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A novel strip meniscometry method for measuring aqueous tear volume in dogs: Clinical correlations with the Schirmer tear and phenol red thread tests

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Abstract

Objectives: The strip meniscometry test (SMT) is a novel method for quantitative measurement of tear volume with only five seconds. We aimed to evaluate clinical correlations of SMT with the gold standard Schirmer tear test (STT) and phenol red thread test (PRT) in dogs, including normal and tear-deficient eyes.

Animals studied: Left eyes from 621 outpatient dogs with and without ocular disorders were evaluated.

Procedures: Each subject underwent SMT, PRT, and STT without topical anesthesia in the described order with five-minute intervals. The total population was divided into four groups by classifying tear deficiency severity based on STT results: "severe" (0-5 mm/min), "moderate" (6-10 mm/min), "subclinical" (11-14 mm/min), and "normal" (15 or more mm/min).

Results: The strongest correlation coefficient was found between SMT-STT (0.676), followed by PRT-STT (0.637) and SMT-PRT (0.600) pairs. Mean(SD) scores of SMT, PRT, and STT in total population were 9.47 (4.08) mm/5 s, 33.30 (8.52) mm/15 s, and 16.47 (7.01) mm/min. Significant differences were found among STT-classified groups, both using SMT and PRT results. Receiver operating characteristic (ROC) curves revealed that SMT better agreed with STT than PRT; agreement increased with increasing STT severity. A cutoff for SMT was identified at 10 mm/5 s to discriminate normal eyes from tear-deficient eyes, yielding high sensitivities and acceptable specificities.

Conclusions: SMT could be superior to PRT for discriminating tear-deficient eyes. The high sensitivity of SMT could be useful as an initial diagnostic tool to rule out normal eyes with the short testing time.

KEYWORDS

ocular surface, phenol red thread, Schirmer tear test, SMTube, strip meniscometry, tear volume

1 | INTRODUCTION

Tear volume is an important parameter with regard to understanding the pathological state of the ocular surface. The Schirmer tear test (STT) has long been the gold standard used to quantify the aqueous component of the tear film.[1-3] The phenol red thread test (PRT) also quantifies the aqueous tear film and entails a shorter testing time (15 seconds) than that required for the STT (60 seconds for veterinary application).[4-7] The effectiveness of both tests for lacrimal quantification in humans and veterinary patients has been previously discussed.[8-13]

In 2006, Dogru *et al*[14] reported a novel method for assessing the aqueous component of the human tear film in a swift and noninvasive manner, which has been coined the "strip meniscometry test" (SMT). Like the conventional STT, the SMT uses a tear-absorbing strip; however, in the SMT, the strip only touches the tear meniscus (without anesthesia) rather than being inserted into the conjunctival sac as is done in the STT and the PRT. The testing time of the SMT (5 seconds) is considerably shorter than that of the conventional STT. The clinical efficacy and correlations with other ocular surface examinations in the diagnosis of dry eye disease (or keratoconjunctivitis sicca) have been evaluated.[15,16] In 2013, a commercial version of the SMT strip was produced and called the strip meniscometry tube (SMTube; Echo Electricity Co. Ltd., Tokyo, Japan). Alternatively, in Canada and the United States, the SMTube is available with a different product name but has the same material and structure (i-Tear Test; I-MED Pharma Inc, Dollard-Des Ormeaux, QC, Canada). Material and structural details of the SMTube can be found elsewhere,[16,17] and we employed the SMTube for the SMT in the present study. Various other SMT applications beyond the diagnosis of dry eye disease have also been reported, such as time-line measurements of tear volume and quick evaluation of treatment outcomes.[18-25] The first assessment of SMT using the SMTube in veterinary species was reported by Rajaei *et al* in conjunction with the STT results in dogs, cats, and rabbits.[26] They aimed to establish the normal scores for the SMT and the correlations between the SMT and STT. To date, no investigator has ever reported the sensitivity and specificity of the SMT with respect to conventional STT results in veterinary patients with tear deficiency.

Here, we describe the SMT method for measuring tear volume in dogs with and without aqueous tear deficiency. On the basis of a large sample size, the correlation between the SMT and conventional tests (STT, PRT) are assessed. Further, the clinical use of SMT in dogs is investigated based on accepted STT cutoffs[27] suggestive of tear deficiency in this species. Last, the optimal cutoff values of SMT in dogs are determined[28] based on the referential STT scores.

2 | MATERIALS AND METHODS

2.1 | Subjects

This study was approved by the Ethics Committee at Triangle Animal Eye Clinic (Tokyo, Japan). Canine subjects were recruited from outpatients that visited the Triangle Animal Eye Clinic from December 2013 to July 2016. Patients were excluded if diagnosed with ulcerative keratitis to avoid the potential impact of reflex tearing on the lacrimal test scores, or if excessive mucoid discharge was present to avoid a potential failure of tear absorption. The study comprised 621 left eyes of 621 dogs, as follows: 127 eyes from intact male dogs, 182 from castrated male dogs, 81 from intact female dogs, 226 from sterilized female dogs, and 5 from sexually undefined dogs. The breeds primarily consisted of the following: Shih Tzu (78 eyes), Toy Poodle (75 eyes), Chihuahua (67 eyes), Miniature Dachshund (54 eyes), Yorkshire Terrier (39 eyes), Shiba Inu (28 eyes), Cavalier King Charles Spaniel (25 eyes), Boston Terrier (21 eyes), Pembroke Welsh Corgi (21 eyes), Pug (20 eyes), Miniature Pinscher (18 eyes), French Bulldog (16 eyes), Miniature Schnauzer (16 eyes), West Highland White Terrier (15 eyes), American Cocker Spaniel (14 eyes), Pomeranian (14 eyes), Poodle (12 eyes), Jack Russell Terrier (10 eyes), Papillon (nine eyes), Italian Greyhound (nine eyes), Pekingese (nine eyes), and Maltese (six eyes). Forty-five dogs were from 26 other breeds. The ages of the dogs ranged from 0.4 years to 17.0 years, and the mean age was 8.0 3.8 years.

2.2 | Lacrimal tests

Individual dogs were first placed on the examination table for the initial diagnostic observation of the ocular surface. A

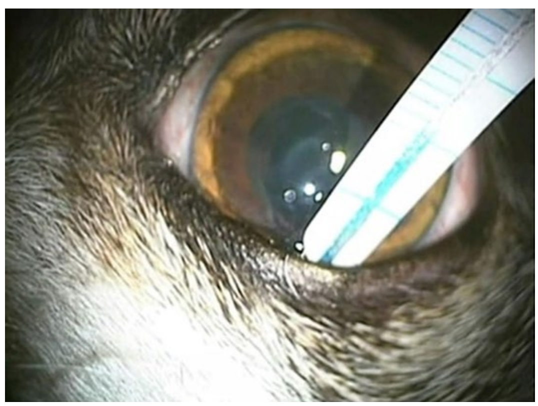

FIGURE 1 A strip meniscometry tube (SMTube; Echo Electricity Co. Ltd., Tokyo, Japan) is applied to the lower tear meniscus of the left eye of a dog under gentle illumination from a slit lamp. The length of the blue-colored part in the absorption column is 11 mm

slit lamp and biomicroscopy system (model 900BQ; Haag-Streit AG, Zug, Switzerland) was used to examine the cornea precisely. Each subject then underwent three lacrimal tests in the following order: SMT using the SMTube (Echo Electricity Co. Ltd., Tokyo, Japan), PRT using the Zone Quick (Showa Pharmaceutical Chemical Co., Tokyo, Japan), and STT using the Tear Production Measuring Strips (Showa Pharmaceutical Chemical Co.) without topical anesthesia.[29] The STT was intentionally conducted last to avoid the influence of reflex secretion on the other two tests. At least five minutes of interval between lacrimal tests were taken to ensure tear turnover in the meniscus. Temperature and humidity of the examination room during all tests were maintained at 25-28°C and 47%-59%, respectively.

As shown in Figure 1, the SMT was performed with the help of a slit lamp (×6.3 magnification, low light intensity) in the following manner: soon after the initial observation of ocular surface, a tip of the SMTube strip was gently immersed in the inferior tear meniscus, slightly off-center temporally, and held there still for 5 seconds. An assistant counted the testing time. The eyelid position remained neutral with no manual eversion performed during testing. The blue-colored indicator then gradually stained the column portion of the SMTube from the tip as tear fluid was absorbed into the absorbent part of the tube. The blue-stained portion of the column was then read immediately, and the SMT score was recorded in mm/5 s.

In the PRT, the short-bent tip of a Zone Quick thread was inserted into approximately the lateral half of the lower conjunctival sac in the eye, such that the thread was in contact with the cornea, and maintained there for 15 seconds. Upon removal of the thread from the eye, the tear-wetted length along the thread was then measured immediately by using a ruler. The results were recorded in mm/15 s. The STT was performed without topical anesthesia.[29] A standardized strip of filter paper was placed in the same position as for the PRT and remained there for 1 minute with the eye closed. The length of the wet portion was then read immediately after removal of the strip, and results were recorded in mm/min. Throughout the study, two veterinarians (YK and HI) performed the lacrimal tests in different time periods: YK from Dec 2013 to Jan 2016, and HI from Mar 2016 to Jul 2016.

2.3 | Statistical analyses

Unpaired *t* test was used to test the statistical difference between the results obtained by the two veterinarians performing the lacrimal tests in different time periods. Regression analysis was individually applied to detect any statistically significant associations between the age and the each of the lacrimal test results. A correlation test based on the Pearson's product-moment was conducted to evaluate pairwise correlations between the SMT, PRT, and STT scores. The canine population was classified into four groups

TABLE 1 Descriptive statistics of each lacrimal test for the whole population and for each subgroup of dogs (based on the STT classification)

	Total population (n = 621)	STT-classified Severe (n = 55)	Moderate (n = 48)	Subclinical (n = 83)	Normal (n = 435)
SMT (mm/5 s)					
Mean	9.47	2.56*	5.17*	8.66*	10.97*
Standard deviation	4.08	3.26	3.22	3.52	2.93
Median	10	1	5	9	11
Range	0-21	0-12	0-11	0-21	0-20
PRT (mm/15 s)					
Mean	33.30	17.42#	27.77#	31.02#	36.35#
Standard deviation	8.52	10.62	8.80	5.57	5.45
Median	35	15	30	31	36
Range	3-55	3-40	7-55	10-45	10-55
STT (mm/min)					
Mean	16.47	1.53	6.71	12.19	20.25
Standard deviation	7.01	1.44	1.34	1.33	3.58
Median	18	2	7	12	20
Range	0-35	0-5	6-10	11-14	15-35

Statistical differences were confirmed for the SMT (indicated using superscripts of *) and PRT (superscripts of #), in each pair of the "severe," "moderate," "subclinical," and "normal" states (one-way ANOVA; $P < 0.01$). SMT, strip meniscometry; STT, Schirmer tear test: PRT, phenol red thread test.

according to the STT results: "severe" (0-5 mm/min), "moderate" (6-10 mm/min), "subclinical" (11-14 mm/min), and "normal" (15 or more mm/min). One-way analysis of variance (ANOVA) was used for SMT and PRT results to assess the presence of statistical differences among the STT-classified four groups. Receiver operating characteristic (ROC) curve analysis was performed to obtain the area under the curve (AUC) values of SMT and PRT in reference to the STT classification. The ROC analysis also yielded calculations of the sensitivity and specificity as a function of cutoff values of SMT score. All computations were programmed using Mathematica ver.11 (Wolfram Research, Champaign, IL).

3 | RESULTS

Results derived from the total subject pool (n = 621 left eyes of 621 dogs) were analyzed first. The mean (standard deviation [SD]) lacrimal test scores were 9.47 (4.08) mm/5 s for SMT, 33.30 (8.52) mm/15 s for PRT, and 16.47 (7.01) mm/min for STT (Table 1). The SMT and PRT mean values conformed with a previous report.[26] There were no significant differences between the results obtained by the two veterinarians involved in this study ($P > 0.1$). The patients' age had no significant association with the lacrimal test results ($P > 0.1$). Figure 2 exhibits the frequency distributions of the lacrimal tests used in this study along with the values of kurtosis and skewness inset. The kurtosis and skewness are convenient measures to characterize statistical distributions by the peak sharpness and asymmetry. A comparison of these measures in each test suggested that the distribution of SMT is close to that of STT, and the distribution of PRT is to some extent different from that of the other tests. The results of correlations for each pair of lacrimal tests are summarized in Figure 3A-C in which three-dimensional (3D) representation consisting of scatter plots in the x-y plane, and frequency distributions along z-axis are presented together with the correlation coefficient (r). Figure 3D shows the transition of p-value as a function of the null-hypothesized r value (r_{null}) used for the correlation test. In all pairwise comparisons of the lacrimal tests, the correlations were statistically robust at a remarkably significant level (eg, $P < 10^{-60}$ when $r_{null} = 0$). The r values were 0.600 for SMT-PRT, 0.676 for SMT-STT, and 0.637 for PRT-STT.

The data were then divided into four groups according to the aforementioned STT classifications.[27] Of the 621 left eyes of 621 dogs examined, the state for 55 eyes was "severe"; 48 eyes, "moderate"; 83 eyes, "subclinical"; and 435 eyes, "normal." The descriptive statistics of these groups are reported in Table 1, where statistically significant differences were observed for comparisons between the STT-classified groups ("severe," "moderate," "subclinical," and "normal" states), both using SMT and PRT results.

The ROC curve analysis was then used to obtain the AUC values of the novel SMT and the PRT in reference to the STT classifications. As shown in Figure 4, the AUC values of SMT and PRT were 0.925 and 0.902 for the STT = 5 mm/min criterion; 0.916 and 0.855 for the STT = 10 mm/min criterion; and 0.826 and 0.824 for the STT = 15 mm/min criterion, respectively. The corresponding ROC curves are plotted together. Numerical results of the ROC curve analysis are presented in Table 2, including the sensitivity and specificity values of each cutoff selected for SMT.

4 | DISCUSSION

In this study, we investigated a novel method, called "strip meniscometry test" (SMT), for quantitatively measuring the aqueous component of the tear film and evaluated its clinical effectiveness in dogs. Our findings indicate that the results of the gold standard lacrimal test, the STT, were more

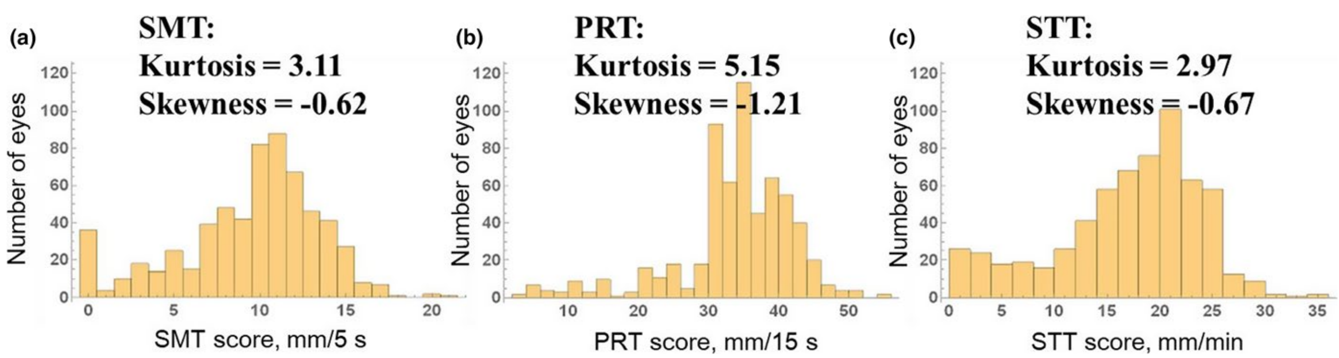

FIGURE 2 Histograms showing the frequency distributions of (a) the SMT scores, (b) the PRT scores, (c) and the STT scores. Values of kurtosis and skewness are inset at the top of each histogram. All frequency distributions are left-skewed as these skewness values are all negative, and this skewing is most pronounced for PRT. The presence of the skewing is concordant with the fact that the mean values were lower than the mode values (ie, the most frequently observed values) in all distributions. SMT, strip meniscometry test; PRT, phenol red thread test; STT, Schirmer tear test

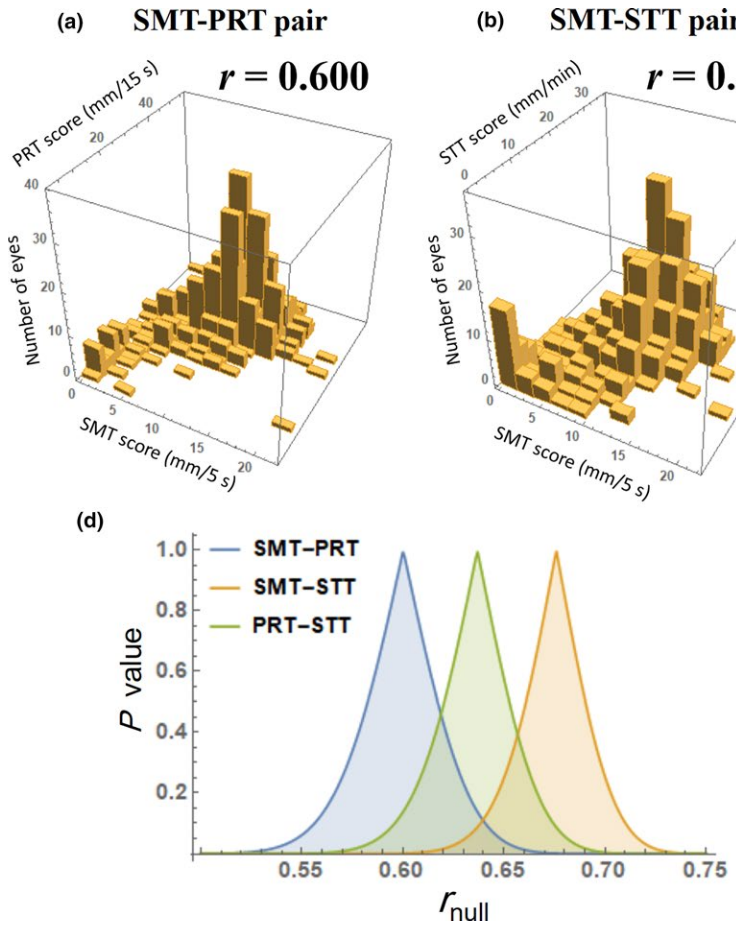

FIGURE 3 Correlations between the lacrimal tests, derived from the total subject pool based on the Pearson's product-moment. Three-dimensional (3D) scatter plots depict (a) the SMT-PRT pair, (b) the SMT-STT pair, and (c) the PRT-STT pair. The correlation coefficients (r) are at the top of each plot. (d) The transition of the P-value as a function of the null-hypothesized r value (r_{null}) used for the correlation test is presented for all pairs. SMT, strip meniscometry test; STT, Schirmer tear test; PRT, phenol red thread test

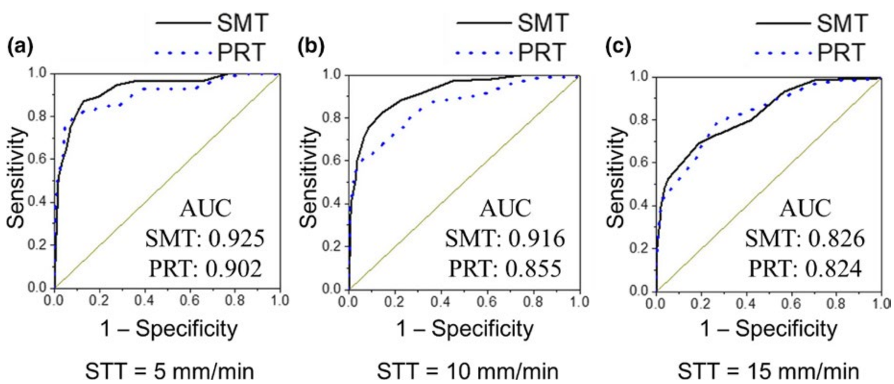

FIGURE 4 Receiver operating characteristic (ROC) curves of the SMT and PRT are shown for different STT cutoff criteria: (a) 5 mm/min, (b) 10 mm/min, and (c) 15 mm/min. These criteria are given at the bottom of each figure. The area under the curve (AUC) is an important measure to assess the predictive accuracy of a test. These values for the SMT and PRT are inset in each plot. The sensitivity, specificity and the Youden index associated with the cutoff points for the SMT are correspondingly reported in Table 2. SMT, strip meniscometry test; STT, Schirmer tear test; PRT, phenol red thread test

strongly correlated with the SMT results than with PRT results, which suggested that the SMT may be better than PRT for discriminating tear-deficient eyes from normal eyes.

All test score results had non-normal distributions (Figure 2). However, we employed parametric methods for the statistical analyses because the robustness to non-normality[30] is valid, owing to the large sample size used in this study (n = 621). As can be seen from the 3D scatter plots in Figure 3A-C, the relationship of each pair of lacrimal tests appears to depict linearity, including frequency (ie, z-axis). The Pearson's correlation coefficient r values all show moderately strong associations at remarkably significant levels. The highest r occurred with the SMT-STT pairing, followed by the PRT-STT pair and the SMT-PRT pair. Figure 3D demonstrates that the P-value peaks of each pair are well-separated from each other, suggesting that results of r values are statistically robust. This robustness stems from the large sample size employed in this study. Thus, the SMT has the strongest correlation with the STT beyond chance. It is an intriguing result that the highest r was obtained in the SMT-STT pair, because the PRT and SMT are characterized by their comparatively short testing times relative to the 60 seconds required to conduct the STT (15 seconds for the PRT and 5 seconds for the SMT for one eye). In humans, because of these short testing times, the effect of reflex tearing on the score is minimal.[9,14] Thus, it is amenable to predict a higher r value for the SMT-PRT pairing than for the other two pairings; however, this was not what was observed in the current study.

The STT classification used in the present study comprises three cutoff criteria: 5 mm/min, 10 mm/min, and 15 mm/min, to which the ROC analysis was applied. The AUC is a single measure that summarizes the discriminative ability of a test over the full range of cutoff lengths.[31] A higher value indicates better accuracy.[32] The comparisons in Figure 4A–C reveal the following: (a) The SMT and PRT showed moderate accuracy (0.7 < AUC <0.9) at the STT cutoff of 15 mm/min, (b) AUC of the SMT over the PRT was most pronounced at the STT = 10 mm/min criterion, and (c) both tests showed high accuracy (AUC > 0.9) at the STT = 5 mm/min criterion. The SMT showed better discriminative ability than the PRT under all conditions. These findings suggested that both SMT and PRT are able to identify aqueous deficiency in a "severe" state, while SMT is more accurate than PRT in a "moderate" state, using STT as the gold standard.

A suitable SMT cutoff range should be dependent on the purpose and situation for which it is applied.[31] A common measure to decide the optimal cutoff in ROC analyses is the Youden index (J) in which J is given as sensitivity + specificity − 1. The point maximizing J can be regarded as the optimal cutoff for balancing the sensitivity and specificity.[33] Based on the calculation of J in Table 2, the optimal SMT cutoff lengths corresponding to the STT criteria of 5 mm/

TABLE 2 Summary of the receiver operating characteristic (ROC) analyses results (corresponding to Figure 4.) Various sensitivity, specificity, and Youden index (J) values are tabulated, based on each STT cutoff criteria (ie, 5 mm/min, 10 mm/min, and 15 mm/min)

	STT criterion = 5 mm/min			STT criterion = 10 mm/min			STT criterion = 15 mm/min		
SMT cutoff (mm)	Sensitivity	Specificity	J	Sensitivity	Specificity	J	Sensitivity	Specificity	J
<1 mm/5 s	0.49	0.98	0.48	0.31	0.99	0.30	0.18	1.00	0.18
<2 mm/5 s	0.53	0.98	0.51	0.35	0.99	0.34	0.20	1.00	0.20
<3 mm/5 s	0.58	0.97	0.55	0.42	0.99	0.40	0.25	0.99	0.25
<4 mm/5 s	0.65	0.94	0.60	0.50	0.97	0.47	0.33	0.98	0.31
<5 mm/5 s	0.75	0.93	0.67	0.60	0.96	0.56	0.39	0.98	0.37
<6 mm/5 s	0.84	0.89	0.73	0.71	0.93	0.64	0.48	0.96	0.44
<7 mm/5 s	0.87	0.87	0.74	0.76	0.92	0.67	0.53	0.94	0.47
<8 mm/5 s	0.89	0.80	0.69	0.83	0.85	0.68	0.60	0.89	0.48
<9 mm/5 s	0.95	0.72	0.67	0.88	0.77	0.66	0.69	0.81	0.50
<10 mm/5 s	0.96	0.65	0.61	0.91	0.69	0.61	0.73	0.73	0.46
<11 mm/5 s	0.96	0.51	0.47	0.97	0.55	0.52	0.80	0.58	0.38
<12 mm/5 s	0.96	0.35	0.31	0.98	0.38	0.36	0.93	0.43	0.36
<13 mm/5 s	1.00	0.23	0.23	1.00	0.26	0.26	0.98	0.30	0.28
<14 mm/5 s	1.00	0.15	0.15	1.00	0.17	0.17	0.99	0.20	0.18
<15 mm/5 s	1.00	0.08	0.08	1.00	0.09	0.09	0.99	0.10	0.09
<16 mm/5 s	1.00	0.03	0.03	1.00	0.04	0.04	0.99	0.04	0.03
<17 mm/5 s	1.00	0.02	0.02	1.00	0.02	0.02	0.99	0.02	0.02
<18 mm/5 s	1.00	0.01	0.01	1.00	0.01	0.01	0.99	0.01	0.00
<19 mm/5 s	1.00	0.01	0.01	1.00	0.01	0.01	0.99	0.00	0.00
<20 mm/5 s	1.00	0.01	0.01	1.00	0.01	0.01	0.99	0.00	0.00

J, Youden index; SMT, strip meniscometry test; STT, Schirmer tear test.

min, 10 mm/min, and 15 mm/min are 7 mm/5 s, 8 mm/5 s, and 9 mm/5 s, respectively. The cutoff length obtained, based on maximizing *J*, is mathematically optimal; however, it is not necessarily useful in practical clinical circumstances, as discussed elsewhere.[31.]

An advantage of SMT is its short testing time. Ishikawa *et al*[34] previously reported that SMT can be useful for medical health checkups in humans because it is rapid and easy to perform. The SMT may also be suitable as a first-screening tool for ruling-out tear deficiency in dogs given its short duration (5 seconds) and its sensitivities associated with high negative predictive values.[35] Indeed, when using a SMT cutoff of 10 mm/5 s, the sensitivity values were 0.96 for “severe,” 0.91 for “moderate,” and 0.73 for “subclinical” states, respectively. These high sensitivities are obtained at the expense of the test specificity (0.65, 0.69, and 0.73, respectively). Negative predictive values are important for a ruling-out diagnosis, and these values were 0.99, 0.98, and 0.86 for “severe,” “moderate,” and “subclinical" states in the current study population. These outcomes suggested that the SMT is useful to rule out normal and subclinical patients with high accuracy. For this purpose, it should be performed at the very beginning of diagnosis.

Of all lacrimal tests currently available, the testing time of the SMT is the shortest. The difference in testing time between SMT and STT is important with regard to its application in dogs in actual clinical practice because some dogs would be unwilling to endure the application of STT strips for the required 60 seconds. In this respect, the PRT (which takes 15 seconds) and the SMT (which takes 5 seconds) are both preferable to the STT, and indeed the subject animals were more cooperative. It has previously been reported that most dogs tolerate the SMT well.[26] On account of the pre-impregnated color indicator on the SMT strip, the SMT score can be read easily without any supplementary tools. This capability contrasts with that of the PRT; It requires a ruler to determine the score, and for which the color change in the PRT thread (from yellow to red) is not always easy to appreciate.

The SMT is the least invasive among current lacrimal tests because it is fastest to perform, and there is no need to touch the ocular surface. For these reasons, Rajaei *et al*[26] suggested that the SMT could be used in young animals with low tear production. However, to perform the SMT adequately, an examiner needs to receive certain training until becoming accustomed to the examination procedure.[15] If reflex tearing is obviously induced because of inadvertent contact between the SMT strip and the cornea, the result should be discarded and a new strip should be applied after an interval for tear turnover. Our experience implies that a training using approximately 10 strips could be sufficient for an examiner to become accustomed to performing the SMT procedure.

In human ophthalmology, the SMT may be useful for the diagnosis of dry eye disease in patients with different conditions, which includes an assessment of tear quality and the ocular surface state.[14-16] Further research of dogs is needed that emphasize the relation between the SMT results and clinical signs. The present paper could serve as a basic referential report for such research. The increasing agreement between the SMT and STT with increasing severity of tear deficiency (Figure 4) suggested an influence of reflex tearing with STT, which is an important difference between these two tests. This point should also be a research focus in future works.

5 | CONCLUSIONS

In this paper, we have described a novel lacrimal test for measuring the volume of the aqueous component of the tear film in dogs. This study included a sufficient number of eyes (n = 621 left eyes) from outpatients, which allowed statistically robust estimates of the correlations between SMT-PRT-STT and allowed reference values of the SMT to be established with regard to the gold standard STT classifications for tear deficiency severity. The STT results were more strongly correlated with the SMT results than with the PRT results, suggesting that the SMT may be superior to the PRT for discriminating tear-deficient eyes from normal eyes. Comparisons of the ROC results revealed that the AUC of the SMT exceeded that of the PRT for all STT criteria conditions. The SMT showed increasing accuracy with increasing severity, based on the STT criteria. A SMT score of 10 mm/5 s is suggested as a cutoff to be used clinically as a first-screening ruling-out tool, as it showed high sensitivity for identifying normal tear volume in dogs. The short testing time and minimally invasive nature of the SMT, compared to the current lacrimal tests, could facilitate tear volume measurement in dogs and could be useful as an initial diagnostic tool to differentiate normal eyes.

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