

The Role of Different Tear Volume Detection Methods in the Evaluation and Diagnosis of Mild Dry Eye Disease

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Purpose: To compare the diagnostic power of strip meniscometry (SM), Schirmer test (ST), and tear meniscus (TM) in mild dry eye disease (DED) and to evaluate the association with DED-related parameters.

Methods: Forty left eyes with mild DED and 40 left eyes of control participants were investigated. All participants underwent a comprehensive ocular surface examination, including the Ocular Surface Disease Index (OSDI), fluorescein tear film break-up time (FTBUT), ocular surface staining grades, meiboscores, and tear film volume examinations, including SM, ST, tear meniscus height (TMH), and tear meniscus cross-sectional area (TMA) measurements, respectively, by optical coherence tomography (OCT) and Keratograph 5M (K5M). The correlation between these parameters was evaluated, and the receiver operating characteristic (ROC) curve was used to verify the diagnostic power by the area under the curve (AUC).

Results: All tear film volume examinations significantly correlated with DED parameters. Among them, the most relevant factor to OSDI scores and FTBUT was SM. In addition, SM (AUC = 0.992), TMH-OCT (AUC = 0.978), and TMA-OCT (AUC = 0.960) showed better diagnostic power than ST (AUC = 0.650) in DED, in which the cutoff value of SM was 3.5 mm (sensitivity, 97.5%; specificity, 95.0%).

Conclusions: Compared with ST, SM and TM parameters obtained by OCT were more relevant to ocular surface parameters and can provide a more valuable approach to discriminate mild DED from control participants.

Translational Relevance: This study made a comprehensive comparison of the existing tear volume detection methods and provided a basis for the clinical selection of appropriate detection methods and the diagnosis of mild DED.

Introduction

Dry eye disease (DED) is a multifactorial chronic disease of the ocular surface characterized by unstable tear film and accompanying various ocular and visual symptoms.^{1,2} In the common process, the diagnosis of DED starts with screening questions for subjective symptoms, followed by a series of examinations, such as tear film breakup time (TBUT), osmolality, staining tests, meibomian gland/lid margin changes, and tear volume examinations.³ Among them, TBUT is the key diagnosis factor, which reflects the stability of tear film.

In contrast, tear volume examinations are not directly mentioned in the diagnostic conditions of DED and are mostly used as further tests for subtype classification. However, tear film volume is still an important pathogenic mechanism and a diagnostic sign in patients with DED, which was mentioned in the 2017 Tear Film and Ocular Surface Society–Dry Eye Workshop II (TFOS-DEWS II) reports.^{1,2} Accurate assessment of tear volume is essential for the evaluation of DED severity and guidance of tear film-oriented therapy.

Several studies have reported that acknowledged tear film volume examinations, including the Schirmer test (ST) without anesthesia, meniscometry, and strip

meniscometry (SM), showed good diagnostic power and correlation with other DED parameters.^{4–11} However, each inspection method has its own characteristics, so there is no consensus on which method to use as the standard.

ST is the most traditional and commonly used method by clinical ophthalmologists to evaluate tear film volume, but its invasion and poor repeatability make the diagnosis ineffective.^{12,13} The tear meniscus (TM) can be detected by slit-lamp techniques, optical coherence tomography (OCT), and Keratograph 5M (K5M) minimally invasively or even noninvasively, including TM height (TMH) and TM cross-sectional area (TMA). They have good correlation with other DED tests and show good diagnostic accuracy. However, due to the shortcomings of strong subjectivity, poor repeatability, expensive equipment, time consumption, and operator dependence, these tests have not been widely used in general ophthalmic clinics.^{4,14–17} Strip meniscometry (SM) is a swift and noninvasive method for quantitative evaluation of tear film volume by inserting a strip into the lower TM for 5 seconds, which was first reported by Dogru et al.¹⁸ in 2006 and has been proven to have good reproducibility. Since then, some studies have compared the correlation between SM and DED-related symptoms and examination results with ST, which included TBUT and ocular surface staining, and the results showed that SM seemed to have a stronger correlation.^{5,18–27} There are also some studies comparing the role of SM and TM parameters detected by OCT or K5M in the diagnosis of DED that indicated both SM and TM parameters have excellent diagnostic power.^{17–19,22–24}

However, there is no research report on the application of SM in the Chinese population. Additionally, a consensus has not yet been reached regarding which examination would perform better in the diagnosis and evaluation of DED.

In the present study, the role of tear volume examinations, including SM, ST, and the tear meniscus, by OCT and K5M in both the diagnosis and evaluation of DED was investigated, assessed by the diagnostic power with the receiver operating characteristic (ROC) curve and correlations with DED-related parameters.

Methods

Participants

The research was a prospective cross-sectional controlled study that was approved by the local ethics committee and followed the tenets of the Declaration

of Helsinki. Written informed consent was obtained from all participants before the study.

DED was defined following the Asia Dry Eye Society reports¹ and met two criteria: (1) DED symptoms assessed by increased Ocular Surface Disease Index (OSDI) score (≥ 13) and (2) fluorescein TBUT (FTBUT) < 5 seconds. In addition, mild DED was defined according to the results of ocular surface staining that was described in the Oxford scheme: Oxford grades ≤ 2 .²⁸ All participants were older than 18 years, and those with a history of systemic diseases, atopy, allergic diseases, Stevens-Johnson syndrome, ocular trauma, contact lens use, previous ophthalmic treatment history, or any ocular and systemic disease that may affect the ocular surface were excluded.

Clinical Examinations

Each participant underwent comprehensive ocular surface examinations in the following order: completing the OSDI questionnaire, undergoing TM generated by the OCT and K5M, meiboscopes, SM, slit lamp, FTBUT, ocular surface fluorescence staining, and ST. Considering the influence of the environment on dry eye examinations,²⁹ the temperature and humidity of the examination room during all tests were maintained at 20°C to 26°C and 45% to 65%, respectively.

The OSDI questionnaire was used to assess DED symptoms and consisted of 12 questions and three subcontent items, including ocular symptoms, vision-related functions, and environmental triggers.³⁰ Total score and three subscores were recorded.

TM measurement was captured by an OCT system (RTVue; Optovue, Inc., Fremont, CA, USA) at the lower lid–cornea junction at the highest level of TM in the middle third. Patients were asked to blink, and the images were quickly acquired to avoid TM instability. Three high-quality images were chosen to save and used for subsequent analysis. The images were retrieved and analyzed to measure the TMH and TMA by ImageJ software (version 1.51p22; National Institutes of Health, Bethesda, MD, USA). [Figure 1](#) shows a typical cross-sectional image of a lower TM obtained by OCT.

TM was also measured using the infrared TM measurement mode in the OCULUS Keratograph (Keratograph 5M; OCULUS, Inc., Wentzler, Germany). Before the TM images were taken, all participants were instructed to blink normally to maintain TM in a normal state. Images were taken immediately after blinking and repeated three times, and then TMH was measured with built-in measurement software that was loaded onto the K5M. The measurement of TMH was performed at the 6-o'clock

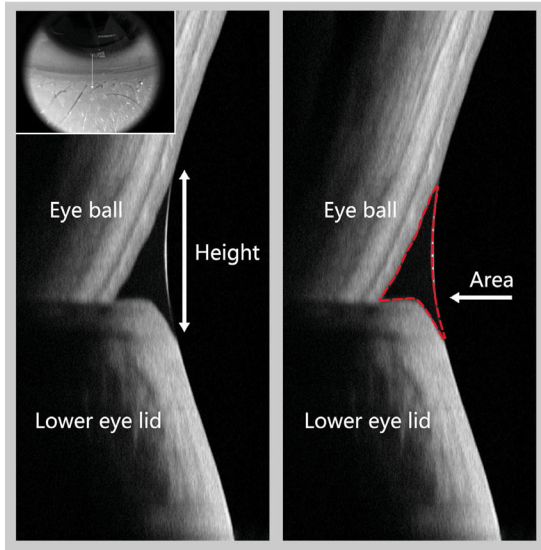


Figure 1. Optical coherence tomography image of the lower tear meniscus. Tear meniscus height was defined as the distance between the eyelid–meniscus junction and the meniscus–eye junction, and tear meniscus cross-sectional area was defined as the area encompassing the area between the two points above and the eye–eyelid junction.

zone between the cornea and the lower eyelid. TMH measurement in the K5M is the length between the darker edge of the lower eyelid and the upper border of the reflex line of the tear meniscus.

The upper and lower eyelids were observed by the Meibo-scan mode of the K5M system. ImageJ was used to calculate the proportion of the area loss in the total meibomian gland area, which was divided into 0 to 3 grades according to the severity.³¹

Strip meniscometry (SMTube; Echo Electricity, Shirakawa city, Fukushima, Japan) was used to evaluate the lower tear meniscus volume. The detailed structures and usage of SM have been previously described in studies by Dogru et al.¹⁸ and Shinzawa et al.²⁰ In short, there is a ditch with an aperture of 20 μm in the center of the strips. When the strip is inserted into the TM, due to the hydrophobic coating on both sides of the central ditch, the tears will extend upward along the central ditch without infiltrating into the periphery and will be dyed blue by the dye at the top for easy observation. On the side of these strips, a scale strip in millimeters was printed to measure and record the test scores. Under a slit-lamp microscope, one end of the strip was immersed in the tear meniscus of the lateral third of the lower eyelid without contact with the cornea, conjunctiva, and eyelid (Fig. 2). After 5 seconds, the results were immediately removed, read, and recorded.

FTBUT and ST were conducted as per the accepted protocol for examination of the ocular surface. After

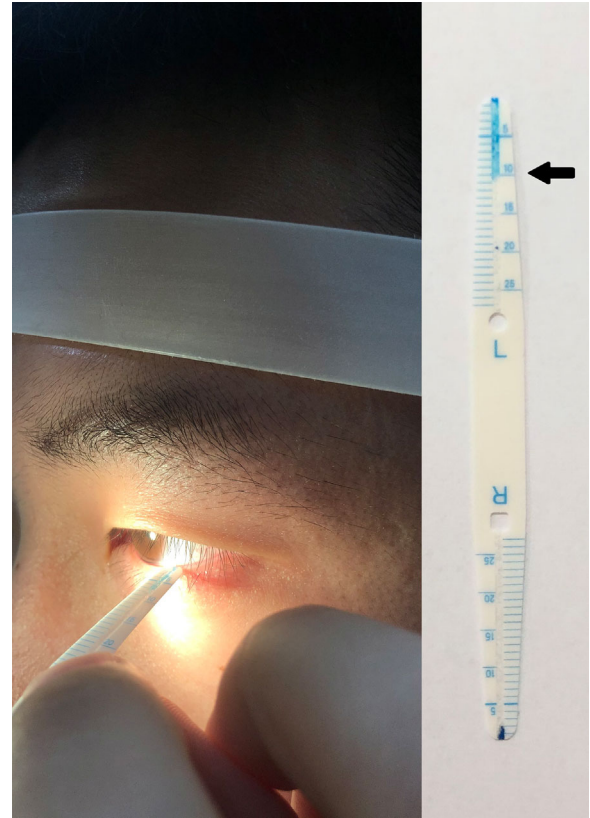


Figure 2. Inspection method of strip meniscometry. The length of the blue-stained line represents the inspection result.

a drop of normal saline, a single fluorescein strip (Jingming, Tianjin, China) was gently placed on the lower eyelid conjunctiva to measure FTBUT. The participants were asked to blink several times and then open their eyes wide. The time of the first corneal black spot on the stained tear film was measured and repeated three times to take the average value. ST was performed by folding the Schirmer paper strip (Jingming) at the notch and hooking the folding end to the lateral third of the lower lid margin without topical anesthesia. The score is the wetted length measured from the notch after 5 minutes. Ocular surface staining was performed as described in the Oxford scheme and divided into six grades according to severity.²⁸ The result was recorded and defined as Oxford grades.

Statistical Analysis

Before starting the formal study, we conducted a preexperiment, which included 15 participants in the mild DED group and 15 participants in the control group. The sample size calculations were performed using Power Analysis and Sample Size (PASS, version 15.0; NCSS Corp., Kaysville, UT, USA), based on a power calculation with an α of 0.05 and a power

of 0.90, to detect differences in SM results between groups. The mean value of SM in the mild DED group was 2.6 mm, which in the control group was 4.3 mm, and the standard deviation was 2.3 mm. On this basis, 40 eyes in each group were required to detect the difference of SM between DED and control groups. Statistical analyses were performed using the Statistical Package for Social Sciences for Windows (version 20; IBM Corp., Armonk, NY, USA). All results are expressed as the mean ± SD. The independent-samples *t*-test or Mann–Whitney *U*-test was used to compare the tear volume examinations and other tests between DED and control participants. Spearman correlation was applied to determine the association among these examinations. ROC analysis was performed to assess the diagnostic power with the area under the curve (AUC). *P* < 0.05 was considered statistically significant.

Results

There were 40 participants in the DED and control groups (only the left eye was included). Demographics and DED-related parameters are shown in Table 1. No statistically significant differences were found in either age or sex ratio between the DED and control groups.

Table 1 is a comparison between the DED and normal control groups. Except for the lower eyelid meiboscore, all other examination results were significantly different between the two groups. FTBUT and all tear volume examinations were significantly lower in DED participants than in the control group (*P* < 0.05), while the OSDI scores, upper eyelid meiboscores, and Oxford grades were significantly higher (*P* < 0.05).

The correlation between all inspection results is shown in Figure 3. SM, ST, TMH-OCT, TMH-K5M, and TMA-OCT were all correlated with ocular surface examination results except meiboscore. Among them, SM had the strongest correlation with OSDI (*r* = −0.78, *P* < 0.001) and FTBUT (*r* = 0.81, *P* < 0.001), while ST was the weakest (*r* = −0.36, *P* = 0.001 and *r* = 0.22, *P* = 0.046, respectively). There was a correlation between all tear volume examination results, among which SM had a strong positive correlation with both TMH-OCT (*r* = 0.76, *P* < 0.001) and TMA-OCT (*r* = 0.77, *P* < 0.001), while ST had the worst correlation (*r* = 0.27, *P* = 0.018 and *r* = 0.22, *P* = 0.047, respectively). The Spearman correlation coefficient after Bonferroni adjustment is shown in Figure 4. The main change after adjustment was that ST had only a weak correlation with SM and no significant correlation with other test results. However, considering that the statistically significant *P* value became extremely small due to the numerous correlation tests, some weaker correlations may lose statistical significance.

Table 2 displays correlations between the OSDI subscores and tear volume parameters. Except for no statistically significant correlation between vision-related subscores and ST, all other subscores and tear volume detection parameters had significant negative correlations. The correlation between SM, TMH-OCT, and TMA-OCT and each subscore was stronger than that of ST and TMH-K5M. Among them, the ocular symptom subscore had the strongest correlation with SM, TMH-OCT, and TMA-OCT. Bonferroni adjustment was also performed in Table 2. Similar to the results in Figure 3, the main adjusted change was that ST was not statistically significantly correlated with all three subscores.

Table 1. Comparison of Demographic Characteristics and DED Parameters Between the Patients With Mild DED and Controls

Parameters	Mild DED (<i>n</i> = 40 Eyes)			Controls (<i>n</i> = 40 Eyes)			<i>P</i> Value
	Mean ± SD	Range	Median (Q1, Q3)	Mean ± SD	Range	Median (Q1, Q3)	
Sex (male/female), <i>n</i>	22/18			22/18			1.000
Mean age, <i>y</i>	23.6 ± 1.9	18–27	24 (23, 24.25)	23.4 ± 3.2	18–31	24 (22, 25)	0.755
OSDI	22.6 ± 11.2	13.6–60.4	17.5 (15.7, 25.0)	7.2 ± 3.9	0–12.5	7.2 (4.4, 10.6)	<0.001
FTBUT, <i>s</i>	3.31 ± 0.90	1.19–4.87	3.36 (2.73, 4.00)	6.56 ± 1.14	5.0–9.3	6.45 (5.55, 7.09)	<0.001
SM, mm	2.5 ± 0.7	1.2–3.8	2.8 (2.1, 3.0)	5.6 ± 2.2	3.4–14.5	5.2 (4.1, 6.1)	<0.001
ST, mm	9.7 ± 10.0	0.3–30.0	5.2 (2.5, 15.0)	12.9 ± 9.5	1.5–30.0	9.05 (6.45, 17.0)	0.022
TMH-OCT, mm	0.20 ± 0.04	0.10–0.31	0.20 (0.16, 0.23)	0.38 ± 0.12	0.22–0.83	0.35 (0.29, 0.45)	<0.001
TMA-OCT, mm ²	0.012 ± 0.004	0.002–0.024	0.012 (0.009, 0.014)	0.036 ± 0.023	0.014–0.113	0.030 (0.020, 0.043)	<0.001
TMH-K5M, mm	0.18 ± 0.07	0.09–0.37	0.19 (0.13, 0.22)	0.29 ± 0.07	0.14–0.49	0.29 (0.25, 0.33)	<0.001
Upper eyelid meiboscore	1.4 ± 0.6	0–3	1 (1, 2)	1.1 ± 0.6	0–3	1 (1, 1)	0.021
Lower eyelid meiboscore	1.6 ± 0.7	0–3	2 (1, 2)	1.6 ± 0.5	1–2	2 (1, 2)	0.912
Oxford grades	0.5 ± 0.8	0–2	0 (0, 1)	0.1 ± 0.2	0–1	0 (0, 0)	0.001

Oxford grades indicate ocular surface staining described in the Oxford scheme.

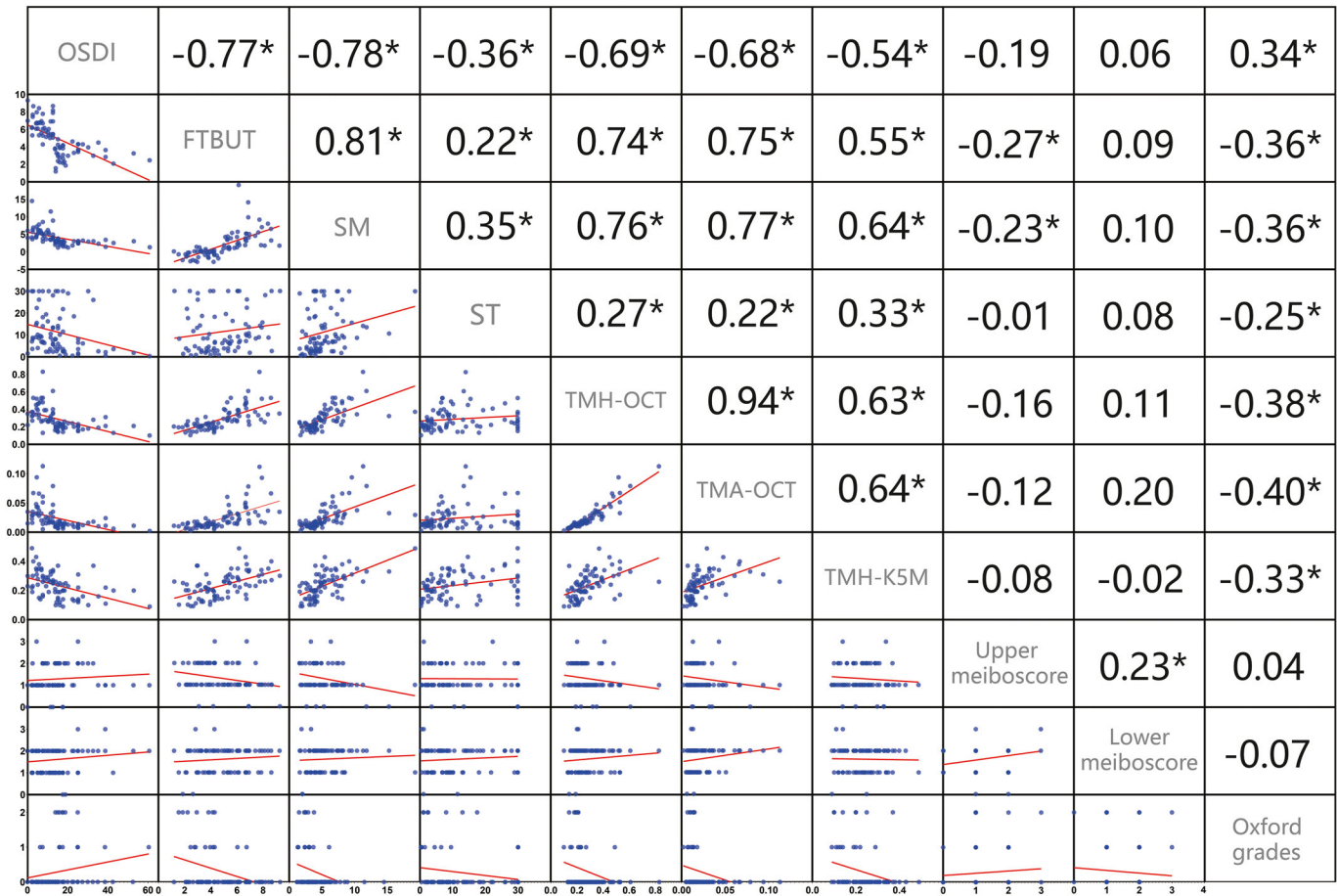


Figure 3. Spearman correlation of the tear meniscus and DED test parameters. Each value in the table cell indicates the Spearman correlation coefficient between horizontal and vertical examinations list in the *diagonal line*. Each subfigure in the table cell shows the scatter diagram and fitting regression line. * $P < 0.05$.

The ROC of SM, ST, and TM parameters is depicted in Figure 5. The AUCs of SM, TMH-OCT, and TMA-OCT were 0.992, 0.978, and 0.960, respectively, which were significantly better than the AUCs of TMH-K5M and ST. The cutoff values were <3.5 mm with a sensitivity of 97.5% and a specificity of 95.0% for SM, 0.25 mm with a sensitivity of 97.4% and a specificity of 90.0% for TMH-OCT, and 0.015 mm² with a sensitivity of 97.4% and a specificity of 77.5% for TMA-OCT.

Discussion

A total of 40 participants with mild DED were included in this study. After comparing five parameters representing tear volume, this study demonstrated that SM, TMH-OCT, and TMA-OCT were strongly correlated with subjective symptoms, as well as ocular surface parameters, including FTBUT and ocular

surface staining grades. In addition, these examinations showed high diagnostic power in mild DED. In contrast, the results of ST were relatively poor, both in terms of correlation with other DED parameters and in terms of the diagnostic performance. In addition, although the mean OSDI scores could classify the DED group as mild to moderate, this study defined DED as mild according to the criteria in Oxford scheme.²⁸

Accurately diagnosing DED has always been a complicated problem in DED research. With the continuous progress and deepening of DED research over the past 10 years, the core feature of DED has gradually been defined as the loss of tear film homeostasis. Therefore, TBUT, tear osmotic pressure, and ocular surface staining, which can reflect the steady state of the tear film, have attracted increasing attention and become one of the diagnostic criteria for DED.^{2,3} Compared with TBUT, the examination of tear volume appears to be less important clinically and may only be used when judging the type or severity

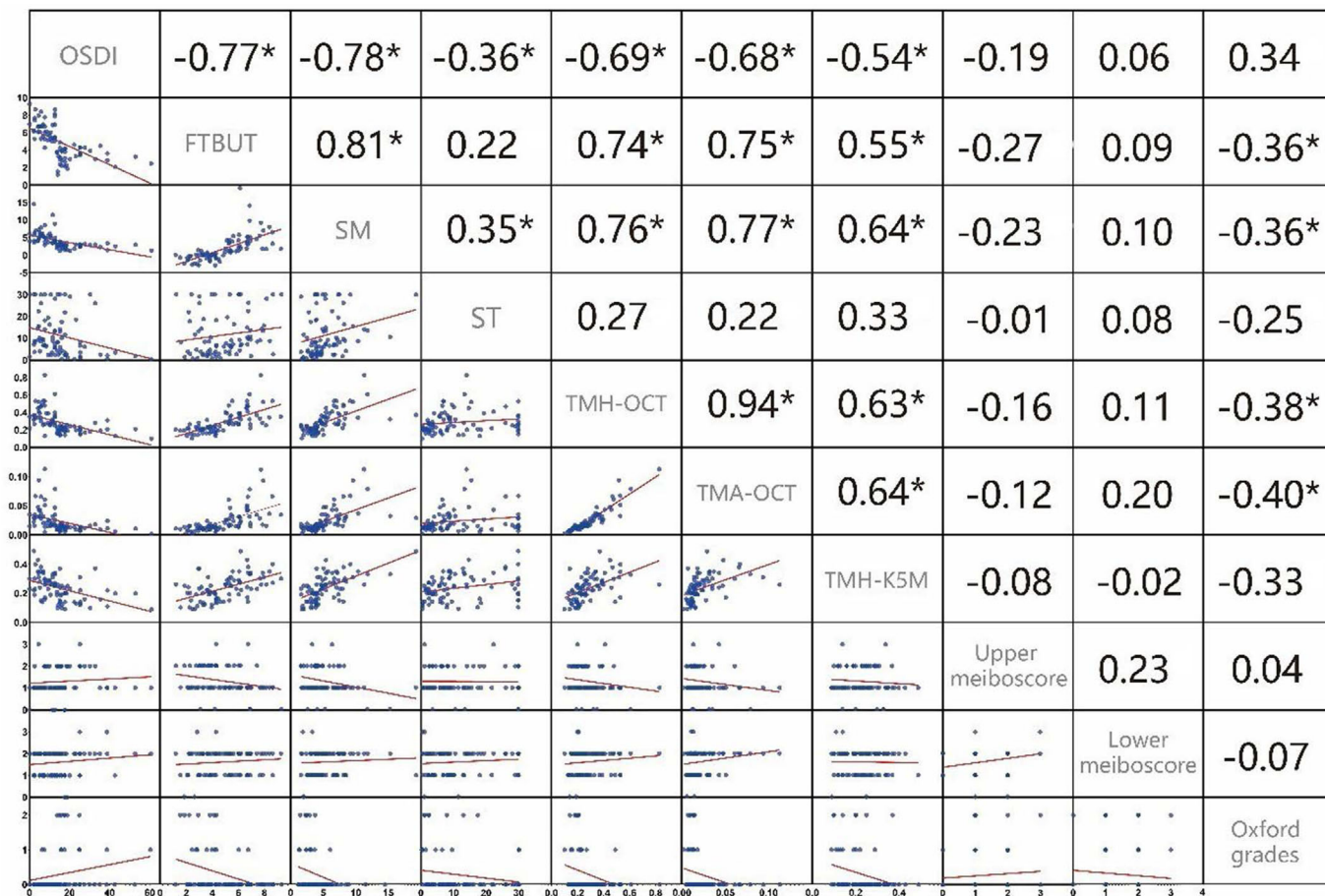


Figure 4. Spearman correlation coefficient after Bonferroni adjustment. *Still statistically different after adjustment.

Table 2. Correlations between Ocular Surface Disease Index Scores and Tear Volume Parameters in All Participants

Parameter	Ocular Symptom Subscore		Vision-Related Subscore		Environmental Triggers Subscore	
	R	P Value	R	P Value	R	P Value
SM	-0.579	<0.001 ^{a,b}	-0.468	<0.001 ^{a,b}	-0.525	<0.001 ^{a,b}
ST	-0.314	0.005 ^a	-0.219	0.051	-0.249	0.026 ^a
TMH-OCT	-0.578	<0.001 ^{a,b}	-0.333	0.003 ^{a,b}	-0.482	<0.001 ^{a,b}
TMA-OCT	-0.597	<0.001 ^{a,b}	-0.354	<0.001 ^{a,b}	-0.465	<0.001 ^{a,b}
TMH-K5M	-0.441	<0.001 ^{a,b}	-0.28	0.012 ^a	-0.423	<0.001 ^{a,b}

Numbers are Spearman correlation coefficients.

^aStatistically significant.

^bStill statistically different after Bonferroni adjustment.

of DED. A major reason for this situation is the lack of accurate and cost-effective detection methods. Take ST as an example. Although it has been one of the most commonly used tear volume assessment methods in the clinic and research due to its inexpensive and convenient advantages, ST is invasive, and its reproducibility is less reliable and has always been

controversial. However, in recent years, tear volume inspection methods have ushered in great developments, including the emergence of noncontact and accurate evaluation methods such as TM evaluation and SM, which have greatly compensated for the above shortcomings. There have also been many related studies, but there is no overall evaluation study

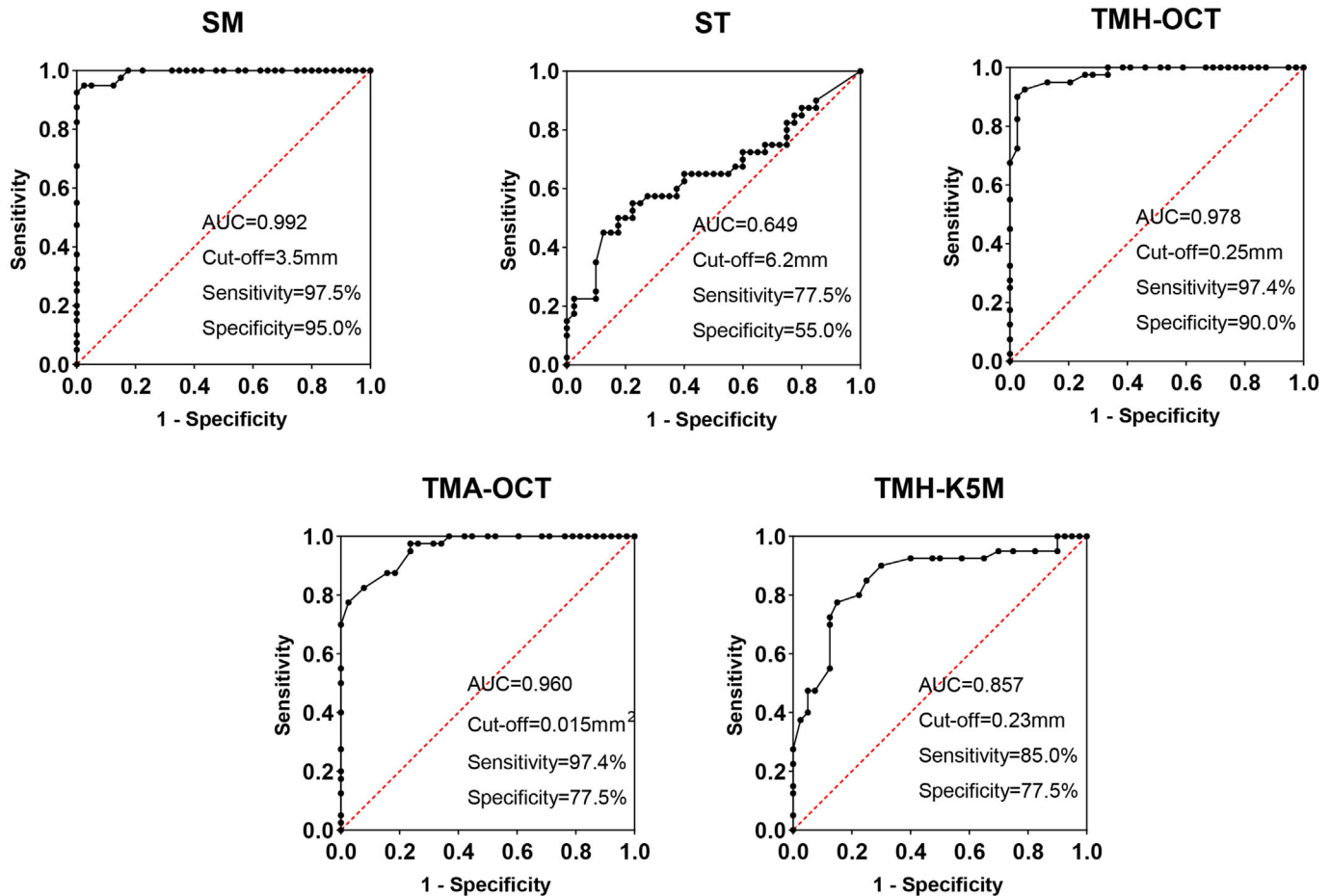


Figure 5. The receiver operating characteristic analysis for cutoff values, sensitivities, and specificities of strip meniscometry, Schirmer test, and tear meniscus parameters.

comparing the correlation of each tear volume evaluation method with DED parameters and the diagnostic efficacy of DED. This research fills the gap for this field.

The study evaluated the correlation between tear volume test results, DED symptoms, and common clinical examinations. The current diagnosis and evaluation of DED include subjective symptoms and objective signs. Therefore, OSDI, FTBUT, and ocular surface staining scores as the main indicators for DED evaluations were selected. After analyzing the correlation, the results showed that there was a strong correlation between SM and DED symptoms and signs. The strong positive correlation between SM, TMH, and TMA obtained by OCT showed that SM could reflect the volume of tears well. Similarly, TMH-OCT and TMA-OCT had a strong correlation with DED parameters and SM, while the correlation results of K5M and ST were weak. Lee et al.²³ reported a similar correlation between ST, SM, and TMH-K5M, but Dogru et al.¹⁸ and Shinzawa et al.²⁰ reported that ST has a stronger positive correlation with SMT and TM parameters by OCT. The results of SM are highly

correlated with FTBUT, and the correlation between SM and OSDI and Oxford grades is close to that of FTBUT, which means that SM may even replace FTBUT in some specific occasions because SM is less invasive than FTBUT. The obvious negative correlation between SM and the ocular symptom subscore also means that SM can reflect eye discomfort. More important, SM is low cost, simple, easy to operate, and highly comfortable, which also gives it potential in large-scale DED screening and epidemiologic investigations.²⁷

In addition to the correlation results, the study also conducted a comparative evaluation of the diagnostic efficacy. When the cutoff value of SM was set to less than 3.5 mm, the sensitivity and specificity of diagnosing mild DED reached 97.5% and 95.0%, respectively, and the AUC of SM was as high as 0.992, indicating that SM had good diagnostic efficiency for mild DED. The TMH-OCT and TMA-OCT cutoff values were identified to be 0.25 mm and 0.015 mm², respectively, and had high sensitivity and specificity, while TMH captured by K5M had a relatively poor result.

The diagnostic performance of ST was the worst, and when the cutoff value of ST was set at less than 6.2 mm, the sensitivity and specificity of ST were found to be only 77.5% and 55.0%, respectively. The cutoff value of SM was consistent with the research conducted on SM in Japan^{18,20,24} but was smaller than the result of the study conducted by Singh et al.¹⁹ in India. Therefore, more studies are needed to confirm whether the cutoff value this study obtained can be applied to various regions of China.

For TMH-OCT and TMA-OCT, many studies have demonstrated that they have good repeatability and a strong positive correlation with the results of SM.^{19,20,24} Several diagnostic cutoff values of TMH-OCT have been proposed, from $\leq 191 \mu\text{m}$ to $\leq 204.96 \mu\text{m}$, and a range of sensitivity (67%–98.3%) and specificity (78%–96.67%) values have been reported,^{11,19,20} which support the evaluation of TM by OCT as an accurate and effective inspection method. Both K5M and OCT are instruments that can obtain the TMH noninvasively, but from research results, TMH-K5M is less capable of diagnosing dry eye than the results obtained by OCT and is similar to that reported by Lee et al.²³ Arriola-Villalobos et al.¹⁷ reported that the TMH obtained by K5M had difficulty accurately depicting the tear meniscus due to poor image resolution, resulting in poor repeatability, which may explain this result.

This study found that the sensitivity and specificity of ST were 77.5% and 55.0%, respectively, which is relatively poor compared to the results of Danjo³² (the cutoff values were $< 5.0 \text{ mm}$ with a sensitivity of 80.0% and a specificity of 53%). A possible explanation for these differences is that this study included patients with DED who had relatively mild symptoms and signs. In addition, although the commonly accepted value of ST is 5.0 mm, 6.2 mm was used as the cutoff value in the study. Statistically speaking, the cutoff value and AUC were affected by the population and severity of DED. In this study, young people with mild DED were recruited, which aimed to support the comparison results rather than provide a widely applicable cutoff value. The irritating tear secretion caused by the ST strip contacting the ocular surface masks its own lack of tears, which leads to differences in the results of ST and other tear volume detection methods and a lower diagnostic sensitivity and specificity. As suggested by TFOS-DEWS II, ST may be more suitable for severe aqueous deficiency.

As mentioned above, a limitation of the study was that only patients with mild DED were included; therefore, the lack of evaluation of patients with more severe DED may cause some deviations in the results. However, the aim of the current study was to release

how different tear volume detection methods work in young patients with mild DED. A large part of the participants was recruited from the refractive surgery center of the hospital, and most were aged 18 to 30 years and fit the above characteristic with dry eye symptoms. In clinical work, it is important to determine which method is better to reflect the severity of dry eye in such a subpopulation. Furthermore, this is a single-center study focused on Wenzhou. If it is necessary to verify the effectiveness of SM in the Chinese population, a multiregional and multicenter study is needed.

This study comprehensively compared the currently commonly used methods for evaluating tear volume for the first time, and it is understood that this is the first time that SM has been used and studied in China. The present research found that compared with ST and K5M to evaluate tear volume, the results of using SM and OCT showed a better correlation with other ocular surface examination indicators. When the cutoff values of SM, TMH-OCT, and TMA-OCT were $< 3.5 \text{ mm}$, 0.25 mm , and 0.015 mm^2 , respectively, they had high sensitivity and specificity in mild DED diagnosis, suggesting that they should be effective methods for evaluating and diagnosing mild DED.

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* YW and ZX contributed equally to this study as first authors.

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