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Optimising subjective grading of corneal staining in Sjögren's syndrome dry eye disease

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ABSTRACT

Aim: To assess whether smaller increment and regionalised subjective grading improves the repeatability of corneal fluorescein staining assessment, and to determine the neurological approach adopted for subjective grading by practitioners.

Methods: Experienced eye-care practitioners (n = 28, aged 45 ± 12 years), graded 20 full corneal staining images of patients with mild to severe Sjögren's syndrome with the Oxford grading scheme (both in 0.5 and 1.0 increments, globally and in 5 regions), expanded National Eye Institute (NEI) and SICCA Ocular Staining Score (OSS) grading scales in randomised order. This was repeated after 7–10 days. The digital images were also analysed objectively to determine staining dots, area, intensity and location (using ImageJ) for comparison.

Results: The Oxford grading scheme was similar with whole and half unit grading (2.77vs2.81,$p = 0.145$), but the variability was reduced (0.14vs0.12,$p < 0.001$). Regional grade was lower ($p < 0.001$) and more variable ($p < 0.001$) than global image grading (1.86 ± 0.44 for whole increment grading and 1.90 ± 0.39 for half unit increments). The correlation with global grading was high for both whole ($r = 0.928$,$p < 0.001$) and half increment ($r = 0.934$,$p < 0.001$) grading. Average grading across participants was associated with particle number and vertical position, with 74.4–80.4% of the linear variance accounted for by the digital image analysis.

Conclusions: Using half unit increments with the Oxford grading scheme improve its sensitivity and repeatability in recording corneal staining. Regional grading doesn't give a comparable score and increased variability. The key neurally extracted features in assigning a subjective staining grade by clinicians were identified as the number of discrete staining locations (particles) and how close to the vertical centre was their spread, across all three scales.

1. Background

Corneal staining with fluorescein dye has been long recognised as a biomarker of ocular surface disease [1,2]. The Tear Film and Ocular Surface Society (TFOS) Dry Eye Workshops (DEWS) included ocular surface staining as a marker of a loss of homeostasis of the tear film, which together with symptomology, constitutes one of the criteria for the diagnosis of dry eye disease [3]. The ODISSEY European Consensus Group agreed that following diagnosis, symptom-based assessment and corneal fluorescein staining are sufficient to determine the severity of dry eye disease in the majority of patients [4]. The Asia Dry Eye Society's stated definition of dry eye: "Dry eye is a multifactorial disease characterized by unstable tear film causing a variety of symptoms and/or visual impairment, potentially accompanied by ocular surface damage" also emphasises the importance of fluorescein staining [5]. Additionally, both the American–European Consensus Group (AECG) criteria [6] and the 2016 American College of Rheumatology/European League Against Rheumatism (ACR–EULAR) criteria [7], that are the most widely accepted classification criteria for primary Sjögren's syndrome, include fluorescein staining assessment.

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It is important for follow-on care that damage to the ocular surface is accurately assessed and recorded. Grading scales, with broad increments, were developed for ocular conditions such as corneal damage in the 1990′s to provide reference images against which observed damage could be recorded in a easy and straight forward way. These scales, such as the Oxford grading scheme [8], are well accepted in clinical practice and have been used by some international eye-care specialists for over 30 years. It has been proposed, following modelling, that the sensitivity of grading can be improved by interpolating to 0.1 unit steps between grade images, rather than reporting 1 unit steps [9]; however, sub-unit grading is rarely adopted by practitioners [10]. It has recently been demonstrated for the grading of ocular redness, that half unit sub-increments can increase sensitivitiy at least as much as using 0.1 unit steps [11], but this approach has not been investigated for corneal staining.

Scales with a limited number of steps typically have good repeatability, but lack sensitivity [12]. Dividing the ocular surface into regions could aid in relating the staining to clinical impact such as symptomology [13]; however no study to date has explored how a global score relate to regional grading beyond anecdotal reporting of differences between three clinicians [14]. It has also been suggested that zonal grading can help in the differential diagnosis of ocular surface disease, with more temporal conjunctival staining found in Sjögren's syndrome than other forms of keratoconjunctivitis sicca [15].

The lack of a single, widely accepted, "gold standard" staining scale [13], has an important impact on the endpoints of clinical trials of ocular surface treatments. Of the most commonly adopted scales, the National Eye Institute (NEI)/Industry scale [16] adopts the approach of grading 5 corneal zones and scoring the zones by the density of stained dots on a 0–3 scale. The Oxford grading scheme [8] also grades the density of stained dots within the cornea and both the nasal and temporal conjunctiva, but introduced the concept of log unit increases in the number of stained dots between grades. The Sjögren's International Collaborative Clinical Alliance (SICCA) Ocular Staining Score (OSS) scale [17] includes this feature of coalescence by adding a single grade point for each of the following features present on the cornea: confluent staining, filaments or staining in the pupillary area. The OSS also advocated using fluorescein dye to stain the cornea and lissamine green to stain the conjunctiva, with the scores from each equally weighted in the overall score, although no scientific evidence was provided to justify this approach [17] and interobserver consistency was poor [18].

The aim of this study was to determine whether subjective grading to smaller increments and regionalised grading with established scales improves the sensitivity and repeatability of corneal staining recording. The study also compared grading between the expanded National Eye Institute/Industry Workshop Corneal Fluorescein Staining scale (expanded NEI), Oxford grading scheme and corneal part of the SICCA Ocular Staining Score (SICCA OSS) to investigate their comparability and repeatability. Finally, the approach adopted for subjective grading by practitioners was identified by correlating investigator ratings with objective image analysis of staining dot counting, staining area, intensity and location.

2. Method

The study was given a favourable opinion by the Aston University Research Ethics Committee and followed the tenets of the Declaration of Helsinki. Participants were experienced eye-care practitioners (n = 28, aged 45 ± 12 years, 6 female, qualified for 19 ± 11 years, 15 ophthalmologists and 13 optometrists, examining 237 ± 360 ocular surface patients a month [median 95, range 15 to 1600]), involved in corneal staining as part of their practice, recruited from professional body lists (Tear Film and Ocular Surface Society and European Dry Eye Society), who gave written informed consent after the nature and risks of the study had been explained to them. Training was provided in the form of sample images to grade using the electronic format followed by discussion on how they differed from a group of five experienced graders (non-participants in the study), repeated with a second set of images. They were provided with an electronic file with a series of 20 randomly sequenced full corneal images of patients with mild to severe dry eye disease owing to Sjögren syndrome with positive fluorescein corneal staining imaged with blue light and a yellow observation filter. They were asked to view them for around 30s each and to grade them with the Oxford grading scheme, expanded NEI and SICCA OSS scales in randomised order. For the Oxford grading scheme they were required to report the image with the nearest whole number increment from the grading scale reference images to the global amount of staining, and in central, superior, inferior, nasal and temporal regions (see Fig. 1a). They also graded the resequenced images again (altered in a Latin square approach) with the Oxford grading scheme to the nearest half unit increment, in a randomized sequence (Fig. 1b). The eye care practitioners then repeated the complete exercise a second time 7–10 days later in the opposite questionnaire order, but with the image sequence again randomized. One image of the 20 was repeated to allow intra-session repeatability to be assessed; reviewing of previous scores was not permitted.

Image Analysis was performed using ImageJ (v1.53t http://imagej.nih.gov/ij). Pixel to millimeter calibration was achieved by imaging a ruler with the same slit lamp and settings as the image was captured with. Color thresholding was applied to sample the green pixels in HSB color space and Huang thresholding was applied, with a saturation and brightness in the range 20–80% found to best highlight the area of observed staining. The cornea was manually segmented and particle analysis applied to identify the number of particles, the average size (mm^2), the proportion >0.1 mm^2, the proportion of total staining area consisting of particles >0.1 mm^2, the proportion of corneal area covered by staining, the average intensity (8-bit green percentage), average horizontal position of the centroid of staining (with 100% being on the inferior limbus) and distribution (the average distance between particles).

2.1. Data analysis

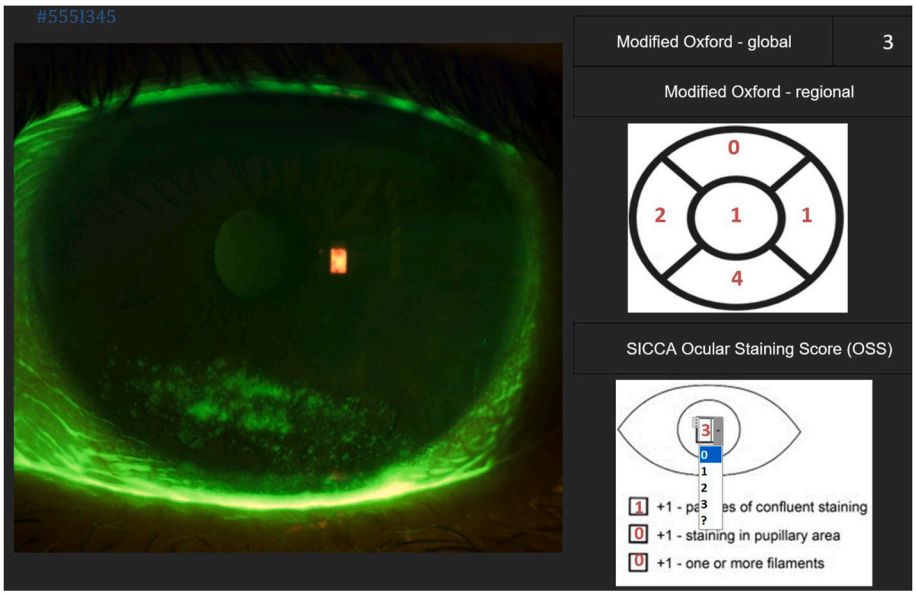
Based on a 0.4 SD for subjective grading [19], a sample size of 24 clinicians was required to allow the detection of a 0.25 difference in mean with 80% power ($p < 0.01$ significance level) (G*Power, National Institute for Health) [20]. As corneal staining subjective grading scales are ordinal in nature, non-parametric related-sample Wilcoxon signed rank test and Spearman's rank correlations were conducted with $p < 0.05$ taken as significant. Multivariate analysis was conducted to determine the contribution of objectively extracted staining features to subjective grading using stepwise and enter methods (SPSS Statistics v29.01, IBM, USA). Spearman rank correlations were also performed for an individual grader between each of the grading scales.

3. Results

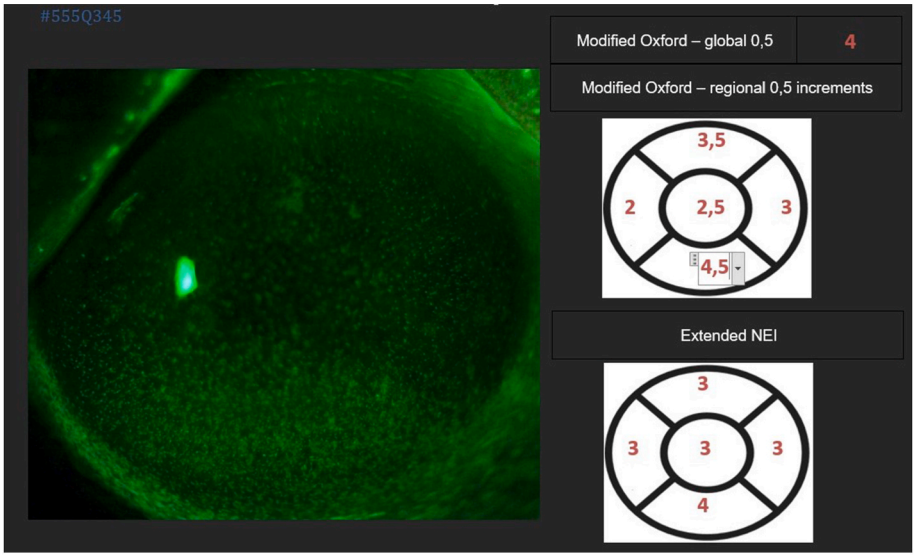
Despite initial training, one experienced grader attributed a 4 or 5 for all images with the Oxford grading scheme except one at both visits, resulting in an average score 20% higher than the next highest grader and therefore their results were excluded from the analysis.

3.1. Grading increment

The average grade with the Oxford grading scheme was similar with whole and half unit grading (2.77 vs. 2.81, $p = 0.145$), but the variability with the former was reduced (average standard deviation 0.14 vs. 0.12, $p < 0.001$). When the grading was repeated 7–10 days later, the average staining grade was 0.08 grade units lower with a 95% confidence interval of 0.19 when grading to whole units, whereas the second repeat was almost identical (0.01 higher) with a 95% confidence interval of 0.17 when grading to 0.5 increments, with a significant



A



B

Fig. 1. Grading report form examples.

difference between them (p = 0.007, Fig. 2). The intrasession repeatability was −0.09 ± 0.05 (mean ± 95% confidence interval) for whole unit grading (p = 0.006), but reduced to 0.02 ± 0.01 for half unit grading (p = 0.824).

3.2. Regional grading

The average regional grade was lower (p < 0.001) and the variability higher (p < 0.001) than global image grading (1.86 ± 0.44 for whole increment grading and 1.90 ± 0.39 for half unit increments). The correlation with global grading was high for both whole unit (r = 0.928, p < 0.001) and half increment (r = 0.934, p < 0.001) grading. Regional grading (1.0 increments) increased the intersession repeatability to ±1.06 units (95% confidence interval), which was larger as a proportion of the scale, to global grading (5.3% versus 3.9%).

3.3. Comparison between scales

The Oxford grading scheme (1.0 increments) average grade for all the participants for each image was strongly associated with that of the OSS (r = 0.802, p < 0.001) and NEI (r = 0.912, p < 0.001). The OSS and NEI were also strongly correlated (r = 0.888, p < 0.001). However, for an individual grader, the correlations between scales was much more variable (Oxford vs NEI: r = 0.070 to 0.668; Oxford vs OSS: r = 0.050 to 0.546; NEI vs OSS: r = 0.019 to 0.726). The repeatability as a percentage of the scale range was greatest (worst) for the OSS (16.6%) which was higher than the NEI scale (13.4%; 1.0 increments; p = 0.022) and lowest with the NEI (9.4%, p < 0.001). The 0.5 increment Oxford grading scheme (11.9%) was also more variable than the NEI (p = 0.015).

The intrasession repeatability was −0.09 ± 0.05 units (mean ± 95% confidence interval) for the Oxford grading scheme (1.0 increments), −0.07 ± 0.59 units for the OSS and −0.04 ± 1.56 units for the NEI scale. The intersession repeatability was 0.19 units (95% confidence interval)

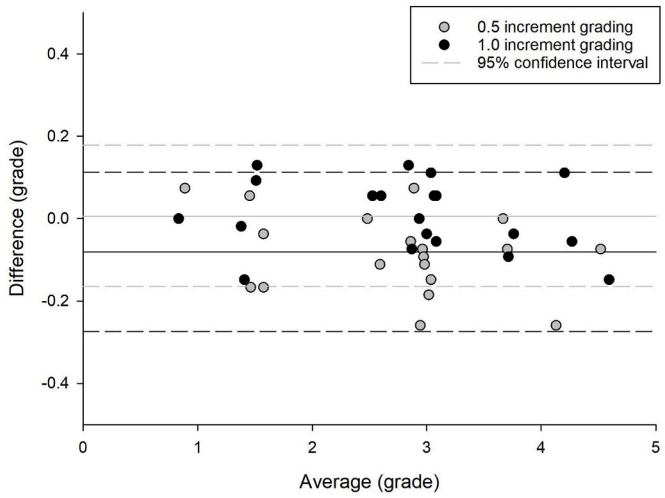


Fig. 2. Bland-Altman plot of mean versus difference in repeated grading with 0.5 of 1.0 increment units of 20 corneal staining images of patient with Sjogren's syndrome.

for the Oxford grading scheme (1.0 increments), 0.37 units for the OSS and 0.74 units for the NEI scale.

3.4. Effect of experience

The years of qualification was generally negatively associated with absolute mean difference from the mean with each image for the Oxford scale (1.0 increments: $r = -0.382$, $p = 0.049$; 0.5 increments: $r = -0.476$, $p = 0.012$), NEI scale ($r = -0.262$, $p = 0.186$) and OSS ($r = -0.354$, $p = 0.070$).

However, the number of gradings performed per month was not associated with absolute mean difference from the mean with each image for the Oxford scale (1.0 increments: $r = -0.230$, $p = 0.248$; 0.5 increments: $r = -0.143$, $p = 0.477$), NEI scale ($r = -0.202$, $p = 0.311$) and OSS ($r = -0.057$, $p = 0.777$).

3.5. Features associated with subjective grading

The correlation between each of the objective staining metrics and mean subjective grading score (average of both completitons) are presented in Table 1. Average grading across participants was associated with particle number (accounting for 47.1/48.9% of the variance) and vertical position (accounting for a further 17.2/16.2%) with a total of 75.4/78.7% of the linear variance accounted for by the digital image analysis for the Oxford (0.5/1.0 increments respectively) grading scheme. Average grading across participants was associated with vertical position (accounting for 45.0% of the variance) and particle number (accounting for a further 13.3%) with a total of 74.4% of the linear variance accounted for by the digital image analysis for the OSS scale. Average grading across participants was associated with particle number (accounting for 49.0% of the variance) and vertical position (accounting for a further 14.3%) with a total of 80.4% of the linear variance accounted for by the digital image analysis for the OSS scale.

4. Discussion

Water-soluble dyes are excluded from the normal epithelium by tight junctions, the plasma membranes and the surface glycocalyx. Shed cells, or those with a compromised glycocalyx barrier, have been hypothesized to 'stain' through transcellular entry and diffusion across defective tight junctions [21]. Due to its low molecular weight compared to other ocular dyes, fluorescein can spread from initial sites of punctate staining initially by a paracellular route and then by transcellular diffusion [21]. This can be minimised by reducing the amount of fluorescein applied [22]. Fluorescein staining is best visualised following the minimum application of dye, illuminated with a blue light with a peak around 495 nm, observed through a yellow filter with a sharp cut off around 500 nm, between 20 and 160s after instillation [2].

The first aim of this study was to determine whether subjective grading to smaller increments and regionalised grading with established scales improves the repeatability of corneal staining recording. While the average grade with the Oxford grading scheme was similar with whole and half unit grading, allowing studies that use either approach to be directly compared, the variability among observers within a visit and across two visits was statistically reduced with half unit grading. This supports a previous study on other types of ocular physiological feature grading, that grading to half increments is more repeatable than whole unit grading [11]. While the difference may not be considered clinically significant, the overall benefits of half increment grading outweigh any disadvantages. Dividing the ocular surface into regions has been adopted by many clinical studies as a potentially more accurate way to grade ocular physiological features such as staining [13]; the present study was unique in systematically assessing how a global score relates to regional grading. Interestingly, the diameter of the central zone has only been specified (beyond stating zones should be of similar size [23,24]) by Woods and colleagues [12], who stated the central zone was to have a diameter of half that of the cornea. The assigned average regional grade was lower than the global image approach for both whole and half unit grading. This would suggest a tendency for clinicians to base their overall grade on the intensity of staining in a localized area of staining, rather than as a percentage of the whole ocular surface. The correlation between global and regional grading was strong, accounting for around 86% of the variance for both whole and half unit grading. However, the 95% confidence interval was statistically higher (indicating more variability) for regional grading, even when scaled for the higher range of scores generated, which will require a larger sample size to be powered to detect differences between groups by adopting regionalised grading.

Table 1
Means and correlations of objectively analysed features influencing eye care practitioner subjective grading of corneal staining images Note vertical position scaled from 0 (superior limbus) to 100 (inferior limbus). *p < 0.05; **p < 0.01, ***p < 0.001.

Metric	Range across images	Assocation with Oxford grading scheme (0.5 increments)	Assocation with Oxford grading scheme (1.0 increments)	Assocation with NEI scale	Assocation with OSS scale
N° of particles	8–4232	0.865***	0.851***	0.652**	0.765***
Average size of particles (mm^2)	0.01–0.16	−0.094	−0.020	0.146	0.022
Proportion >0.1 mm^2 (%)	0.0–91.7	−0.213	−0.187	0.057	−0.007
Proportion coalesced (%)	0.0–98.7	0.176	0.160	0.350	0.362
Corneal coverage (%)	0.1–37.1	0.657**	0.657**	0.475*	0.587**
Average intensity (%)	8.1–26.4	−0.647**	−0.685***	−0.630**	−0.636**
Vertical position	31.7–88.9	−0.795***	−0.775***	−0.640**	−0.714***
Distribution (mm)	0.1–0.4	0.435	0.507*	0.430	0.553*

Hence while the differences may not be considered clinically significant, the disadvantages of this approach seem to outweigh any advantages.

The present study also compared three commonly used staining grading scales. Grading scales for ocular surface staining adopt different approaches to what defines severity. The expanded NEI [16] and SICCA OSS [17] scale grades increase with the number of dots and the actual numbers for each grade are stipulated in the SICCA OSS Scale. The authors of the Oxford grading scheme [8] do not recommend counting punctate staining dots, but the number of dots in each grade increase in a logarithmic nature as the grade increases; drawings depict the increasing density of dots with each grade, unevenly distributed within each zone, clustering and eventually coalescing (Grade IV) around the limbus across the interpalpebral zone. Coalescent rather than punctate staining is seen in DED with more conjunctival damage and with lower reflex tear volume as found in Sjogren syndrome patients [25]. Mucus plaques (containing mucus, epithelial cells and proteinaceous and lipoidal material) of varying size and shape, attached to the corneal epithelium, which stain with fluorescein dye, have been described in patients with accompanying system disease such as Sjogren's Syndrome. This sign is more common when filaments are present [26]. The possible mechanisms responsible for the manifestation of coalescent patches of staining are the increase in MUC16 concentration in tears due to inflammation induced, increased shedding, the accumulation of mucins due to delayed tear clearance, the reduction in repulsive forces from the corneal surface due to both of these factors and the increased friction due to reflex tear deficiency [25]. The terms "confluence" or "coalescence" of stained dots are included in several scales. In the CCLRU scale [23], coalescence is a category of stain, while in the SICCA OSS Scale [17], a point is added for confluent staining of the cornea. Therefore, it is clear that the local density of staining, which may be so dense as to be coalesced or confluent, is considered an important aspect of grading scales for dry eye and other ocular surface conditions [17,23,27].

The expanded NEI scale is not linear as grades 0.5 to 1.5 are attributed to a non-linear increase in micropunctate staining spots, 2.0 and 2.5 to moderate macropunctate area, 3.0 and 3.5 to clumped macropunctate area and 4.0 to diffuse macropunctate stain. A pharmaceutical company has created another modified version of the NEI scale using 0.5 grade increments with a linear increase in punctate dots up to grade 3, but still with coalesced areas a requirement of grades 3.5 and 4.0; however, the reliability and repeatability was no better than the previous expanded NEI scale [28]. The CORE scale [12] aimed to generate continuous data to facilitate parametric analysis, but still attributed a type of staining (micropunctate, macropunctate, coalescent and patch staining) as anchors to point values; staining type (1–100), extent (1–100) and depth (1–4, based on the timing and extent of stromal glow) are graded and multiplied together (max 40,000). This is repeated in 5 zones to create Zone Staining Scores. However, the 15 separate grades are time consuming to score and is likely to decrease inter-grader concordance. In practice, the modified Oxford grading scheme has been shown to be subjective and observer dependent, besides being susceptible to poor reproducibility and high inter-observer and intra-observer variability in contrast to computer-assisted, objective digital analysis [29–31].

Due to these differences in scoring range and approach, staining grading scales cannot be directly compared. However, the average grading score correlation between the group of clinicians was strong (ranging from $r^2 = 0.65$ to 0.83). However, for an individual grader, the correlations between scales was much more variable (from $r^2 = 0.01$ to 0.53), which would be statistically significant (80% power) with the number of graders involved [32]. This could, in part, have been due to differing amounts of grader experience with the individual scales, although consistently those with more years of experience were closer to the mean score for each image with each scale. In addition, this result was calculated after one clinician's grades were removed due to their very different approach, thus highlighting that individual clinician's can interpret grading scoring guidance very differently even after training. A limitation of the study was the time the clinician took to make their grading decision was not monitored. When assessing repeatability as a percentage of the scale range, the NEI was the most repeatable and the OSS the least repeatable. If the NEI reflects the findings with the Oxford grading scheme, its regional grading approach will have reduced the average score and hence the variability between measures would be expected to be lower (although this was unexpectantly not the case with the Oxford grading scheme analysis). The additional grades that can be added to the OSS on the presence of certain features being noted (excluding filaments in this study due to the static nature of the images being graded) is likely to have resulted in the poorer repeatability, as proposed previously [18].

Finally, the approach adopted for subjective grading by practitioners was identified by correlating investigator ratings with objective image analysis of staining. Techniques for objective analysis of corneal staining have been developed and tested using: edge detection and color extraction [33,34]; an observer-dependent thresholding technique [35]; luminance correction across the image [36]; green channel isolation and thresholding, along with size thresholds for particles [37]; intensity green thresholding [30]; green channel isolation and automated contrast enhancement, convoluted background subtraction, auto-threshold "triangle-white" following manual corneal selection with size and circularity thresholds for particles identified applied by an ImageJ macro [31]; and a combination of the difference of Gaussians (DoG), edge detection for morphologic properties of corneal erosions, and the red-green-blue (RGB) systems and hue-saturation-value (HSV) color model for detection of colour [38]. The effect of prior image enhancement with a median filter, Otsu thresholding, and a contrast-limited adaptive histogram equalization has been investigated [38], but the correlation to subjective grading using a number of different scales remained strong ($r = 0.85$ to 0.92). The expanded NEI scale correlated slightly more strongly with objective measurement ($r = 0.90$) than the Oxford grading scheme ($r = 0.85$), but the subjective grading of the two scales was not compared directly [38]. The corneal staining index (the ratio between the staining and total corneal area) has been found to be strongly correlated with the expanded NEI and Oxford (accounting for 60 and 68% of the variance) and showed good inter-observer reliability; the circularity and roundness of staining spots (manually traced and quantified objectively) were significantly higher in patients with ocular graft versus host disease compared to those diagnosed with Sjogren's Syndrome, with a distinguishing sensitivity and specificity of 65% and 60% respectively for circularity and 80% and 70% for roundness [29]. However, while objective grading of staining has advantages, it relies on high quality image capture which can be influenced by practitioner skill, instrumentation as well as the iris colour and features.

Chun and colleagues acknowledged that despite a strong correlation between their objective punctate staining count and the subjective grading by two experienced ophthalmologists, their objective strategy "could not account for the human eye's detailed perception of corneal staining morphology characteristics, such as coalescence and dispersion" [38]. Therefore the objective analysis conducted in this study chose to analyse not only the number of particles detected, but also their average size, intensity of fluorescence, the covered area (in relation to the corneal area), the proportion and relative area covered by coalescence (defined as a detected area of staining greater than 0.1 mm^2, based on the average punctate dot being 15–27 μm [39]), vertical centration of the staining within the cornea and spread across the cornea. With all of the subjective scales, the average clinical subjective grade related principally on the number of particles (accounting for 43.5–74.8% of the variance), vertical centration (accounting for 40.1–63.2% of the variance), fluorescent intensity (accounting for 39.7–46.9% of the variance) and corneal coverage (accounting for 22.5–43.2% of the variance). However, these metrics are inter-related, such as more particles and greater coalesence will be related to the corneal area covered by staining, and as the staining is more centred within the cornea the distribution is likely to increase. Hence linear multivariate analysis identified

that the main neurally extracted features in assigning a subjective staining grade were the number of discrete staining locations (particles) and how close to the vertical centre was their spread, across all three scales. As the images had a wide range of punctate and coalescent staining between them, this might suggest that separate scoring criteria for coalescence may not be required, allowing the scale grade decriptions to be more linear. The overall variance accounted for was similar in this study to that reported by Chun and colleagues for the Oxford grading scheme (75.4% versus 72.3%) and NEI scale (80.4% versus 81.5%, both finding the NEI subjective grading to be slightly more strongly associated with objective staining analysis [38].

In conclusion, using half unit increments with the Oxford grading scheme improves its repeatability in recording corneal staining, whereas regional grading increased variability. The three commonly used staining grading scales (the Oxford grading scheme, SICCA OSS and expanded NE). I have different scale ranges, so their mean scores are not comparable; however, the mean score of a group of clinicians with each of the scales are strongly correlated. Individual clinician approaches to grading with each of the scales are quite variable and therefore it is important to use multiple subjective graders in clinical trials. Finally, despite the limitations of applying objective image analysis to complex staining patterns, the correlation with subjective grading is strong and demonstrates that the key features extracted in assigning a subjective staining grade by clinicians were the number of discrete staining locations and how close to the vertical centre was their spread; this novel finding may inform more linear grading scale design in the future.

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CRediT authorship contribution statement

James S. Wolffsohn: Writing – original draft, Software, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Alberto Recchioni:** Writing – review & editing, Resources, Methodology. **Olivia A. Hunt:** Writing – review & editing, Investigation, Data curation. **Sònia Travé-Huarte:** Writing – review & editing, Investigation, Data curation. **Giuseppe Giannaccare:** Writing – review & editing, Investigation, Data curation. **Marco Pellegrini:** Writing – review & editing, Investigation, Data curation. **Marc Labetoulle:** Writing – review & editing, Investigation, Data curation.

Declaration of competing interest

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