Clinical Profile of Dry Eye Disease at the Philippine General Hospital

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ABSTRACT

Objectives: To describe the population of dry eye disease (DED) patients seen at the Philippine General Hospital (PGH) Dry Eye Clinic, and to compare the diagnosis, type, and severity of DED using Oculus Keratograph® 5M (Oculus GmbH, Wetzlar, Germany) with clinical diagnosis.

Methodology: This was a single-center comparative, cross-sectional study. Newly-diagnosed DED patients were recruited for the dry eye group. A subset of healthy volunteers without DED was also recruited for the control group. The clinical data for both groups were collected, and the Ocular Surface Disease Index (OSDI) questionnaire was administered. Standard clinical dry eye testing and Keratograph testing were subsequently done. The PGH Dry Eye Clinic definitions were used to classify the types of dry eye.

Results: Eighty (80) eyes of 40 patients per group were examined. For the dry eye group, the mean age and OSDI scores were significantly higher, while the average tear break up time (TBUT) was significantly lower. There was no significant difference in average basal secretion test (BST) and Schirmer 1 measurements between the two groups. 73% had evaporative type dry eye, while 27% had mixed type. Majority of the DED patients were females of >50 years old with mild evaporative type. Foreign body sensation was the most common symptom. Overall, there was poor agreement between clinical and Keratograph assessments of diagnosis and severity among patients in the dry eye group, but there was acceptable agreement when assessment was done in the control group.

Conclusions: DED patients at the PGH have similar characteristics to reported DED of other Asian populations. Evaporative or short TBUT type dry eye is the most frequently seen. Further formal validity study is needed for Oculus Keratograph® 5M to increase the value of its data to be included in routine dry eye screening.

Keywords: Dry eye disease, evaporative, short TBUT, Philippines, clinical diagnosis, Keratograph

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Introduction

Dry eye disease (DED) is one of the most common reasons for an ophthalmological consult among the middle and older aged groups, and is becoming a growing public health problem.[1] With the advent of globalization and continuous shifting to digitalization, many health problems have been gearing towards lifestyle-related diseases.[2] In many developing Asian countries including the Philippines, DED is becoming a public health concern not only with middle and old aged groups but also the younger ones. The change in the age groups of the affected individual is due to the new lifestyles driven by information technology with a rapidly changing ageing process.[3]

The prevalence of DED ranges from 5 to 50% according to many population studies in Asia and Europe.[1] Locally, Panggat, Covar, and Lim Bon Siong noted it to be at 23% in a community in the City of Manila.[4] This prevalence will entail a high clinical burden among ophthalmologists with an even higher economic burden for the society. Although the DED symptoms usually do not lead to severe visual impairment and blindness, they are still highly related to reductions in vision-related quality of life and can limit daily activities. These indirect costs, which comprise the largest proportion of the overall cost to the society, are mainly due to substantial loss in productivity at work.[3] Furthermore, the DED symptoms improve most of the time, but it is usually not curable and will require long-term treatment to provide sustainable benefits, which may cause frustration to both ophthalmologists and patients.[5]

The etiologies of DED are usually from increased tear evaporation, tear hyposecretion and/or mucin dysfunction.[6] Some risk factors include advancing age, female sex, hormonal changes, eyelid disease, refractive surgery, smoking, connective tissue diseases, increase use of video display terminals such as mobile phones, computers and televisions, and environmental factors such as wind, altitude and humidity.[7]

The consensus for diagnostic algorithms is constantly evolving, and until now there is still no gold standard diagnostic test available for dry eye. While most clinicians still practice the traditional clinical dry eye tests such as Schirmer testing and fluorescein break up time, there is mounting evidence which suggests that there needs to be a shift from traditional clinical testing methods to non-invasive diagnostics, particularly the Oculus Keratograph® 5M (Oculus GmbH, Wetzlar, Germany) **(Figure 1).**[8]

Figure 1. Oculus Keratograph® 5M (Oculus GmbH, Wetzlar, Germany) utilized in the study

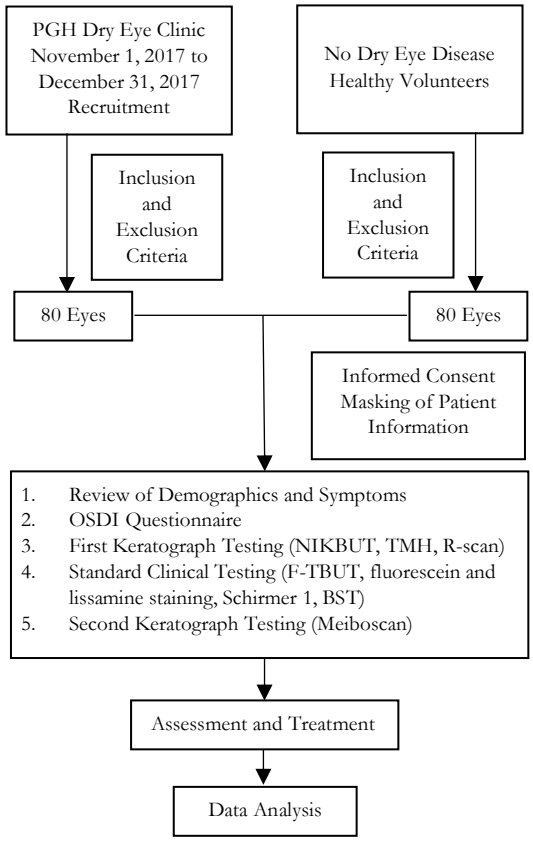
Only one published literature suggested how prevalent this condition is locally. Many information and facts about DED locally have yet to be known. The researchers aimed to describe the population of newly-diagnosed DED patients based on the diagnostic guidelines of the Dry Eye Clinic of the Philippine General Hospital (PGH), and to compare the diagnosis, type and severity of DED using a semi-automated topography-based dry eye diagnostic instrument (Oculus Keratograph® 5M) with clinical diagnosis.

Methodology

The study was a single-center, comparative, cross-sectional study design. Newly-diagnosed DED patients seen at the PGH Dry Eye Clinic from November 1 to December 31, 2017 were

recruited for the dry eye group **(Figure 2).** A subset of healthy volunteers without DED was also recruited during the same period using convenience sampling for the control group **(Figure 2).** The patients included in the dry eye group were newly diagnosed with dry eye who have had no previous treatment, and otherwise did not have any other ophthalmologic condition requiring medication or surgery. The control group included patients who did not have dry eye (as confirmed with clinical testing) nor any ophthalmologic condition requiring medication or surgery. Patients who did not satisfy the inclusion criteria, did not give written consent or those with hypersensitivity to fluorescein or lissamine dye were excluded.

Figure 2: Protocol Flowchart



*OSDI: Ocular Surface Disease Index; NIKBUT: non-invasive keratography tear break-up time; TMH: tear meniscus height; R-scan: redness scan; F-TBUT: fluorescein tear break-up time; BST: basal secretion test

Once a patient was eligible for inclusion in the study and gave written consent, the baseline demographic data and characteristics, clinical history and symptoms, review of ocular, systemic and medication history were recorded. The patient was also asked to answer the Ocular Surface Disease Index (OSDI) questionnaire either in English or Filipino (whichever was preferred) as administered by the investigator. The Filipino version of the OSDI questionnaire was validated by a previous study.[9] After getting the pertinent history, each patient then underwent non-invasive testing using the Oculus Keratograph® 5M (Oculus GmbH, Wetzlar, Germany), which was administered by a designated masked technician who was not aware of the patient's grouping. The keratograph tests done were the non-invasive keratograph break-up time or NIKBUT (measures the tear breakup time [TBUT] based on placedo-based imaging technology), tear meniscus height or TMH (measures the tear film pooling at the center of the lower lid margin), and redness or R-scan (grades the severity of vessel engorgement as a function of inflammation of the ocular surface). Next to the keratograph testing, the patients underwent the standard clinical testing done at the dry eye clinic which was administered by a designated, trained ophthalmologist. Testing was carried out in a specific order, starting with gross slit-lamp examination of the ocular surface, followed by fluorescein TBUT (F-TBUT, abnormal value is 10 seconds or less), observation of fluorescein and lissamine staining on the cornea, conjunctiva and superior posterior lid margin, and Schirmer testing both without (Schirmer 1, abnormal value is 10 mm or less) and with topical anesthesia (basal secretion test or BST, abnormal value is 5 mm or less). Meiboscan (infrared imaging of the eyelids to detect meibomian gland dropout) by the keratograph was the final test done. The designated examiner was blinded to the results of the keratograph until after all the examinations have been done. Patients deemed necessary to receive treatment were given the standard and appropriate care, and follow-up schedule.

For the dry eye group, diagnosis of dry eye was made according to the PGH Dry Eye Clinic diagnostic guidelines and based on the output of the Keratograph result. For the PGH diagnostic guidelines, DED was diagnosed when a patient answered a score of at least 2 (which means a particular dry eye symptom is experienced half of the time in a week) in at least one symptom listed in the OSDI, with or without a positive dry eye test result. The assessment of DED type per patient was categorized into 3 types: evaporative, aqueous tear deficiency (ATD), and mixed type. For the

local diagnostic guidelines: evaporative type was diagnosed when there was an abnormal F-TBUT with normal Schirmer 1 and BST tests; ATD was diagnosed when either Schirmer test was abnormal but with normal F-TBUT; and mixed type was diagnosed when both F-TBUT and Schirmer results were abnormal. Keratograph diagnosis was done using the counterpart non-invasive tests: evaporative type was assessed when there was decreased NIKBUT but normal TMH; ATD was assessed when there was normal NIKBUT but low TMH; and mixed type was assessed when both TMH and NIKBUT had abnormal results.

The diagnosis of DED was also assessed by severity grades of situational, mild, moderate, and severe. For the local diagnostic guidelines: situational dry eye is diagnosed when a patient qualifies as having dry eye based on the OSDI, but has normal Schirmer tests and F-TBUT; mild DED when there is an abnormal result in either F-TBUT or Schirmer; moderate DED if there is conjunctival staining with lissamine; and severe DED when there is corneal staining with fluorescein. Keratograph severity grading was based on the severity grading given by the machine as mild, moderate, and severe.

The data were collected by the investigators, and all the information were manually entered into an electronic spreadsheet file. The subsequent data processing and analysis were then carried out using the statistical software, Stata 13 (StataCorp, Texas, USA). The patient identity was not included in the electronic spreadsheet and was replaced by a patient sequence number to ensure privacy and confidentiality. A master list of the patients' names with corresponding sequence number was kept in a separate password-protected electronic spreadsheet.

The investigators adhered to the principles of transparency, legitimate purpose, and proportionality in the collection, retention, and processing of personal information (Data Privacy Act of 2012). The privacy and confidentiality of each subject were upheld. The study was a minimal risk study which was conducted in full compliance with principles of the Declaration of Helsinki, Good Clinical Practice of the World Health Organization, Philippine Health Research Ethics Board, and the ethical standards of the University of the Philippines Manila. The protocol was submitted for ethical evaluation to the University of the Philippines Manila Research Ethics Board and was conducted upon approval (OVS 2017-390-01). Informed consent was obtained from each study participant.

Statistical Analysis

Data analysis consisted of descriptive statistics such as means, frequency counts, and percentages, as appropriate. Agreement between clinical and Keratograph assessments were analyzed using Kappa Coefficient testing. All p-values <0.05 were considered significant. All computations were done using statistical software, Stata 13 (StataCorp, Texas, USA).

Results

A total of 160 eyes of 80 patients were recruited for the study. The dry eye group and the control group had 80 eyes of 40 patients each. There were more females (85%) than males (15%) in both groups. The average age of the dry eye group was 59 years, while that of the Control Group was 44 years as shown in **Table 1. Table 2** shows that most of the patients in the dry eye group belonged to the 50s to 70s age range, while those patients in the control group were younger (ranging from 30s to 50s). Average OSDI score was 23.9 for the dry eye group, and 3.6 for the control group. Both average age and OSDI scores were significantly different between the groups **(Table 2). Table 3** shows that the most common dry eye-related complaints were as follows: 1) foreign body sensation (52.5%); 2) intolerance to wind (47.5%); 3) sensitivity to light (35%).

Table 1. Baseline Characteristics of the Study Population

	Dry Eye Group	Control Group	P-value
Number of patients recruited	40	40	-
Number of eyes	80	80	-
Number of males (%)	6 (15)	6 (15)	-
Number of females (%)	34 (85)	34 (85)	-
Mean age (Range)	59.0 (30-79)	44.1 (20-69)	*<0.0001*
Mean OSDI* Score (Range)	23.9 (4.5-72.7)	3.6 (0-15.9)	*<0.0001*

*OSDI- Ocular Surface Disease Index

Table 2. Baseline Characteristics of the Study Population

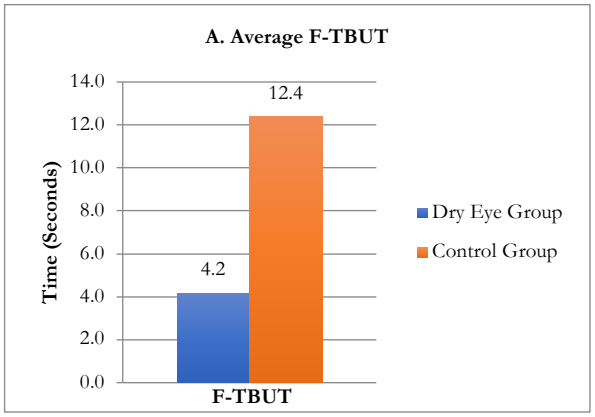
Age Range	Dry Eye Group (N = 40)	Control Group (N = 40)
Ages 20-29	0 (0%)	4 (10%)
Ages 30-39	2 (5%)	11 (27.5%)
Ages 40-49	5 (12.5%)	11 (27.5%)
Ages 50-59	12 (30%)	9 (22.5%)
Ages 60-69	13 (32.5%)	5 (12.5%)
Ages 70-79	8 (20%)	0 (0%)

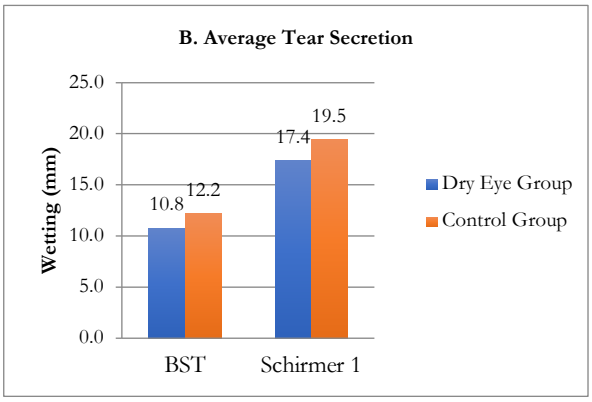
Table 3. Frequency of Dry Eye Complaints in the Dry Eye Group

Dry Eye-related Complaints	Frequency of Dry Eye Complaints (N = 40)
Sensitivity to Light	14 (35%)
Gritty/ Foreign Body Sensation	21 (52.5%)
Pain/ Discomfort	10 (25%)
Blurring of Vision	12 (30%)
Difficulty Reading	12 (30%)
Difficulty with Night Driving	2 (5%)
Difficulty using Computer/ ATM	3 (7.5%)
Difficulty Watching TV	10 (25%)
Intolerance to Wind	19 (47.5%)
Intolerance to Low Humidity	9 (22.5%)
Intolerance to Air Conditioned Areas	3 (7.5%)

The mean F-TBUT for the dry eye group was 4.2 seconds; this was significantly lower ($p < 0.00001$) compared to the control group (mean of 12.4 seconds). Mean BST and Schirmer 1 scores were 10.8 mm and 12.2 mm for the dry eye group, and 17.4 mm and 19.5 mm for the control group, respectively. There were no significant differences in these values between the two groups **(Figure 3).**

Figure 3. (A) Comparison of average F-TBUT measurements between dry eye group and control group *(p<0.00001)*; (B) Comparison of average BST *(p=0.21616)* and Schirmer 1 *(p=0.11419)* results between groups





Corneal and conjunctival staining were seen only in patients in the dry eye group, but posterior lid margin sign was seen in both groups. Posterior lid margin sign was seen in more eyes in the dry eye group (85%) than in the control group (22.5%).

The types of dry eye diagnosis, and severity grading among eyes of patients in the dry eye group are summarized in **Table 4**; only evaporative and mixed types were seen. Majority of eyes (73%) had evaporative type dry eye, and the rest (27%) had mixed type. Most eyes only had mild DED (53.8%).

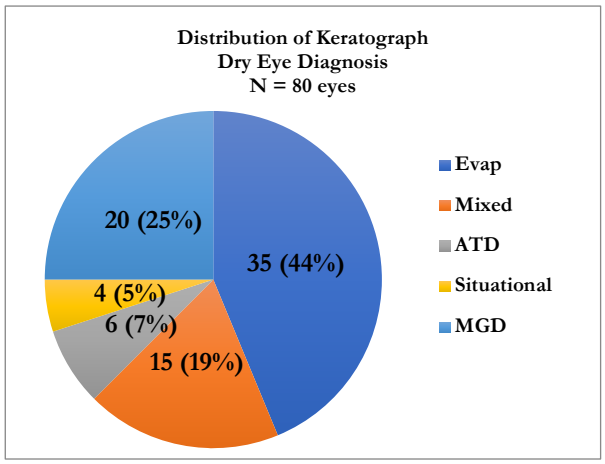
Table 4. Dry Eye Diagnosis and Severity Grading Based on PGH Dry Eye Clinic Diagnostic Criteria

Dry Eye Type	Mild	Moderate	Severe
Situational (N=0)	0	0	0
Aqueous Tear Deficiency (N=0)	0	0	0
Evaporative (N=58)	31 (53.4%)	6 (10.3%)	21 (36.2%)
Mixed (N=22)	12 (54.5%)	5 (22.7%)	5 (22.7%)
Total (N=80)	43 (53.8%)	11 (13.8%)	26 (32.5%)

Most eyes (85%) of patients in the dry eye group had concomitant lid margin changes; the most common of which was meibomian gland dysfunction (MGD), seen in 50%. Majority (72.5%) of eyes in the control group did not have lid margin changes; among those who did were mostly MGD.

While only two types of dry eye diagnosis (evaporative and mixed type) were seen in the dry eye group based on clinical evaluation, more varied diagnoses were seen in the Oculus Keratograph® 5M screening **(Figure 4).** Among eyes diagnosed with DED, only 44% were assessed to have evaporative type, 19% had mixed type, 7% had purely ATD, and 5% had situational DED (wherein there were no abnormal test results seen in the Keratograph) only. One-fourth of the eyes had normal NIKBUT and TMH, but had meibomian gland dropout and was assessed with MGD.

Figure 4. Distribution of Keratography Dry Eye Diagnosis



*Evap: evaporative; ATD: aqueous tear deficiency; MGD: meibomian gland dysfunction

Overall, the Keratograph registered the same diagnosis in only 32 out of the 80 eyes in the dry eye group, with positive percent agreement (PPA) of 44.8% and negative percent agreement (NPA) of 59.1% in assessment of evaporative type; and PPA of 27.3%, NPA 84.5% in assessment of mixed type. Unweighted Kappa coefficient was 0.050 (SE 0.063, 95% CI 0 – 0.172), suggestive of a poor overall agreement in DED diagnosis between the two diagnostic methods **(Table 5).** The assessment of severity between clinical diagnosis and Keratograph testing had similarly poor agreement (Unweighted Kappa coefficient 0.006, SE 0.063, 95% CI -0.117 – 0.128), with only 21 out of 80 eyes assessed to have the same severity in both testing methods **(Table 6).**

For the control group, the Keratograph agreed with a diagnosis of no DED in 63 out of the 80 normal eyes, with PPA of 78.8%. Unweighted Kappa Coefficient was 0.788 (SE 0.048, 95% CI 0.694 – 0.881), showing good overall agreement **(Table 7).**

Table 5. Agreement Between the Clinical Diagnosis and the Keratograph Diagnosis in the Dry Eye Group

N = 80 eyes	Eyes Diagnosed using Clinical Diagnosis	Same Diagnosis Using Keratograph	Positive Percent Agreement	Negative percent Agreement
Evaporative / Tear Film Instability	58	26	44.8%	59.1%
Mixed	22	6	27.3%	84.5%
Unweighted Kappa Coefficient: 0.050 (SE: 0.063; CI: 0-0.172)				

Table 6. Agreement Between the Clinical Severity and the Keratograph Severity Assessment in the Dry Eye Group

N = 80 eyes	Eyes Assessed using Clinical Diagnosis	Same Assessment Using Keratograph	Positive Percent Agreement	Negative percent Agreement
Mild	43	6	14.0%	78.4%
Moderate	11	5	45.5%	52.2%
Severe	26	10	38.5%	66.7%
Unweighted Kappa Coefficient: 0.006 (SE: 0.063; CI: -0.117 - 0.128)				

Table 7. Agreement Between the Clinical Diagnosis and Keratograph Diagnosis in the Control Group

N = 80 eyes	Eyes Diagnosed using Clinical Diagnosis	Same Diagnosis Using Keratograph	Positive Percent Agreement	Negative rcent Agreemer
No Dry Eye	80	63	78.8%	-
Unweighted Kappa Coefficient: 0.788 (SE: 0.048; CI: 0.694 - 0.881)				

Discussion

The results of this survey suggest that Filipinos with DED have similar characteristics with dry eye patients in other Asian countries. Recent published data show that the incidence of dry eye increases with age (with a peak incidence among persons aged 60 and above), and has a female predilection.[4,10-15] In our results, the majority of the patients referred to the Dry Eye Clinic were women in their 50s to 70s; all of them had decreased F-TBUT, and most had some form of lid margin changes (predominantly MGD) which is

also implicated in evaporative DED.[16] Evaporative dry eye or short TBUT dry eye, as labeled by the Asia Dry Eye Society is the predominant form of DED (73%) in our study population.[17] If we include the 27% of mixed type, 100% of our patients showed abnormal F-TBUT values. These findings are consistent with a local prevalence study where 68% had evaporative dry eye and 15% had mixed type.[4] Comparing our results to neighboring Asian countries, a study done in Korea showed a similar result with 60% of the 158 patients with DED examined had the evaporative type.[18] Furthermore, a study among Japanese patients with DED showed that 95% of the 449 patients examined had a shortened F-TBUT, which also accounted for their most common dry eye finding.[19] In this study, we have also shown that compared to Schirmer test, F-TBUT is the more useful test in detecting DED.

It was also noted that while all patients in the dry eye group were symptomatic, more than half of them had only a mild form of DED, and only 1/3 of eyes had staining of the conjunctiva and/or cornea. This is also consistent with reports that dry eye symptoms may occur before evidence of ocular surface damage, and thus, staining is not required in the diagnosis.[17] The most common symptom was foreign body sensation (52.5%). In contrast to a previous local study done in an urban setting wherein the most common dry-eye related complaint was itching.[4] The difference is due to the absence of itching in the OSDI questionnaire.

Upon comparison of diagnosis and severity assessment of the Oculus Keratogaph® 5M with clinical assessments, we observed very poor agreement in eyes seen within the dry eye group. While there was statistically acceptable agreement seen within the control group, there were still 17 out of 80 control eyes which were incorrectly diagnosed with DED by the Keratograph. The review the published literatures showed similar comparative studies that have been done between Keratograph assessments versus clinical testing, and these studies presented conflicting results. Some studies found that the Keratograph NIKBUT showed good clinical correlation (albeit significantly lower average break-up times) compared to F-TBUT[20-22], and that TMH had good correlation with Schirmer testing.[22] But others believed that the Keratograph results suggestive of dry eye did not correlate well with clinical data. Best *et al.* suggested that some modifications and calibrations in the Keratograph were needed to obtain useful data with good clinical correlation.[8] A comprehensive review done by McMonnies regarding NIKBUT studies revealed inconsistent reports, with some studies reporting NIKBUT measurements that are significantly too long, while others reported times that are too short, when compared to controls. Factors identified to be potentially responsible for such variation in results included the measurement protocols (which were heavily operator-dependent and prone to human error), and software issues that may have affected the conversion of data. They also pointed out factors related to tear film characteristics, as well as elements external to the tears (such as temperature, humidity, air movement, blink frequency) which can all have different consequences in both invasive and non-invasive break-up time testing. McMonnies suggested that F-TBUT and NIKBUT might still not be considered interchangeable at this time, unless better protocols and software are developed.[16]

In our experience from this study, clinical diagnosis was made by an ophthalmologist, while the Keratograph was operated by a non-physician. There may have been examiner bias at this point since the ophthalmologist would have had the benefit of the clinical history and ocular surface examination for formulating a diagnosis, while a machine (operated by someone without clinical training and experience in dry eye management) would not. The Keratograph would also have been dependent on the proper cooperation and performance of instructions by each patient assessed, so it can also be assumed that differences in ability to follow instructions may also affect outcome. But more importantly, the difference in definitions, diagnostic criteria, and cut-off values of the two methods could have affected the agreement between clinical diagnosis and the Keratograph algorithm.

While our objective of comparing diagnosis and severity output given by the Oculus Keratograph® might then seem ambitious, given that data from previous comparative studies of the individual diagnostic features of the machine (especially the NIKBUT) appear inconclusive, and given the various factors identified that may

adversely affect the results, our findings nevertheless provided a gauge of reliability of the Keratograph diagnostics for DED, and can serve as a good jump-off point for formal validation studies of this instrument.

This study showed that patients presenting with DED are mostly elderly females. All of them presented with some evaporative component or short TBUT on their DED, and half of them had mild severity. OSDI scores and age were statistically higher as compared to normal patients. Foreign body sensation was the most common symptom. The mild evaporative DED noted in this study is very comparable to the DED reported among other Asian populations. Analysis of DED using the Oculus Keratograph® 5M showed that it was able to detect abnormal signs in majority of the eyes in the dry eye group and showed acceptable agreement when detecting absence of dry eye signs compared to standard clinical testing. However, there was poor overall agreement when comparing diagnosis of specific dry eye type and severity grading between the two testing methods. Formal validity studies (and possibly calibrations in the instrumentation and processing software, as well as improvements in assessment protocols) are needed to increase the value of the data given by this instrument.

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