A new software for automated counting of glistenings in intraocular lenses in vivo

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Abstract

● AIM: To assess the performance of a bespoke software for automated counting of intraocular lens (IOL) glistenings in slit-lamp images.

● METHODS: IOL glistenings from slit-lamp-derived digital images were counted manually and automatically by the bespoke software. The images of one randomly selected eye from each of 34 participants were used as a training set to determine the threshold setting that gave the best agreement between manual and automatic grading. A second set of 63 images, selected using randomised stratified sampling from 290 images, were used for software validation. The images were obtained using a previously described protocol. Software-derived automated glistenings counts were compared to manual counts produced by three ophthalmologists.

● RESULTS: A threshold value of 140 was determined that minimised the total deviation in the number of glistenings for the 34 images in the training set. Using this threshold value, only slight agreement was found between automated software counts and manual expert counts for the validating set of 63 images (κ=0.104, 95%CI, 0.040-0.168). Ten images (15.9%) had glistenings counts that agreed between the software and manual counting. There were 49 images (77.8%) where the software overestimated the number of glistenings.

● CONCLUSION: The low levels of agreement show between an initial release of software used to automatically count glistenings in in vivo slit-lamp images and manual counting indicates that this is a non-trivial application. Iterative improvement involving a dialogue between software developers and experienced ophthalmologists is required to optimise agreement. The results suggest that validation of software is necessary for studies involving semi-automatic evaluation of glistenings.

● KEYWORDS: new software; automated counting; glistenings; intraocular lenses; slit-lamp images

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INTRODUCTION

Glistenings are vacuoles that can develop within intraocular lenses (IOLs) implanted as part of routine cataract surgery. They occur in all materials used for IOLs but are mostly associated with hydrophobic acrylic polymers[1-11]. Glistenings form when water permeates through micro-channels within the material to create small fluid-filled inclusions that are typically up to 30 mm in size and may affect visual function[1,12-19]. Improved manufacturing processes have led to a reduction in the incidence of glistenings in IOL models[1,3]. Nevertheless, glistenings persist even in the latest so-called ‘glistenings-free’ materials[1,3,20]. Current methods for quantifying glistenings in clinical studies, (number and sometimes size and shape), have largely centred on subjective grading[1,3,12,17,20-21]. Image processing provides an objective method for quantifying glistenings from digital images either obtained in vivo or from laboratory studies. Most publications that have taken this approach have used a public domain image processing programme - Image J (National Institutes of Health, Bethesda. Available at: http://rsb.info.nih.gov/ij/. Accessed 1 March 2022.)[5,14,22-25]. These studies focus on the clinical or laboratory results, or clinical consequences of laboratory findings. As a result, very little detail is given about the methods used to quantify glistenings or results presented to confirm that the methods produce valid results. Digital images obtained in laboratory studies can be imaged with uniform illumination, include the entire IOL and have
far less variability than in vivo images. A few reports give
details of the image processing steps and validation of the
software methods against ground truth images\textsuperscript{[26]}. In contrast,
attaining in vivo images poses a significant challenge due to
multiple optical media and intraocular structures involved and
the potential for artefacts in images such as IOL scratches and
scuff marks, pigment granules, posterior capsule irregularities
and the anterior capsulorrhexis. Furthermore, in vivo imaging
is sensitive to movements of both the subject and the examiner
as well as the ambient illumination. High-quality clinical
imaging and automated image processing including utilization
of artificial intelligence is becoming increasingly popular in
ophthalmology\textsuperscript{[27-29]}. The aim of the current work is to evaluate and validate the first
release of bespoke software designed by Sparca Ltd. (Croydon,
Surrey, United Kingdom) for the quantification of glistenings
from in vivo slit-lamp images. To our best knowledge, it is
the first study where software developers and clinicians
with experience of IOL glistenings, image processing and
evaluation, have collaborated to assess the performance of
image processing software to quantify glistenings.

**MATERIALS AND METHODS**

**Software Description** The software was designed and
developed by Sparca Ltd (Croydon, Surrey, United Kingdom),
an ophthalmic software and technology firm. The technology is
based on digital signal processing (DSP) and operates in both
image processing and computer vision (CV) fields of study.
The newly developed software and technology retains all
original data points as part of the processing, ensuring accurate
pixel and therefore data representation. This software is the
first attempt by our team to deliver software that automatically
detects and counts glistenings. The glistening analysis was
designed to detect glistenings from in vivo digital slit-lamp images using a proprietary technique employing DSP and CV
algorithms, which delineate the DSP signal based on channel
and classify pixels as either glistening or not glistening. The
data point classification can be manually controlled via a
threshold setting that affects the specificity and sensitivity of
the algorithm output. This is necessary given the variability of the
in vivo images and the preferred subset classification, such
as signal to noise ratio. The threshold is based on class-based
pixel values, in which each pixel within the areas of interest is
assigned to a class because of the quantification algorithm.

The major steps in obtaining glistenings counts are indicated
in Figure 1. Semi-automatic glistenings detection begins with
uploading an in vivo slit-lamp image into the online software
system. A DSP iris detection algorithm is applied to the image
and a circle fitted to the detected iris delineating the pupil.
The software overlays five 1 mm\(^2\) measurement squares in a
vertical strip centred on the pupil. The user then chooses either

![Figure 1 Steps taken by the software in obtaining glistenings counts](image)

**IOL**: Intraocular lens.

the three central or all five 1 mm\(^2\) measurement squares for
analysis. The software deploys the glistenings quantification
function, with the threshold selected by the user (range 0-254),
and glistenings counts are presented based on distribution
between the three or five areas, with results shown as a
function of area. Figure 2 shows the software interface.

For the initial development of the software, a set of 12
anonymized images from previous studies\textsuperscript{[3,12]}
demonstrating a full range of IOL glistenings densities [grade 0-7 on the
Guy’s and St Thomas’ Trust (GSTT) scale\textsuperscript{[12]}] were used. In the
images, glistenings were manually drawn and labelled pixel by
pixel by one of the authors (Stanojcic N), who is experienced
in glistenings imaging, grading, and counting. These were used
as ground truth images when developing the alpha version of
the software.

**Training Set** The training set comprised 34 images obtained
from a previously published study from our group\textsuperscript{[12]}. Images
were obtained from patients implanted with the same-design
monofocal, spherical, hydrophobic acrylic IOLs (Alcon
AcrySof SA60AT) at different post-operative follow-up times
(median 14mo, range 5-66mo). This study was approved
by London Bloomsbury Research Ethics Committee (REC
reference 17/LO/1074) and this research conformed to the
tenets of the Declaration of Helsinki\textsuperscript{[12]}. Images of glistenings
were taken with a 5MP digital camera (Topcon DC-4, Topcon
Corporation, Tokyo, Japan) mounted on a slit-lamp (Topcon
SL-701, Topcon Corporation, Tokyo, Japan). All images
were taken under the same mesopic conditions; the ambient
illuminance on the slit-lamp table did not exceed 0.3 lx. A
vertical slit beam, 10 mm high by 2 mm wide, was used at an
angle of 40 degrees. Magnification was 16\(\times\) with the slit-lamp
set to maximum brightness to illuminate the centre of the IOL
within the pupil. For the Topcon DC-4 camera, an ISO of 800
was used with a shutter speed of 1/30 second, a sharpness of
‘+32’ (default), a denoising of ‘0’ (default), a contrast of ‘50’
(default) and the ‘auto-brightness’ setting at “off”.

The initial software thresholds were chosen based on
preliminary testing of the software by authors O’Brart D

[12]

[26]

[27-29]

[3,12]

[12]
and Stanojcic N on 8 images from a previous study. Four images had less than five manually counted total glistenings and the remaining four images had more than 40 glistenings. At thresholds lower than 70, the software was incorrectly identifying image noise as glistenings. Based on preliminary findings, the graders agreed the following four threshold values for initial formal software testing: 70, 90, 170, and 254. Each image in the training set (n = 34) was then analysed independently by the one author (Stanojcic N), using the software at these four pre-determined threshold values. The glistenings counts generated by the software were then passed to an independent researcher for statistical analysis (Hull CC). The software counts were compared to the manual counts agreed between three experienced, ophthalmologist graders prior to the start of software development. For each threshold an error score was calculated by taking the automated software count and subtracting the expert agreed subjective count, considered the ‘gold standard’. A negative score therefore meant the software was finding fewer glistenings than the manual graders. The total deviation was then computed by summing the error scores for the central 3 zones of all 34 images and threshold plotted against the total deviation to determine a threshold value that minimised the error. This threshold value was then applied to all images in the validating set to test the ability of the software to detect glistenings without user intervention.

Validating Set The validating set of images was a sub-sample (n=63) selected from a dataset of 278 images collected in a previous study where glistenings had been graded by three experts. This study was approved by West Midlands Solihull Research Ethics Committee (REC reference 17/WM/0414) and this research conformed to the tenets of the Declaration of Helsinki. Stratified sampling was used to create the subsample used in the current study so that the number of images with low, medium, and high numbers of glistenings was as balanced as possible. This is because there were a significant number of images with low levels of glistenings in the original data set. One expert grader (Stanojcic N) manually counted the number of glistenings in all 63 images prior to testing the software. Manual counting of the total numbers of glistenings in each image (all five zones) was compared to the results from the software using the optimum threshold determined from the training set of images.

Statistical Analysis Agreement between the number of glistenings determined by software, and manual counting by an ophthalmologist experienced in glistenings evaluation (Stanojcic N), was assessed using both qualitative and quantitative methods. Scatter plots were used to indicate bias and agreement and Cohen’s weighted kappa calculated to give a quantitative measure of agreement. Quadratic weighting was employed to give more credit to near disagreements in the number of glistenings found by each method. Data organisation and manipulation was carried out using Excel (Microsoft Corporation, WA, USA). Graphs and curve fitting were generated using SigmaPlot v14 (Systat Software Inc, Chicago, IL, USA) and agreement statistics calculated using the Real Statistics Resource Pack software Release 7.6 [copyright (2013-2021) Charles Zaiontz available from www.real-statistics.com].

RESULTS Training Set The variation in the total deviation with threshold for the 34 images in the training set is shown in Figure 3. The relationship is non-linear and so a second-order polynomial curve fit was used, which had an R² of 96.8%. The polynomial only has one root within the valid range of threshold values (0 to 254), which was at 140. This threshold was used for subsequent testing using the validating set of images.

Figure 2 Software interface indicating steps in the detection process and a sample image with output.
Validating Set

Figures 3 and 4 show the number of glistenings counted by a manual grader versus the number detected by the software. The line has a gradient of 1 and passes through the origin; points falling on this line represent perfect agreement between the two methods. In our study, both sets of images were taken using the same slit-lamp system and protocol. However, although the same IOL had been implanted in all 34 patients in the training set, the follow-up times varied (median of 14mo; range 5 to 66mo)\(^[12]\). In comparison the validating set contained images from only two glistenings resistant IOLs at 12-month follow-up. As a result, very few glistenings were observed in this set of images potentially leading to a signal to noise ratio problem for the software where a similarly small number of artefacts detected (non-glistenings) will significantly impact the agreement. In contrast, the percentage error when a few artefacts are detected and added to a large glistenings count is much lower. Many modern IOLs develop only small numbers of glistenings so any software needs to perform well in this situation. It is also appropriate to question the acceptance of manual counting as the “gold standard” for comparison. For the training set of 34 images, three graders had previously used the GSTT scale and had graded all five zones. The overall grade for each image was calculated as the sum of the grades for all five zones for each rater. Inter-rater reliability for grading was “good” with an intra-class correlation coefficient of 0.84 (CI: 0.72-0.91). The graders were ophthalmologists with different levels of experience lending support to the idea that manual grading is appropriate as a reference standard for clinical trials or testing the performance of semi-automatic or automatic methods.
Glistenings grades, rather than raw numbers, have been widely used in IOL research and may be more clinically relevant\cite{1,2,3}. We have therefore investigated how well the software counts are associated with the grades determined by experienced graders. Arguably the grading scale with the best resolution for modern IOLs is the recently published GSTT scale. Its grade boundaries correspond to the much smaller numbers of glistenings that are commonly observed in modern IOL materials. To assess the association between software counts and manual grading, we took the median grade of the three raters for the training set of 34 images mentioned above. The association between this grade and the number of glistenings counted by the software was 0.42 (Spearman’s rho, $P=0.015$) indicating only a moderate association between software counts of glistenings and GSTT grades.

The most likely reason for poor agreement between automated and manual expert counts are artefacts such as anterior or posterior IOL surface particulates (e.g. pigment), IOL scratches and scuff marks (e.g. from the IOL loading device or forceps), posterior capsule irregularities and vitreous floats\cite{4,5,6} that posed a challenge for the software. Unlike the software, expert graders can exclude artefacts based on subjective determination and experience. To assess how our results are affected by artefacts, we have conducted a sensitivity analysis on the agreement statistic. In this analysis we have progressively removed images with errors in total glistenings counts of more than 30 (one image), 20 (four images) and 10 (14 images) from the validation data set of 63 images. This resulted in weighted kappa statistics of 0.073 (CI: 0.017, 0.128), 0.114 (CI: 0.046, 0.182) and 0.165 (CI: 0.048, 0.282) respectively. Although the level of agreement improves, removing images that may have been affected by artefacts and where there are large differences in counts does not make a significant difference to the overall agreement which remains slight. This could be a signal to noise ratio problem where a difference in counts by only one or two when the number of glistenings is very small will still not produce a kappa value close to one. In contrast, even when there are differences in the number of glistenings counted by the two methods, it is possible to get a value for kappa close to unity provided the results from most images agree and also when there are relatively few images with large differences.

The issue of artefacts affecting the automated counting software has been explored further. Images were ranked according to the difference in the number of glistenings between the two methods and an experienced ophthalmologist reviewed the four images where the difference was 20 glistenings or more. The four images all exhibited one or a combination of the following: opacity or a scratch mark on the anterior surface of the IOL (presumed to be from a loading device or intra-operative manipulation with metallic instruments); posterior capsule irregularities combined with vitreous strands/floaters or pigment granules anywhere on IOL surface. In all instances glistenings in these areas were overestimated. IOL scratch marks do indeed appear like glistenings (granular metallic debris reflecting light) but their distribution pattern does not. Pigment granules on the IOL surface (anterior or posterior) also resemble gistenings in size and shape but their distribution pattern and proximity to the IOL surface do not.

In summary, we have presented findings to validate the initial release of new software designed to count glistenings in in vivo slit-lamp images. Our results demonstrate this is a challenging problem and an iterative development process is required between software developers and ophthalmologists to improve on software performance. Our results also indicate that studies using automated detection and counting software should provide appropriate detail and validation of their methods otherwise it is possible that additional and unwanted variability could affect results.

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Conflicts of Interest: Stanojcic N, None; Hull CC, None; Mangieri E, employee of Sparca Ltd; Little N, employee of Sparca Ltd; O’Brart D is a consultant for and holds equity in Sparca Ltd and also holds non-commercial research grants from Rayner Ltd. and Johnson and Johnson Inc. for intraocular lens research.

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