

# Intra- and interobserver reliability of ocular surface analyzer LacryDiag®

Eva Kos<sup>1,2</sup>, Valentina Cigić<sup>1,2</sup>, Mladen Bušić<sup>1,2</sup>, Mirjana Bjeloš<sup>1,2</sup>, Daliborka Miletić<sup>1,2</sup>, Biljana Kuzmanović Elabjer<sup>1,2</sup>

<sup>1</sup>University Eye Clinic, University Hospital “Sveti Duh”, Sveti Duh 64, Zagreb 10000, Croatia

<sup>2</sup>Faculty of Dental Medicine and Health Care Osijek, Faculty of Medicine Osijek, University Josip Juraj Strossmayer in Osijek, Osijek 31000, Croatia

**Co-first authors:** Eva Kos and Valentina Cigić

**Correspondence to:** Daliborka Miletić. University Eye Clinic, University Hospital “Sveti Duh”, Sveti Duh 64, Zagreb, Croatia; Faculty of Dental Medicine and Health Care Osijek, Faculty of Medicine Osijek, University Josip Juraj Strossmayer in Osijek, Osijek 31000, Croatia. dada.miletic@gmail.com

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## Abstract

• **AIM:** To investigate intra- and interobserver reliability of interferometry, tear meniscus height (TMH) measurement and meibography (MBG) of an ocular surface analyzer, LacryDiag (Quantel Medical, France).

• **METHODS:** Five consecutive measurements and subsequent analysis of interferometry, TMH, and MBG were recorded by two examiners using the LacryDiag. To assess intra- and interobserver reliability, we used Cohen’s kappa for categorical variables (interferometry), or intraclass correlation coefficient for continuous variables (TMH, MBG).

• **RESULTS:** Thirty eyes of 30 examinees were included. For both observers, there was excellent intraobserver reliability for MBG (0.955 and 0.970 for observer 1 and 2, respectively). Intraobserver reliability for observer 1 was substantial for interferometry (0.799), and excellent for TMH (0.863). Reliability for observer 2 was moderate for interferometry (0.535) and fair to good for TMH (0.431). Interobserver reliability was poor for interferometry (0.074) and fair to good for TMH (0.680) and MBG (0.414).

• **CONCLUSION:** LacryDiag ocular surface analyzer in our study proves to be a reliable noninvasive tool for the evaluation of TMH and MBG. As for interferometry, poor interobserver reliability, fair to good intraobserver reliability for observer 1, and moderate for observer 2, leave room for improvement.

• **KEYWORDS:** dry eye; ocular surface analyzer; interferometry; tear meniscus height; meibography

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## INTRODUCTION

Dry eye disease (DED) is a growing problem afflicting millions of people worldwide and one of the most frequent reasons for patient visits to ophthalmologists<sup>[1]</sup>.

Age is one of the well known risk factors for DED<sup>[2]</sup>. According to data from 2022 Revision of World Population Prospects it is expected that the number of persons aged 65 or over will more than double in a period between 2022 and 2050<sup>[3]</sup>. Therefore it is to be expected DED will continue to burden more and more ophthalmology practice over time.

In 2007, the dry eye was first recognized as a disease<sup>[4]</sup>. A decade later, the TFOS DEWS II report declared loss of tear film homeostasis as the central pathophysiological concept of DED<sup>[5]</sup>. However, the diagnosis of DED remains a matter of debate as no single instrument measuring inflammation and hyperosmolarity exists. Instead, evaluation of three tear film components *via* interferometry, tear meniscus height (TMH) and noninvasive break-up time (NIBUT), as well as indirect evaluation meibography (MBG) guide the current treatment strategies<sup>[6-7]</sup>.

LacryDiag (Quantel Medical, Cournon-d’Auvergne, France) is one of the first ocular surface analyzers enabling the evaluation of all three components of a tear film, taking only four minutes<sup>[8]</sup>. Non-automated tests are tied with subjectiveness in the measurement process and analysis. Thus, intraobserver and interobserver reliability may vary<sup>[9]</sup> which should be taken into account before using certain diagnostic procedure as a backbone of diagnosis and follow up. This study was designed to investigate interobserver and intraobserver difference measuring interferometry, TMH and MBG using Lacrydiag in healthy eyes in order to increase validity and precision of this diagnostic tool.



**Figure 1 Photograph of interferometry** On the left is the examinee recording and on the right is the selected pattern type from the proposed seven-point grading scale on the top.

## SUBJECTS AND METHODS

**Ethical Approval** The study was approved by the Ethics Committee of the University Hospital “Sveti Duh” and was in accordance with the tenets of the Declaration of Helsinki. Written consent was obtained from all participants.

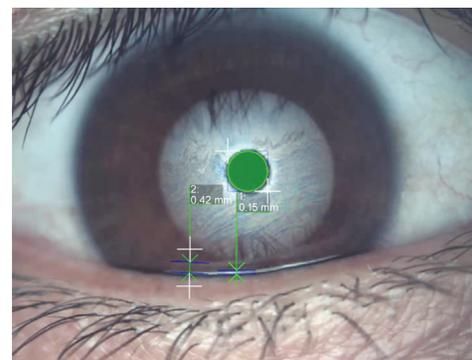
A study of 30 right eyes of 30 consecutive healthy examinees was conducted at the University Eye Clinic, University Hospital Sveti Duh, Zagreb, Croatia from December 2019 to February 2020. All participants were Caucasian with no previous or current systemic or ophthalmological morbidities, eye surgeries or contact lens wear history. Sex and age were recorded.

Tear film components were analyzed by interferometry, TMH and MBG using LacryDiag. Each eye underwent five consecutive measurements performed randomly by the two observers, observer 1 (Kos E) and observer 2 (Cisić V), starting with interferometry and followed by MBG, in a single session. For the selected eye examinations of both observers were performed 30min apart in the same room with unchanged conditions (humidity, temperature and ambient lighting). Both observers analyzed their own measurements that were masked from each other.

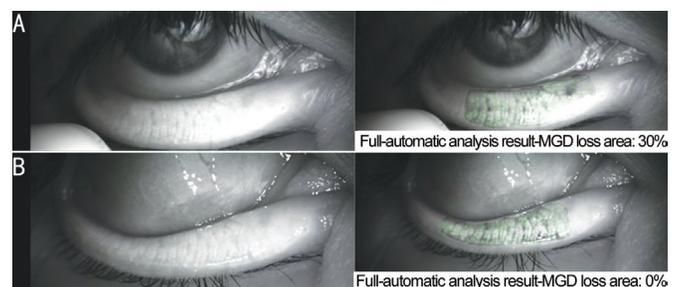
During recording video for interferometry analysis, the examinees were asked to blink slowly three times in a row. Obtained video recording was compared with the proposed seven-point grading scale built in the software (Figure 1).

The data acquired for interferometry were further used for TMH calculation. For this, both observers, by agreement, selected the picture frame recorded right after the third blink. The TMH was defined by manual positioning of upper and lower markers in three points meniscus lengthwise and averaged automatically (Figure 2). Five measurements of TMH were further averaged.

The MBG was performed after everting the lower eyelid with an eyelid everter (provided as a part of LacryDiag). Observers



**Figure 2 Photograph of TMH** 1: Upper marker set correctly on the upper border of meniscus; 2: Upper border set on the reflection of meniscus resulting in overestimation of TMH. TMH: Tear meniscus height.



**Figure 3 Photograph of the same eyelid** A: Poor resolution and pronounced reflection resulting in overestimation of meibomian gland loss; B: Good resolution and no reflection resulting with lower percentage of meibomian gland deficit.

manually adjusted the angle of the incident ray to avoid light reflection and to get best focus to capture sharp photographs. After capturing photographs, the area of meibomian glands was manually outlined. The LacryDiag ocular surface software detected and calculated the percentage of meibomian gland loss (Figure 3). Average of five measurements was documented.

**Data Analysis** To assess interobserver reliability, the five measurements of interferometry, TMH and MBG, were summarized as either median (range) for categorical variables

(interferometry) or mean±standard deviation (SD) for continuous variables (TMH and MBG) and then analyzed using Cohen’s kappa and intraclass correlation coefficient (ICC), respectively. Intraobserver reliability was assessed for both observers, by analyzing the first and the fifth measurement using Cohen’s kappa and ICC. For all effects, 95% confidence intervals were calculated.

Reliability was considered poor for kappa values <0.41, moderate for kappa values 0.41–0.60, substantial for values between 0.61–0.80 and almost perfect (excellent) for values >0.81<sup>[10]</sup>. ICC values were considered as being “fair to good” -0.40–0.75, and values >0.75 were considered excellent<sup>[11]</sup>.

Analyses were performed using the Statistical Package for the Social Sciences (SPSS) statistics software, version 25.0 (IBM Corporation, Armonk, NY, USA).

**RESULTS**

Study included 24 females and 6 males, with the mean age of 34±4y (range 21-58y). Summary of interferometry, TMH and MBG is presented in Table 1.

Table 2 shows inter- and intraobserver reliability for all three measured parameters.

Intraobserver reliability for observer 1 was substantial for interferometry (0.799), and excellent for TMH (0.863) and MBG (0.955). Reliability for observer 2 was moderate for interferometry (0.535), fair to good for TMH (0.431), and excellent for MBG (0.970).

Interobserver reliability was poor for interferometry (0.074) and fair to good for TMH (0.680) and MBG (0.414).

**DISCUSSION**

The diagnosis of DED is very demanding. One of the major reasons is the lack of “gold-standard” or a single conclusive best performing test for determining DED.

Schirmer test measures aqueous component and has limited repeatability and sensitivity<sup>[12-13]</sup>. Thus, it is used only as a method for estimating tear production in severely dry eyes<sup>[14]</sup>. Subjective grading remains the major limitation of various techniques for tear meniscus evaluation<sup>[15-16]</sup>. Tear break-up time (TBUT), although commonly used for tear film stability, has poor reproducibility<sup>[17]</sup>. The LacyrDiag ocular surface analyzer is originally designed for a complete assessment of the tear film. However, scarce data exists in the literature on its validity<sup>[6,18-19]</sup>.

**Interferometry** Evaluation of the lipid layer on LacyrDiag is based on a built-in grading scale in which each category is classified by the lipid pattern type (Table 3), similar to the previously proposed classification<sup>[20-21]</sup>. Each pattern type corresponds to different lipid layer thickness. Although, some authors<sup>[19]</sup> reported small, but not significant difference in interferometry measurements between observers, in our study this parameter proved to be very observer dependent

**Table 1 Summary of interferometry, TMH, and MBG**

Observer	Interferometry	TMH (mm)	MBG (%)
Observer 1			
1 <sup>st</sup> observation	C (B-E)	0.19±0.037	22.5±18.8
5 <sup>th</sup> observation	C (B-F)	0.21±0.043	22.5±15.9
Average	C (B-E)	0.196±0.034	21.6±17.8
Observer 2			
1 <sup>st</sup> observation	C (A-E)	0.024±0.075	24.7±15.9
5 <sup>th</sup> observation	C (A-E)	0.25±0.052	28.7±17.8
Average	C (A-E)	0.243±0.051	28.7±17.8

TMH: Tear meniscus height; MBG: Meibography. Data are expressed as median (range) for interferometry and mean±SD for TMH and MBG.

which is in accordance with the study of Tóth *et al*<sup>[9]</sup>. Possible explanation for that could be the slight difference in angle of incident ray viewing and reflection. Also, the inability to enlarge the built-in scale complicates the task. Furthermore, the classification of the lipid layer was especially challenging for the participants with bright eyes, such as blue or green, due to poor visualization of this layer (Figure 1). This observation was not previously noted in the manufacturer manual or available literature.

**Tear Meniscus Height** Analysis of TMH was performed on the recordings made during interferometry. For assessing TMH, our results show fair to good interobserver reliability. Excellent intraobserver reliability was documented for observer 1, while for observer 2 it was fair to good. Despite the fact both observers, by agreement, selected the picture frame recorded right after the third blink differences between observers could be due to dynamic changes in TMH following a blink as found in some studies<sup>[22]</sup>. Despite obtained differences between observers, TMH values were, for both of them, close to 0.20 mm which is the cut-off value for normal TMH set in LacyrDiag software<sup>[5]</sup>. Ward *et al*<sup>[19]</sup> also found no difference between observers for mean TMH, with moderate intraobserver repeatability. The observers found this analysis the most time-consuming which could present a notable issue in a busy clinical practice. While analysing TMH examiners should carefully mark the upper border of the meniscus, excluding its reflection from the analysis, otherwise it might result in overestimation and false-positive results (Figure 2).

**Meibography** Compared to subjective grading scales, computerized grading of MBG, provides more reliable results and therefore enables more precise assessment of meibomian glands<sup>[23]</sup>. However, in LacyrDiag, the necessity for manual demarcation of the gland area could increase the subjective bias of the measurements, as shown in some studies<sup>[6,19]</sup>.

Our measurements revealed fair to good interobserver reliability and excellent intraobserver reliability for both

**Table 2 Inter- and intraobserver reliability for interferometry, TMH, and MBG**

Items	Interferometry	TMH (mm)	MBG (%)
Interobserver reliability	0.074 (-0.097-0.245)	0.680 (0.328-0.848)	0.414 (-0.230-0.721)
Intraobserver reliability (O1)	0.799 (0.625-0.973)	0.863 (0.712-0.935)	0.955 (0.905-0.979)
Intraobserver reliability (O2)	0.535 (0.361-0.709)	0.431 (-0.196-0.729)	0.970 (0.936-0.986)

TMH: Tear meniscus height; MBG: Meibography; O: Observer. Data are Cohen's Kappa coefficients (95%CI) for interferometry, and intraclass correlation coefficients (95%CI) for TMH and MBG.

**Table 3 Lipid pattern types and thickness**

Built-in grading scale <sup>1</sup>	Lipid thickness	Lipid pattern type
0	<15 nm	Not present
A	~15 nm	Open meshwork
B	~30 nm	Close meshwork
C	30-80 nm	Wave pattern
D	80 nm	Amorphous
E	80-120 nm	Color fringes
F	120-160 nm	Abnormal color

<sup>1</sup>According to software data found in the LacryDiag Quantel Medical device.

observers. Mean values and standard deviations obtained with LacryDiag are comparable with results obtained on healthy individuals by other computerized MBG devices<sup>[24]</sup>. We consider relatively high values of SD are the result of examinees' age heterogeneity. It should be noted that we performed MBG only on the lower eyelid. Tóth *et al*<sup>[9]</sup> documented better results; the intergrader variability was fine and the intragrader variability great, for MBG of the upper eyelid, probably due to a better visualization of the glands and larger area to analyze.

MBG is the only method, out of the three evaluated in our study, that required direct contact, and therefore, could possibly cause discomfort for the patient. We found the MBG the most strenuous because to record the representative photo one should carefully adjust the intensity and angle of the light beam to sharpen the area and to minimize the reflection due to its influence on the calculation of the gland loss (Figure 3).

To summarize, in our study the TMH measurement and MBG showed satisfying inter- and intraobserver reliability. However, the complex concept of the interferometry built-in scale for tear film analysis demonstrated the largest variation in how observers perceive it, so the reliability was not satisfactory, especially interobserver reliability that was poor. Considering our results and possible subjective bias of the measurements, we do recommend that examination and measurements with LacryDiag, especially in the follow-up, is performed by experienced, always the same observer.

The main limitation of the study is its small sample size. Also, we did not measure upper eyelid MBG and noninvasive

tear break-up time, although it is available as a part of the LacryDiag exam.

The gold standard for diagnosing DED must be clearly defined to ensure the consistency of the reported outcomes. Our study included relatively young population with no signs and symptoms of DED. Therefore, challenge presents better standardization of operator procedures as the test may be less likely to be accurate in healthy individuals and in the early course of the disease compared to well-defined or advanced DED<sup>[25]</sup>. Large validation studies are warranted to determine normative values of LacryDiag exams and improve the reliability of the results.

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**Conflicts of Interest:** Kos E, None; Cigić V, None; Bušić M, None; Bjeloš M, None; Miletić D, None; Kuzmanović Elabjer B, None.

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