oculus K5M and IDRA measurements were taken with an interval of 15 min; the order of the instruments was random, with subjects who were randomly assigned an odd number undergoing Oculus K5M first and those who had an even number undergoing IDRA first. Finally, SIT was performed to avoid impact on the CFS evaluation. All examinations were performed between 9 am and 4 pm in a quiet room with a constant temperature (24–26 °C) and humidity (40–50%).

OSDI Questionnaire

The OSDI is one of the most widely used questionnaires for evaluating the severity of DED symptoms in three subsections: ocular symptoms, limitations in vision function and environment-related triggering factors. Ranging from 0 to 100, the OSDI score = 25 × (sum of questionnaire scores)/(numbers of questions answered) [16].

Slit-lamp biomicroscopy

A comprehensive slit-lamp examination was performed to rule out other ocular abnormalities that could influence the tear film. Fluorescein was instilled into the lower fornix using a fluorescein strip (Jingming, China) pre-moisturized with sterile saline without excess fluid. The subjects were instructed to blink naturally multiple times until the fluorescein sodium solution completely covered their corneas and then keep their eyes open as long as they could under the cobalt blue light. The time interval between the final blink and the occurrence of the first black spot on the corneal surface was documented as the FBUT. FBUT measurement was repeated three times to obtain an average value. Within 1–3 min after fluorescein instillation [17], CFS was evaluated according to the US National Eye Institute (NEI) grading scale [14]. Specifically, in 5 areas of the cornea (central, superior, inferior, nasal and temporal), CFS was graded as follows: 0: no staining; 1: < 15 dots; 2: 16–20 dots; and 3: > 30 dots, strip/bulk staining or corneal filaments. The total score was the sum of all the areas and ranged from 0 to 15.

Examination with Oculus K5M and IDRA

In a sitting position, the subjects were instructed to rest their heads in front of Oculus K5M or IDRA cameras. During Oculus K5M examination, participants were required to keep their eyes open as long as possible after several fast blinks. Oculus K5M took images immediately after blinking and recorded continuous videos by using infrared light. Then, the upper and lower eyelids were everted, and meibography was performed. The IDRA examination was divided into 3 parts. First, the subjects were asked to blink freely, and the LLT was measured based on interferometric principles. Next, IDRA automatically recognized the longest eye-opening period during several blinks and collected videos and images of precorneal tear film under LED white light. Finally, meibography was documented in a similar manner to Oculus K5M. Each examination was repeated three times.

Measurement of DED parameters

Based on the projection of the Placido disc on the tear film, Oculus K5M captures image irregularities with an infrared light source. The time between the last complete blink and the first irregularity of the Placido disc was automatically recorded as the fNIBUT, whereas the time of irregularities occurring

in different zones of the entire cornea was averaged as the aNIBUT. The TMH was defined as the distance from the tear meniscus peak to the inferior lid margin at the midpoint corresponding to the pupil centre measured with an integrated calliper tool [7]. Lipid layer colour (LLC) was categorized into five colours: achromatic, hoary, and blue-grey, which were classified as abnormal, and red-green and multicolour, which were classified as normal. The distribution of the lipid layer uniformity (LLU) was recorded as even or uneven according to the flow rate of the tear film. The morphology of the meibomian glands (MGs) was considered normal only when the glands in both the upper and lower eyelid were undistorted. MG loss was defined as the percentage of glandular tissue loss over the entire tarsus. It was divided into 4 grades: a score of 0 represented no dropout, whereas scores of 1, 2 and 3 indicated dropout $\leq 1/3$, between 1/3 and 2/3, and $> 2/3$, respectively [18]. The scores for upper and lower MG loss were summed.

During the automatically identified longest eye-opening period, IDRA measured the fNIBUT and aNIBUT based on the irregularities of the Placido rings. At the same time, the TMH was automatically calculated by averaging the results measured at three locations: the central, medial, and lateral paracentral points of the lower tear meniscus. The evaluations of LLC, LLU, MG morphology and MG loss were performed in the same manner as those of Oculus K5M. Moreover, IDRA can provide the LLT, which was automatically calculated according to a comparison between the reflecting pattern of the tear lipid layer and an integrated grading system [19, 20].

SIT

Tear production was evaluated via SIT without anaesthesia. A standard 5×40 mm Schirmer paper strip (Jingming, China) was folded at the notch, and the folded end was hooked over the temporal 1/3 of the lower lid margin. Then, the participants were asked to gently close their eyes for 5 min. The distance of wetting that extended from the notch was recorded.

Statistical analysis

The statistical analysis was conducted with Stata 17.0 software (Stata Corp., USA), SPSS Statistics 26.0 (IBM Corp., USA) and GraphPad Prism software 9.3.0 (USA). The normality of the data was assessed using the Shapiro−Wilk test. If the data conformed to a normal distribution, they are presented as the means ± standard deviations, otherwise, they are presented as medians (interquartile ranges (IQRs) 25–75). The analyses of normally distributed data, nonnormally distributed data or data with heterogeneous variance, and enumeration data were performed with Student's t test or t' test, the Wilcoxon rank-sum test, and Fisher's exact method, respectively. Differences between Oculus K5M and IDRA were compared using t tests, Wilcoxon matched-pairs signed-rank tests and rectified McNemar tests. Bland−Altman analysis of continuous variables (fNIBUT, aNIBUT and TMH) was conducted to assess the agreement. Among the DED parameters measured by IDRA, those with a p value < 0.250 for the comparison between the DED and non-DED groups were included in logistic regression analysis (method: forwards selection (likelihood ratio)) to assess the summary diagnostic accuracy of IDRA. Receiver operating characteristic (ROC) analysis and kappa concordance analysis were performed for quantitative parameters, and a logistic regression model was established to evaluate the univariate and multivariate diagnostic performance of IDRA. A p value < 0.05 was considered to indicate statistical significance.

Results

Demographic data

A total of thirty-six eyes of 36 young participants (13 males and 23 females) with a median age of 25 (range 18–39) years were enrolled. Among them, 14 eyes met the diagnostic criteria for DED, and the other 22 eyes were non-DED controls. The sex distribution, age and history of wearing contact lenses were similar between the two groups, although the DED group included more right eyes ($p = 0.018$). Compared with the non-DED group, the DED group reported a higher OSDI score, lower SIT score, shorter FBUT and higher CFS ($p < 0.001, < 0.001, = 0.045$ and 0.015, respectively). The demographic data of all patients are shown in Table 1 DED Parameters.

Table 1 Demographic Data of DED and non-DED Groups

	DED Group(n = 14)	Non-DED Group(n = 22)	*p* Value
Sex (male/female)	5/9	8/14	1.000
Age (yrs)	24.43 ± 3.23	25.41 ± 6.61	0.974
Eye (OD/OS)	9/5	5/17	**0.018**
Wearing Contact Lens (yes/no)	9/5	13/9	1.000
OSDI	19.09(14.58–29.55)	5.39 ± 4.97	**< 0.001**
SIT (mm/5 min)	4.50(2–11)	15.77 ± 6.91	**< 0.001**
FBUT (s)	4.00 ± 1.71	5.64 ± 2.59	**0.045**
CFS score	0.5(0–1)	0(0–0)	**0.015**

DED dry eye disease; *OSDI* ocular surface disease index; *SIT* Schirmer I test; *FBUT* fluorescein tear film break-up time; *CFS* corneal fluorescein staining

All DED parameters measured by Oculus K5M and IDRA are presented in Table 2. Compared with the non-DED group, the DED group had significantly lower values of fNIBUT (6.13 ± 2.32 vs. 15.43 ± 3.80, $p < 0.001$), aNIBUT (9.40 ± 3.67 vs. 17.18 ± 2.88, $p < 0.001$) and TMH (0.21 ± 0.06 vs. 0.27 ± 0.06, $p = 0.002$), as measured by Oculus K5M. In contrast, the findings of IDRA only revealed a lower aNIBUT in the DED group (9.45 (7.18–10.3) vs. 10.39 (9.92–11.26), $p = 0.008$). Notably, the LLT, which could be measured only by IDRA, was significantly thinner in DED eyes than in normal eyes (57.64 ± 10.20 vs. 66 (63–72), $p = 0.015$).

Comparisons between the Oculus K5M and IRDA

As shown in Table 2, the parameters obtained by both devices were not significantly different in the DED group. However, in the non-DED group, lower fNIBUT, aNIBUT and TMH values and higher MG loss scores were reported by IDRA ($p < 0.001, < 0.001, = 0.002,$ and $= 0.002$, respectively). The other parameters did not differ between the two devices in the non-DED group. The

Table 2 DED Parameters Measured by Oculus K5M and IDRA

		Oculus	IDRA	IDRA—Oculus	*p* value (IDRA vs. Oculus)
DED Group (n = 14)	fNIBUT (s)	6.13 ± 2.32	5.70 ± 1.22	−0.43 ± 2.49	0.529
	aNIBUT (s)	9.40 ± 3.67	9.45(7.18–10.3)	−0.71 ± 4.07	0.528
	TMH (mm)	0.21 ± 0.06	0.19 ± 0.03	−0.01 ± 0.07	0.469
	Distorted MG	35.71%(5/14)	28.57%(4/14)	−7.14%	1.000
	Score of MG loss	2(1–3)	2(2–3)	0.91 ± 1.19	0.189
	Abnormal LLC	71.43%(10/14)	71.43%(10/14)	0	1.000
	Uneven LLU	57.14%(8/14)	78.57%(11/14)	21.43%	0.375
	LLT	–	57.64 ± 10.20	–	-
non-DED Group (n = 22)	fNIBUT (s)	15.43 ± 3.80	6.40 ± 1.06	−9.03 ± 3.81	**< 0.001**
	aNIBUT (s)	17.18 ± 2.88	10.39(9.92–11.26)	−6.97(-7.93-(-4.43))	**< 0.001**
	TMH (mm)	0.27 ± 0.06	0.20(0.18–0.23)	−0.06 ± 0.08	**0.002**
	Distorted MG	22.73%(5/22)	13.64%(3/22)	−9.09%	0.500
	Score of MG loss	1.32 ± 1.09	2.23 ± 0.87	0.43 ± 1.16	**0.002**
	Abnormal LLC	63.64%(14/22)	77.27%(17/22)	13.64%	0.375
	Uneven LLU	36.36%(8/22)	54.55%(12/22)	18.18%	0.344
	LLT	–	66(63–72)	–	-

DED dry eye disease; *Oculus K5M* Oculus Keratograph 5M; *fNIBUT* first noninvasive breakup time; *aNIBUT* average noninvasive breakup time;*TMH* tear meniscus height; *MG* meibomian gland; *LLC* lipid layer color; *LLU* lipid layer uniformity; *LLT* lipid layer thickness

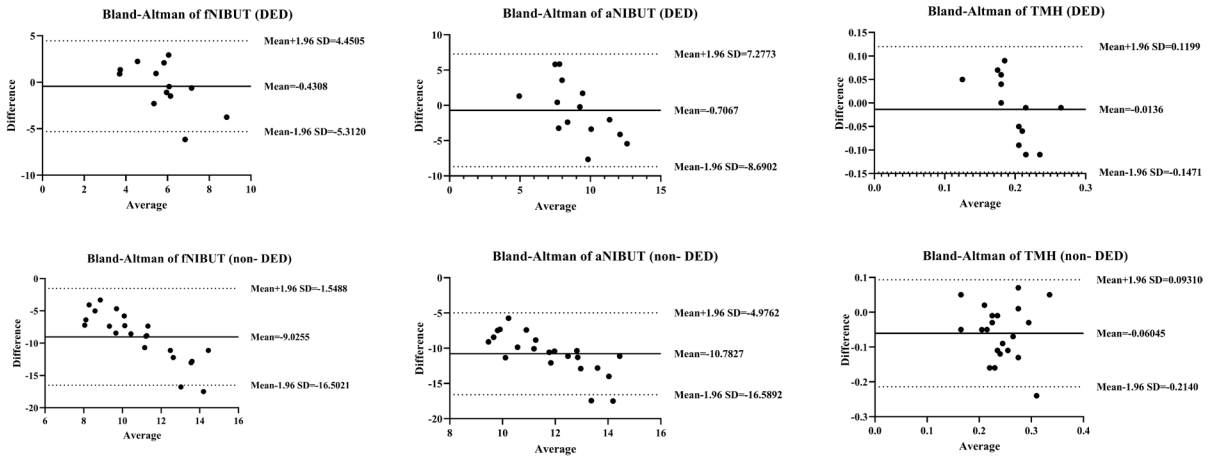

Fig. 1 Bland−Altman scatter plots in DED eyes and non-DED eyes. Mean differences and 95% limits of agreement (mean ± 2 SD) are shown as references lines. fNIBUT, first noninvasive breakup time; aNIBUT, average noninvasive breakup time; TMH, tear meniscus height

Bland−Altman analysis of the quantitative parameters revealed that the agreement in DED patients was good, but that in non-DED patients was poor (Fig. 1).

Logistic regression and ROC analyses

The parameters measured by IDRA with p values < 0.250, which included the fNIBUT, aNIBUT, TMH, MG loss score, LLU and LLT, were included in multivariate stepwise logistic regression analysis. The fNIBUT, TMH, MG loss score and LLU were rejected by the regression model ($\chi^2 = 16.054$, $p < 0.001$).

$$LLT + aNIBUT = \frac{\exp(15.679 - 0.567 * aNIBUT - 0.168 * LLT)}{1 + \exp(15.679 - 0.567 * aNIBUT - 0.168 * LLT)}$$

However, LLT (OR = 0.845, 95% CI: 0.718–0.994, $p = 0.043$) and aNIBUT (OR = 0.567, 95% CI: 0.316–1.016, $p = 0.057$) were significant in detecting DED using IDRA (Fig. 2a).

The ROC curves of the quantitative parameters (fNIBUT, aNIBUT, TMH, MG loss score and LLT)

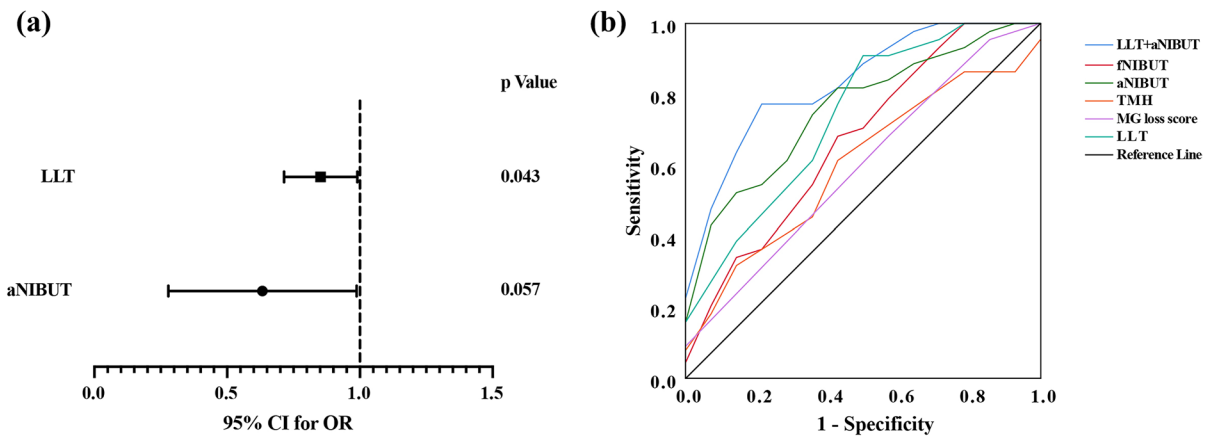

Fig. 2 Diagnostic potential of parameters measured with IDRA. **(a)** Logistic Regression Analysis for DED Parameters Measured with IDRA. (b) Receiver operating characteristic curves of quantitative parameters. LLT, lipid layer thickness; aNIBUT, average noninvasive breakup time; fNIBUT, first noninvasive breakup time; TMH, tear meniscus height; MG, meibomian glands

Table 3 AUC, cutoff values, sensitivity, specificity and Youden index, and agreement analysis (Kappa value) for DED parameters measured by IDRA

	AUC (95%CI)	Cutoff value	Sensitivity	Specificity	Youden index	Accuracy	Kappa Value
fNIBUT	0.669 (0.482–0.856)	6 s	68.18%	64.29%	0.325	66.67%	0.317
aNIBUT	0.765 (0.61–0.92)	9.9 s	81.82%	64.29%	0.461	75.00%	0.467
TMH	0.615 (0.429–0.802)	0.215 mm	36.36%	85.71%	0.221	55.56%	0.191
Grade score of MG loss	0.617 (0.432–0.802)	1.5	18.18%	100.00%	0.182	50.00%	0.147
LLT	0.744 (0.577–0.91)	60.5 nm	90.90%	50.00%	0.409	75.00%	0.438
LLT + aNIBUT	0.841 (0.712–0.969)	0.405[a]	85.70%	77.30%	0.630	80.56%	0.606

[a]The cutoff value of LLT + aNIBUT was obtained based on ROC analysis of 36 individual values calculated from the regression model

AUC area under curve; *DED* dry eye disease; *fNIBUT* first noninvasive breakup time; *aNIBUT* average noninvasive breakup time;*TMH* tear meniscus height; *MG* meibomian gland; *LLT* lipid layer thickness

are presented in Fig. 2b. The combination of LLT and aNIBUT, which was validated by logistic regression analysis, had the highest diagnostic power (AUC: 0.841 and Youden index: 0.630), followed by aNIBUT alone (AUC: 0.765 and Youden index: 0.461) and LLT alone (AUC: 0.744 and Youden index: 0.409), as shown in Table 3. Moreover, at a cut-off of 0.405, the value of LLT + aNIBUT calculated by the regression model showed quite good accuracy (80.56%) and substantial agreement (Kappa value = 0.606, $p < 0.001$) with the current DED diagnostic criteria.

Discussion.

Compared with Oculus K5M, IDRA allows free eye blinking during the examination process, which is faster and more easily accepted by DED patients, especially those with moderate and severe DED. The current study revealed that the objective DED parameters obtained with IDRA were highly consistent with those obtained with the Oculus K5M in DED patients. More importantly, IDRA provides a quantitative analysis of LLT, which is highly important in the evaluation of evaporative DED and meibomian gland dysfunction. Our findings indicate that the application of IDRA might have great clinical potential in the diagnosis of DED.

The current study revealed that aNIBUT and LLT obtained with IDRA had the strongest diagnostic power, which was consistent with previous findings [13]. The combination of the aNIBUT and LLT had a diagnostic sensitivity of 85.7% and a specificity of 77.3%. fNIBUT was also shown to have diagnostic potential despite its lower accuracy than aNIBUT and LLT, which has not been reported in other studies [21]. The LLT is directly correlated with tear film stability [22]. A decreased LLT leads to an unstable tear film [23], which in turn results in tear hyperosmolarity and ocular surface inflammation. Unlike other examinations that measure the LLT in a semiquantitative way using tear interferometric images [24], IDRA provides quantitative measurements of the LLT and improved diagnostic accuracy.

Unexpectedly, compared with Oculus K5M, IDRA reported lower fNIBUT, aNIBUT and TMH values as well as a greater MG loss score in non-DED eyes, which was partially in agreement with the findings of a previous study [25]. These disparities might be attributed to two possible reasons. Oculus K5M requires patients to keep their eyes open as long as possible, which probably leads to reflex tearing in healthy eyes with normal corneal sensation and tear production [1, 26–29]. Moreover, it has been reported that NIBUT in healthy eyes increases when ambient temperatures increase [30]. Equipped with white LED light, IDRA can avoid the increase in temperature on the ocular surface caused by infrared radiation.

Coincidentally, the cut-off values of fNIBUT, aNIBUT, TMH and LLT obtained from the ROC curves in the current study were similar to those suggested by IDRA manufacturer (fNIBUT: 6 s vs. 5 s; aNIBUT: 9.9 s vs. 10 s; TMH: 0.215 mm vs. 0.22 mm; LLT: 60.5 nm vs. 60 nm). The cut-off values of aNIBUT and LLT in our study were higher than those proposed by Vigo et al. [13]. Their

study included more old DED patients, which might be a possible reason. Further studies with a larger number of elderly individuals are needed to assess the aNIBUT and LLT more accurately.

The MG loss score was not found to be a significant parameter for diagnosing DED in the current study, which was inconsistent with Rinert's study [21]. However, their study cohort was not matched for age, and the DED group was much older than the control group [21]. Age is a powerful confounder of MG loss [31, 32], which might be the main cause of these differences. Moreover, the examination locations used to evaluate MG loss were not the same across different studies (inferior eyelid [21], superior eyelid [13] and both eyelids (our study)). Further quantitative analysis of MG loss in the same location in an age- and sex-matched study might be beneficial to address the role of MG loss in the diagnosis of DED.

This study had several limitations. First, this was a single-centre study, and the sample size, especially the number of DED patients, was not large enough, which might cause selection bias. Moreover, DED severity and subtype were not considered during the enrolment and analysis. In addition, the participants in our study were the candidates for refractive surgery, all of whom were younger than 40 years old. Besides, the repeatability and interobserver bias of IDRA were not investigated in the current study. Further large-scale multicentre studies with elderly populations and detailed grading and classification of DED are needed to fully elucidate the diagnostic accuracy of IDRA.

In conclusion, IDRA, a noninvasive and user-friendly device, facilitates the measurement of objective DED parameters and provides a comprehensive evaluation of tear film function, which is highly consistent with Oculus K5M in DED patients. The combination of the aNIBUT and LLT measured by IDRA had the highest sensitivity and specificity for diagnosing DED.

Author contributions JW: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing, Visualization. YS: Data curation, Formal analysis. XZ: Methodology, Resources. ZY: Methodology, Resources. JH: Conceptualization, Project administration, Supervision, Funding acquisition, Methodology. QL: Conceptualization, Methodology, Data curation, Formal analysis, Funding acquisition, Project administration, Supervision, Writing – original draft, Writing – review & editing.

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Declarations

Conflict of interest The authors declare no competing interests.

Ethics approval This study was conducted in accordance with the tenets of the Declaration of Helsinki for medical research and approved by the Institutional Review Board of Eye & ENT Hospital, Fudan University (protocol code EENTIRB-20190301).

Informed consent Informed consent was obtained from all individual participants included in the study.

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