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**Citation**: Huntjens, B., Basi, M. and Nagra, M. (2019). Evaluating a new objective grading software for conjunctival hyperaemia. Contact Lens and Anterior Eye, doi: 10.1016/j.clae.2019.07.003

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# Title: Evaluating a new objective grading software for conjunctival hyperaemia

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## Abstract

*Background/ Aims:* Standardised numeric grading scales are used in ophthalmic practice to improve consistency between clinicians in recording the severity of ocular conditions and to facilitate the monitoring of such changes. We investigated the intra- and inter-observer grading reliability and the agreement between subjective Cornea and Contact Lens Research Unit (CCLRU) and Efron grading scales as well as a new Advanced Ophthalmic Systems (AOS) software which uses an objective approach to grading conjunctival hyperaemia.

*Methods:* One experienced observer graded n=30 bulbar and n=26 palpebral conjunctival hyperaemia images to 0.1 increments. Masked grading of randomised images was undertaken for all three methods, on two separate occasions. The agreement within and between the grading methods was assessed between sessions, and com- pared to the results of a novice observer.

*Results*: There were no statistically significant differences ($P > 0.05$) between test and retest values. However, repeatability in the grading estimates of both bulbar and palpebral conjunctival hyperaemia was improved using the AOS grading method ($R^2$=0.998; Coefficient of Repeatability CoR 0.10–0.13), compared to Efron ($R^2$ = 0.926; CoR 0.62) and CCLRU ($R^2$ = 0.885–0.911; CoR 0.50–0.78). Intraclass coefficient correlations (ICC) improved inter-observer agreement using objective (> 0.995) versus subjective methods (0.853–0.959).

*Conclusion*: These subjective and objective grading methods are not interchangeable. Due to the excellent repeatability and improved agreement between experienced and novice observers, the objective grading method provides a

more consistent approach when grading ocular abnormalities and may achieve greater reliability in record keeping and clinical monitoring in the future.

Keywords: Objective grading, Subjective grading, Agreement, Bulbar, Palpebral, Conjunctiva, Hyperaemia, Imaging

## Introduction

A fundamental aspect of clinical practice is an eye care practitioner's (ECP's) ability to record ocular conditions in an accurate and repeatable manner. Standardised numeric grading scales are used by ECPs in an attempt to improve record keeping and have been shown to make grading more consistent over time [1]. Grading provides opportunities to assess deviations from normal or healthy appearances, to record baseline measurements to which future observations can be compared, and facilitate clinical decision making with respect to management and treatment options [2]. A survey of Australian optometrists found grading scales were used extensively in optometric practice and were considered standard contact lens practice [3]. Similarly, a worldwide study involving primary and secondary ECPs found approximately 85% of practitioners used grading scales [4]. Nevertheless, some ECPs prefer to rely upon sketches, photographs, or descriptions instead of grading scales [3]. An extensive review of grading scales was recently published by Begley *et al.* [5], highlighting the lack of a universally accepted "gold-standard" grading scale for corneal and conjunctival staining. Two of the most widely used grading scales are the Cornea and Contact Lens Research Unit (CCLRU), more recently known as the Institute for Eye Research or Brien Holden Vision Institute scale [6-7], and the Efron Grading Scales for Contact Lens Complications [1,8]. Both the Efron and CCLRU grading scales are inexpensive, portable, and available as hardcopies.

Grading reliability has been defined as the ability of the grader to give similar results time after time [9]. It has been observed that grading estimate variability is due to the subjectivity associated with grading scales and the variation that occurs between different observers, as well as for the same observer on different occasions [10,11].

To overcome the bias observed with subjective grading, objective grading techniques e.g. Keratograph 5M (Oculus, Optikgerate, Germany) using digital software have been developed to improve standardisation of grading [11-13]. Digital image analysis offers a highly repeatable method of clinical monitoring and detection of changes in ocular physiology over time, which often allow a continuous rather than discrete incremental change in grading images. It has been reported that objective analysis can be 16 times more reliable than subjective analysis [11]. Given the likelihood of future utilization of automated objective grading systems in clinical settings, validation of such systems is desirable. One such novel automated objective grading software (https://aos-hub.com) was designed by Advanced Ophthalmic Systems (AOS; Weybridge, United Kingdom). The software can be used to assess a variety of anterior and posterior ocular parameters including redness of the palpebral and bulbar conjunctiva. Using Automated Intelligence to analyse the ocular surface in any digital image, the software identifies all the vessels within the area selected (see Figure 1), and an algorithm analyses environmental lighting of the conjunctiva while translating the redness of the pixels into graded values. The system follows a grading scale format resembling the Efron grading scale (grade 0 to 4) and the CCLRU grading scale (area specific) in 0.1-unit increments. This study investigated by how much the digital AOS method was likely to differ from the conventional subjective CCLRU and Efron grading scales, whether the three scales could be used interchangeably, and whether previously observed variability between experienced and novice observers could be reduced, potentially improving clinical interpretation and management of the patient.

## Methods

The study took place at the Division of Optometry and Visual Sciences, City, University of London (United Kingdom) between December 2017 and March 2018. Ethical approval for the study was obtained from the Optometry Proportionate Review Committee. A series of anonymised images were taken from a private clinical database, the International Association of Contact Lens Educators slide collection, and from the internet. The images consisted of n=30 bulbar and n=26 palpebral conjunctival hyperaemia of different eyes depicting various levels of redness perceived ranging from none to severe. The raw images were numerically labelled and displayed in full colour on a desktop computer with a monitor of resolution 1920 x 1080 pixels, while both subjective grading scales were used in printed version. The following features were assessed for a valid comparison between the 3 grading methods:

1. **Bulbar conjunctival hyperaemia.** This is referred to as conjunctival redness in Efron (Millennium Edition) grading scale and consists of five images depicting 0-4 grading ranging from normal to severe [1]. In the CCLRU grading scale, this is known as 'bulbar redness' consisting of four images covering 1-4 grading, from very slight to severe [6]. Bulbar redness was graded in the largest visible quadrant (nasal, inferior, temporal or superior) depending on the subject's position of gaze.
2. **Palpebral conjunctival hyperaemia.** Since grading of palpebral hyperaemia cannot be differentiated from the grading of palpebral conjunctivitis on the Efron grading scale, only the CCLRU scale was used. Using the CCLRU scale, 'lid redness'' consists of 4 images covering 1-4 grading from very slight to severe. Lid redness can be graded in 5 different areas of the palpebral conjunctiva: this study graded area 2 representing the middle section under the eyelid [6].

Independently of one other, an experienced clinical optometrist (BH) and an optometry student (MB) graded all bulbar and palpebral conjunctival hyperaemia images in a randomised order on the same computer using the Efron grading scale (labelled as *session 1*). To minimize a potential source of bias, randomisation was completed by each observer using an electronic software available online (https://www.random.org/integer-sets/), and graded to the nearest 0.1 [14]. Masked to earlier results, all bulbar and palpebral hyperaemia images were randomised and graded using the CCLRU grading scale on a separate day. The same method was used for the AOS software whereby the area for grading was manually selected and a grade between 0 and 4 was calculated by the software (Figure 1). All steps as described above were then repeated approximately 1 week later (labelled *session 2*) by both observers.

***Grading reliability***

Intra-observer variability is the ability of the grader to give similar results when the process is repeated. For each grading scale, we calculated the numerical differences between *session 1* and *session 2* grading estimates by the experienced optometrist (BH). The standard deviation of this discrepancy distribution describes the grading reliability.

### *Grading agreement*

Agreement between two methods of grading describes the extent to which both methods give similar results. Due to differences in grading scale scoring, it was likely that grading of the same image would produce different outcomes depending on the scale used. To estimate agreement between the methods, we calculated the numeric differences between two grading scales by an experienced optometrist (BH) measured during *session 2*. Data obtained during *session 2* was selected for analysis as previous reports have suggested clinical grading may improve towards the end of a study [15]. In addition, we investigated the agreement between the two observers in grades obtained during *session 2* for all three grading methods.

## Statistical analysis

All statistical analyses were performed using SPSS version 22.0 for Windows (SPSS Inc., Chicago, USA). Values in the text and tables are presented as the mean grading score ± standard deviation (SD). Preliminary analyses ensured that there were no violations of the assumptions of normality (Kolmogorov-Smirnov normality test; $P>0.05$). The Coefficient of Repeatability (CoR) was calculated as 1.96 * SD of the difference between pairs of measurements [16]. Limits of agreement (LoA) were calculated as the mean difference between two sets of data ± CoR, indicating the range in which 95% of the differences between measurements will lie [17]. We determined the correlation between the various methods for grading bulbar and palpebral hyperaemia using Pearson's Correlation Coefficient ($r$). A one-way repeated measures ANOVA was used to assess differences between the three methods, while a paired sample t-test was used to compare between sessions and observers. Intraclass Correlation Coefficients (ICC) [18] and Concordance Correlation Coefficients (CCC) [19] were calculated to express inter-observer and inter-method agreements, respectively. Statistical significance was accepted at $P<0.05$.

## Results

Thirty images were graded for bulbar hyperaemia, and after deletion of 2 images due to incomplete lid area 2 data, 24 images were graded for palpebral hyperaemia. All images were only presented once for each grading scale.

*Intra-observer reliability*

The reliability data for all images per grading scale obtained by an experienced optometrist (BH) is shown in Table 1. The difference between *session 1* and *session 2* was only statistically significant when grading bulbar hyperaemia using the CCLRU grading method (t(29)=3.143; P=0.004). Using Efron or AOS methods, grading was not statistically different between the two sessions for either type of hyperaemia (P>0.05). Reliability scores with the objective AOS system were lowest, indicating better reliability for bulbar as well as palpebral hyperaemia when compared to subjective grading (Table 1). Subjective grading of bulbar hyperaemia was less reliable than palpebral hyperaemia. Using the objective AOS grading system, there was little difference between the reliability of bulbar and palpebral hyperaemia.

***Table 1. Grading reliability data per grading method (between two sessions).***
*Data from experienced observer (BH).*

| | **Bulbar hyperaemia** | | | **Palpebral hyperaemia** | |
|---|---|---|---|---|---|
| | **Efron** | **CCLRU** | **AOS** | **CCLRU** | **AOS** |
| Sample size | 30 | 30 | 30 | 24 | 24 |
| Mean ± SD session 1 | 2.21 ± 1.14 | 3.13 ± 0.60 | 1.80 ± 1.37 | 2.41 ± 1.22 | 2.46 ± 1.18 |
| Mean ± SD session 2 | 2.16 ± 1.14 | 2.98 ± 0.72 | 1.81 ± 1.40 | 2.43 ± 1.05 | 2.46 ± 1.17 |
| Mean difference | -0.05 | -0.15 | 0.017 | 0.021 | <0.001 |
| Reliability | 0.31 | 0.26 | 0.06 | 0.40 | 0.05 |
| Coefficient of Repeatability | 0.62 | 0.50 | 0.13 | 0.78 | 0.10 |
| 95% LoA | 0.57 to -0.66 | 0.35 to -0.65 | 0.14 to -0.11 | 0.80 to -0.76 | 0.10 to -0.10 |
| T-test | P=0.423 | **P=0.004** | P=0.169 | P=0.800 | P=1.000 |
| $R^2$ value | 0.926 | 0.885 | 0.998 | 0.911 | 0.998 |

Bland-Altman plots (Figure 2 top) show the mean of the differences between two sessions for each of the grading scales and both areas of hyperaemia. The continuous line represents the mean of the differences, also known as the line of agreement, which represents the systematic difference or estimated bias between the two methods. It is bound by two parallel dotted lines which represents the 95% LoA above and below the line of agreement. A narrow LoA implies a better agreement between the two sessions.

*Between-method agreement*

Agreement between the three grading scales by an experienced optometrist (BH) measured during *session 2* is presented in Table 2 and Figure 2 (middle). A one-way repeated measures ANOVA was conducted to compares scores between the three methods for bulbar hyperaemia. There was a statistically significant difference between the three methods ($F(2,28)=40.34$, $P<0.0005$, multivariate eta squared = 0.74), whereby post hoc analysis revealed that the mean (± SD) grades using the AOS method (1.81 ± 1.39) were significantly lower than the Efron (2.19 ± 1.13; $P=0.01$) and CCLRU scale (3.06 ± 0.65; $P<0.0005$). In addition, the results from the Efron grading scale were significantly lower than those from the CCLRU ($P<0.0005$). All showed a large effect size (partially eta squared in Table 2). A paired sample t-test was conducted to evaluate the agreement between CCLRU and AOS grading methods for palpebral hyperaemia, which was not statistically significant different ($t(23)=-0.355$, $P=0.726$).

***Table 2. Grading agreement data between methods.*** *The average grade between two sessions was used to calculate the differences between the methods.*

| | **Bulbar hyperaemia** | | | **Palpebral hyperaemia** |
|---|---|---|---|---|
| | **Efron** (method 1) **vs CCLRU** (method 2) | **Efron** (method 1) **vs AOS** (method 2) | **CCLRU** (method 1) **vs AOS** (method 2) | **CCLRU** (method 1) **vs AOS** (method 2) |
| Sample size | 30 | 30 | 30 | 24 |
| Mean ± SD method 1 | 2.16 ± 1.14 | 2.16 ± 1.14 | 2.98 ± 0.72 | 2.42 ± 1.12 |
| Mean ± SD method 2 | 2.98 ± 0.72 | 1.81 ± 1.40 | 1.81 ± 1.40 | 2.46 ± 1.17 |
| Mean difference | 0.82 | -0.35 | -1.25 | 0.04 |
| 95% LoA | 1.90 to -0.26 | 0.86 to -1.56 | 0.56 to -2.90 | 1.11 to -1.03 |
| CCC | 0.603 | 0.850 | 0.436 | 0.899 |
| Confidence Intervals CCC | 0.444 to 0.725 | 0.730 to 0.919 | 0.273 to 0.575 | 0.787 to 0.954 |
| T-test | **P<0.0005** | **P=0.004** | **P<0.0005** | P=0.726 |
| Effect size (partial eta squared) | 0.73 (large effect) | 0.26 (large effect) | 0.67 (large effect) | 0.005 (small effect) |
| $R^2$ value | 0.856 | 0.810 | 0.614 | 0.788 |

Mean grades for bulbar hyperaemia using the CCLRU scale produced a grade 1.17 units higher than the objective AOS system. Bland-Altman plots (Figure 2 middle) showed that the two subjective grading scales differed on average by approximately 1 grade (0.82 units) which may be due to the variation in their presentation of the eye, as well as the small shift in range between the scales (the CCLRU scale offers 4 images while Efron presents a 5-point scale). Increased grading units were noted using CCLRU compared to the Efron gradings scale, which was more apparent in images showing less severe bulbar hyperaemia. As a result, a slanted difference versus mean plot was observed, whereby the agreement between the two methods improved for images of increasing severity. Similarly, Figure 2 (middle) shows that agreement between the subjective Efron grading method agrees and AOS method improved with increasing condition severity. Mean bulbar hyperaemia grading using the Efron grading scale produced a grade 0.35 units higher than the AOS system. The agreement between the CCLRU and AOS also improved for images of increasing severity. For palpebral hyperaemia, mean difference between the CCLRU and AOS methods was found to be close to zero, indicating that a subjective grade using the CCLRU is on average increased by 0.04 in comparison to the objective AOS software over the whole range of severities. Overall, we observed 95-100% of the variability observed for bulbar and palpebral hyperaemia were within a total of 2 grading units.

*Inter-observer agreement*

Table 3 and Figure 2 (bottom) show data for inter-observer agreement. The difference between the two observers was statistically significant when grading bulbar and palpebral hyperaemia using the Efron and CCLRU grading systems, whereby the experienced optometrist graded higher than the student optometrist ($P<0.05$). Using the AOS grading method, there was no statistical difference between the experienced and the novice observer; although the experienced observer did record slightly higher grades for both palpebral and bulbar hyperaemia (0.017 and 0.05 units, respectively). Subjective and objective grading of bulbar hyperaemia was more variable between observers than palpebral hyperaemia, although 92-97% of the variability observed were within maximum one grading unit. The reliability and agreement using the AOS method was much improved for bulbar as well as palpebral hyperaemia when compared to the subjective methods of grading.

***Table 3. Grading reliability data per grading method (between observers).*** *Data collected during session 2 by the experienced optometrist (BH) were compared to those collected independently by the optometry student (MB). ICC = Intraclass Correlation Coefficient*

| | **Bulbar hyperaemia** | | | **Palpebral hyperaemia** | |
|---|---|---|---|---|---|
| | **Efron** | **CCLRU** | **AOS** | **CCLRU** | **AOS** |
| Sample size | 30 | 30 | 30 | 24 | 24 |
| Mean ± SD experienced | 2.16 ± 1.14 | 2.98 ± 0.72 | 1.81 ± 1.40 | 2.43 ± 1.05 | 2.46 ± 1.17 |
| Mean ± SD student | 1.86 ± 1.2 | 2.52 ± 1.00 | 1.76 ± 1.32 | 2.21 ± 1.08 | 2.45 ± 1.15 |
| Mean difference | 0.30 | 0.47 | 0.05 | 0.08 | 0.017 |
| Reliability | 0.37 | 0.48 | 0.20 | 0.78 | 0.06 |
| Coefficient of Repeatability | 0.73 | 0.95 | 0.39 | 1.54 | 0.11 |
| 95% LoA | 1.03 to -0.42 | 1.41 to -0.48 | 0.44 to -0.34 | 1.61 to -1.46 | 0.13 to -0.09 |
| ICC | 0.959 | 0.853 | 0.995 | 0.944 | 0.999 |
| 95% Confidence Intervals ICC | 0.798 to 0.986 | 0.293 to 0.950 | 0.989 to 0.997 | 0.850 to 0.977 | 0.999 to 1.000 |
| T-test | **P<0.0005** | **P<0.0005** | P=0.177 | **P=0.023** | P=0.162 |
| $R^2$ value | 0.904 | 0.802 | 0.982 | 0.829 | 0.998 |

## Discussion

This study investigated the reliability and agreement between a novel objective, automated ocular grading software and two 'gold-standard' subjective grading methods commonly used by ECPs, to determine if objective image analysis of bulbar and palpebral hyperaemia was more reliable than subjective grading.

*Intra-observer reliability*

Objective grading of bulbar as well as palpebral hyperaemia showed substantially less variation between sessions as indicated by its narrow LoA (Table 1). We did note statistically significant differences in grading bulbar hyperaemia between two different sessions using the CCLRU grading scale (P=0.004), although the mean difference of 0.15 units suggests that this was not considered clinically significant [20]. It is possible that the intra-observer variability for CCLRU especially in the higher severities is caused by the lack of reference images for the more severe degrees of redness [15]. Schulze *et al.* found that the CCLRU reference images were perceived to cover only the lower half of the total range of bulbar hyperaemia available [21]. Furthermore, similar to Wolffsohn [12], our data showed that severity did not support linear grading; particularly in the low range of hyperaemia (<2.5 units) sensitivity between the sessions increased and a difference >1.0 units was observed. For bulbar hyperaemia, there were two occasions (out of 30) whereby these lower range grading scores were *reduced* by approximately 1 grading unit during the second session, while for the lower severities of palpebral hyperaemia three (out of 24) grading scores *increased* approximately 1 unit during the second session (Table 1). The underestimation of palpebral hyperaemia during the first session (or overestimation during the second session) may be explained by the learning effect or grading confidence of selecting area 2. The AOS grading software only expressed a mean difference of 0.017 units between visits with narrow LoA (0.14 to -0.11), whereas Efron varied on average 0.05 units and wide LoA (0.57 to -0.66). The ranges imply that 95% of the differences between measurements varied >1 grade for bulbar hyperaemia using the Efron or CCLRU scales and about 1.5 grades for palpebral hyperaemia using CCLRU, while this was only 0.25 grade using the AOS method. Using the objective AOS software, any variability observed between sessions was attributed to the manual area selection for image analysis by the software. In addition, the correlation coefficient identified an improved repeatability of the AOS grading system compared to Efron and CCLRU, with a $R^2$ value close to 1, showing that for nearly every ocular image the grading estimate was the same on visit 1 and on visit 2. CCLRU showed the lowest repeatability between visit 1 and visit 2, with an $R^2$ value of 0.72. Poor repeatability of the subjective gradings may be attributable to inconsistencies in image resolutions. The images were obtained from a variety of databases, and viewed under the same conditions including image size which may have decreased visible resolution. This has shown to be a particular advantage of the objective grading method, which seems to overcome this limitation unless the resolution of the image falls below 150 by 150 pixels.

*Between methods agreement*

Our data showed a lack of agreement between subjective and objective grading systems for bulbar, but not palpebral, hyperaemia. This may be attributable to reflectivity of different ocular surfaces, contrast levels i.e. red on red vs red on white grading, or differences in surface area sampled. In addition, the two subjective grading scales differ on average by approximately 1 grade (0.82 units) mainly due to the disagreement in presentation (drawing versus photographs). Additionally, the absence of a zero scale in CCLRU means that this method presents 4 images for the whole range of severities while the Efron grading scale uses 5 images. This may have caused a small shift in range of scales particularly in the lower severities of hyperaemia. In line with previous studies [11,21], we did indeed observe differences between grading systems to be non-linear whereby the agreement between the two subjective scales seems to improve for images of increasing severity. This reduces the possibility of applying a simple correction factor to interchangeably use different grading systems. However, it has been shown that cross-calibrated scales (after applying a correction factor) can lead to repeatable results between different scales [10]. On the other hand, for palpebral hyperaemia, the agreement between CCLRU and the objective AOS grading methods was excellent with a linear mean difference of 0.04 unit.

*Inter-observer agreement*

The onset of conjunctival hyperaemia can indicate a range of ocular conditions varying from dry eye to scleritis. Therefore, it is important that ECPs are able to evaluate any subtle variations in the anterior eye with confidence [11]. Our findings show that intra-observer repeatability is generally (clinically) acceptable for both the subjective and objective methods of anterior eye grading (bulbar and palpebral hyperaemia), although the objective method produced significantly less disparity between observers with different levels of experience. This was apparent from the statistically significant differences in grading both palpebral as well as bulbar hyperaemia between observers (Table 3). Several reports have shown that experience improves an observer's ability to grade [11,22]. In accordance with such reports, we found significant differences between the experienced and novice observers for the subjective grading methods, and that the novice clinician used a wider range of the subjective scales. High agreement between subjective and objective methods have been reported previously [14,23-24] particularly with higher number (n>5) of graders [25-26]. Critically, over the full range of severities, the objective method of grading (AOS) did express excellent reliability without significant disparities between our two observers, demonstrating its potential as a tool for inexperienced practitioners and/or teaching purposes. Using this objective grading system, experienced ECPs can rely with confidence on the grading recorded by a novice.

Intra-observer reliability and inter-observer agreement were most favourable using the objective AOS system, suggesting that objective methods of grading may establish themselves as the new gold-standard in ocular grading. The software allows for instant analysis of any digital image using a desktop or mobile phone application, providing an opportunity for consistent and extensive (5 separate areas resembling CCLRU plus a combination of vascular presentations including hue, visibility, width of vessels etc) grading with minimal effort.

One limitation of our study was that images were sourced from a variety of databases and so aspects such as magnification and image quality were not standardised. Furthermore, larger-scale studies are required to understand the potential benefits and shortcomings of such objective systems. In particular, ocular characteristics such as disease specific hyperaemia (e.g. allergic or bacterial conjunctivitis, infectious keratitis, or dry eye) and/or corneal staining and lid roughness should be included in future studies. Consideration must be given to whether practice investment in objective grading systems will bring about a significant improvement to clinical diagnosis, monitoring, and quality of patient care.

## Conclusion

Although all three methods showed acceptable repeatability, the novel automated AOS system used for objective grading of bulbar and palpebral hyperaemia was substantially more reliable than the subjective methods of grading using Efron and CCLRU grading scales. Practitioners ought to be dissuaded from attempting to use multiple systems interchangeably to prevent large variability in clinical interpretation and management of the patient over time.

## Acknowledgements

A portion of this work was conducted as part of an unrestricted grant from Advanced Ophthalmic Systems (AOS), who provided a copy of the software. This work was completed independently by MB as part of her undergraduate studies research project.

## Legends Figures

Figure 1. Objective grading method using the AOS software. Manual selection of the area of interest using the AOS software for grading bulbar hyperaemia (A). Bulbar conjunctival hyperaemia grade is displayed as 2.3 units (B). Image C shows manual selection of the area of interest while grading palpebral hyperaemia. Palpebral conjunctival hyperaemia gradings over 5 areas are displayed directly on the image (D) Area 2 is shown as 3.4 units of palpebral hyperaemia.

Figure 2. Bland and Altman plots comparing sessions, methods, and observers for bulbar (left) and palpebral (right) conjunctival hyperaemia.

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Figure 1

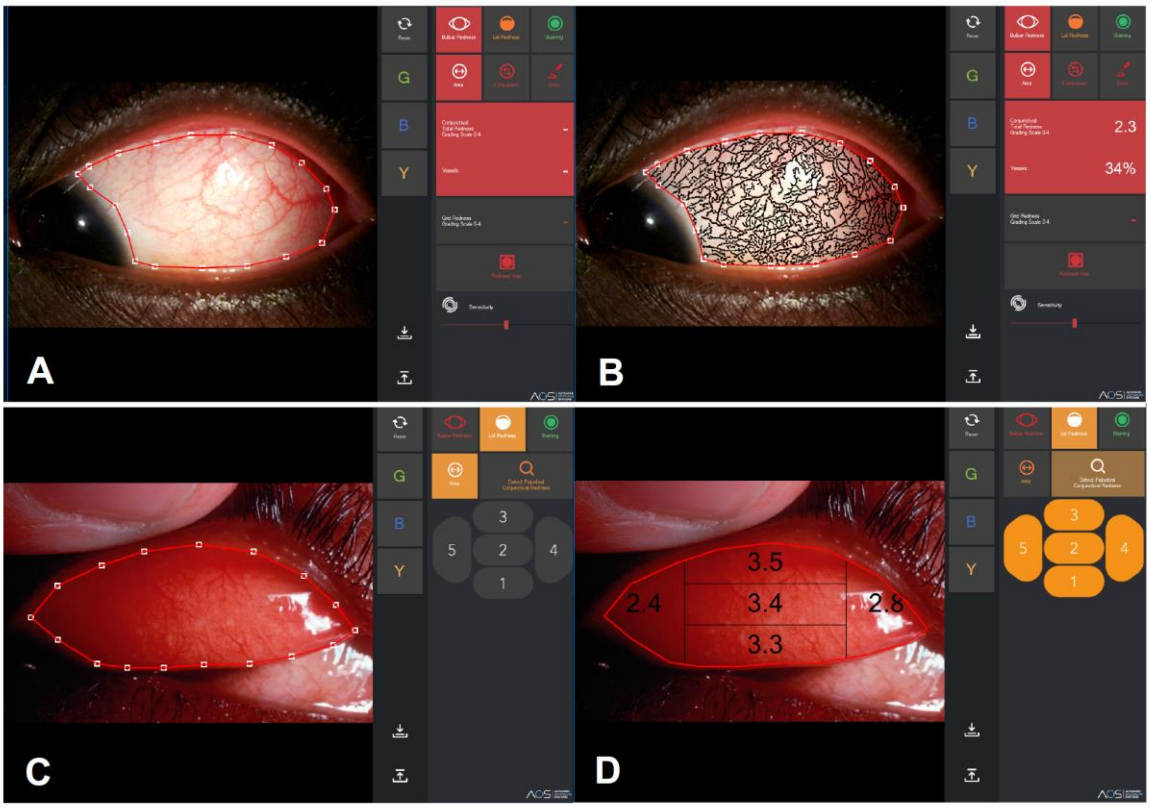
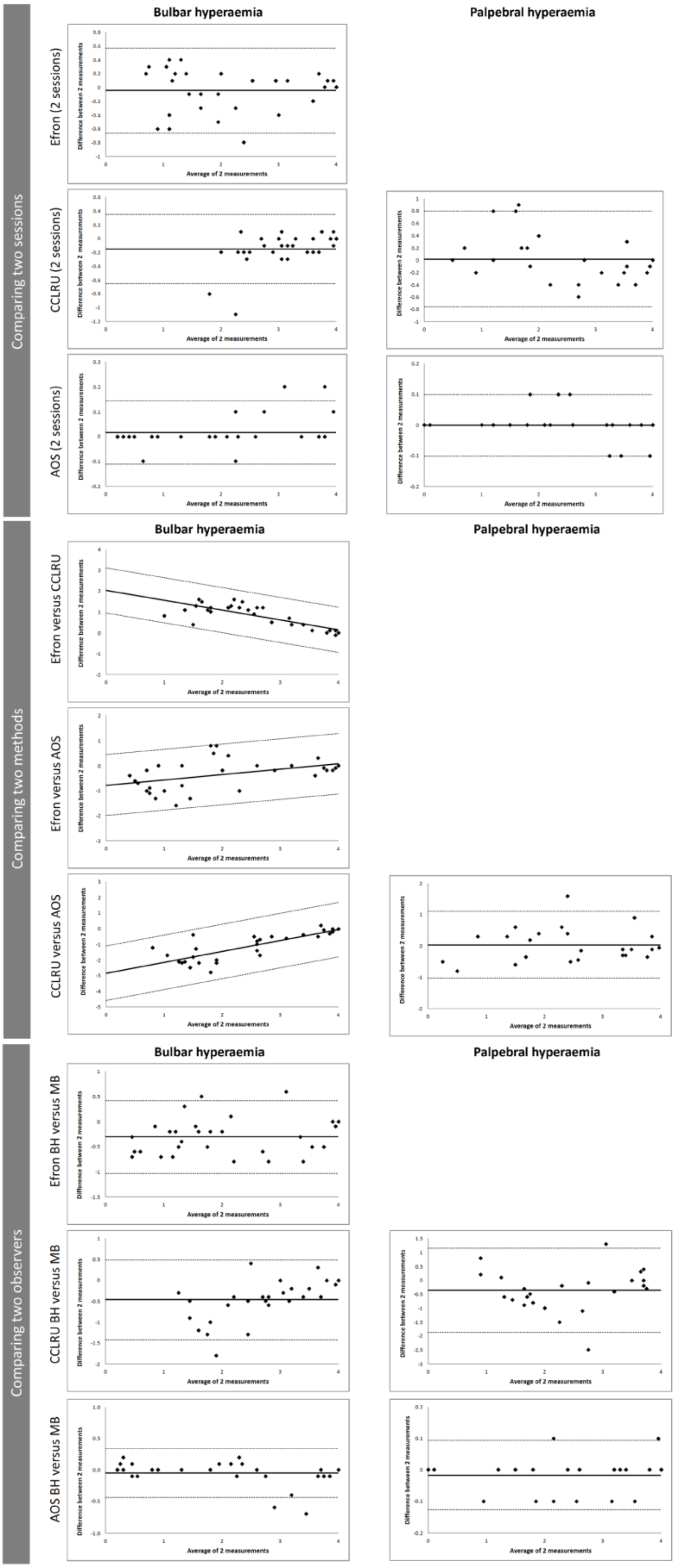


Figure 2


Comparing two sessions
Bulbar hyperaemia
Palpebral hyperaemia
Efron (2 sessions)
CCLRU (2 sessions)
AOS (2 sessions)
Comparing two methods
Efron versus CCLRU
Efron versus AOS
CCLRU versus AOS
Comparing two observers
Efron BH versus MB
CCLRU BH versus MB
AOS BH versus MB
Difference between 2 measurements
Average of 2 measurements