Original Article

Automated iris volume analysis and trabecular meshwork length using anterior segment optical coherence tomography - Application in pseudoexfoliation and pseudoexfoliation glaucoma

Aparna Rao, Kiran Kumar Vupparaboina[1], Debananda Padhy, Niranjan Raj, Amiya Pradhan, Abilash Goud[1], Hari Kumar Peguda[1], Soumya Jana[1], Ashutosh Richariya[1]

Purpose: The aim of this study was to evaluate differences in the iris and angle parameters in psuedoexfoliation syndrome (PXF) and pseudoexfoliation glaucoma (PXG) using anterior segment optical coherence tomography (ASOCT). **Methods:** Patients with PXF or PXG were compared using ASOCT with primary open-angle glaucoma POAG eyes as controls in this noninterventional comparative study conducted at a tertiary eye care center in East India. All angle parameters, TM length, and iris thickness were analyzed from the enhanced depth imaging (EDI) single scans obtained. Quadrant scans were used for the calculation of iris volume using a custom-built in-house software. In particular, the software performs multiple operations including edge detection, connected components, and thresholding to localize and segment the iris. Differences in the iris volume/thickness and TM length in PXF and PXG with POAG were analyzed. **Results:** A total of 225 eyes were included, which included 75 PXG and 98 PXF cases and 52 POAG with a mean age of 67 ± 9.7 years at presentation. The algorithm repeatability and reproducibility was also established with correlation coefficients more than 99% which was substantiated with Bland-Altman plots. The iris volume (calculated in 197 images of 225 eyes) did not differ significantly in PXF and PXG eyes, although both had significantly greater volume compared to POAG eyes. The iris volume or other angle parameters including TM length did not correlate with clinical variables such as IOP, age, or visual field indices. **Conclusion:** Iris parameters or TM length do not explain pathogenesis of glaucoma in pseudoexfoliation.

Key words: Anterior segment optical coherence tomography, glaucoma, Iris volume, pseudoexfoliation, trabecular meshwork

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Optical coherence tomography (OCT), a noninvasive imaging technique, has revolutionized ophthalmic imaging allowing *in vivo* objective visualization of the angle. This has facilitated repeatable quantitative estimation of anterior segment parameters as opposed to the subjective qualitative evaluation using gonioscopy which varies from one expert to the other.[1-3] This has evolved tremendously with regard to resolution, faster acquisition allowing better identification of the Schwalbe's line and scleral spur.[2] With anterior segment optical coherence tomography (ASOCT), it is now possible to visualize as well as quantify the anterior segment structural changes that has helped understand various dimensions of the angle in different forms of glaucoma.[2,3] Several novel anterior segment parameters have been identified using ASOCT.[2,4,5] The iris volume is one such parameter which measures the tonicity or the extent to which the iris can distend or compress under physiological or pharmacological conditions. This is believed to influence the sponginess or water content which in turn determines the angle dimensions when the iris dilates or constricts.[5-7] This aspect has been studied and reported to be significantly different in eyes with angle closure eyes. Such a property is also believed to play an important role in conditions where the iridolenticular contact plays a role in disease pathogenesis like pseudoexfoliation.

Pseudoexfoliation is an age-related fibrillopathy characterized by accumulation of dandruff like material over ocular structure causing mechanical blockage of trabecular meshwork and functional disturbances and impairment of aqueous outflow and progressive optic nerve damage.[8-10] The iris shows definitive changes on histopathology which accounts for functional disturbances seen clinically.[9,10] Our earlier study showed iris as the possible source of exfoliation material.[11] Absence of pupil dilatation, areas of stromal hypoplasia, and pigment loss suggests possible changes in iris function and differences in iris thickness or morphology correlating with evident structural alterations in the eyes with different stages of exfoliation. Yet this aspect is underexplored in exfoliation which may underpin aspects of poor dilatation in eyes with glaucoma and also give clues to

LV Prasad Eye Institute, Patia, Bhubaneswar, Orissa, [1]LV Prasad Eye Institute, Hyderabad, Telangana, India

Correspondence to: Dr. Aparna Rao, LV Prasad Eye Institute, Patia, Bhubaneswar, Orissa, India. E-mail: vinodini10375@yahoo.com

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possible ASOCT iris or other parameters which may portend possible risk of glaucoma in eyes with pseudoexfoliation syndrome (PXF).

Methods

All newly diagnosed patients with PXF or pseudoexfoliation glaucoma (PXG) and primary open-angle glaucoma with open angles on gonioscopy and those that underwent anterior segment imaging with Visante ASOCT (Dublin, California) attending glaucoma service at a tertiary center in east India from January 2015 to 2016 were included for this cross-sectional study. Those with previous laser or surgery were excluded from the analysis. Absolute glaucoma and those with other associations such as corneal opacification, retinal vein occlusions and previous trauma/uveitis were also excluded. The study was approved by the institutional review board and adhered to the tenets of the declaration of Helsinki. A written informed consent was taken from all patients included into the study.

All subjects underwent detailed comprehensive ophthalmic examinations including refraction, slit lamp evaluation, Goldmann applanation tonometry, fundus biomicroscopy, gonioscopy, and standard automated perimetry using the Humphrey Visual Field Analyzer (Carl Zeiss, Dublin, California, 24-2 Swedish Interactive Threshold Algorithm (SITA) software program).

Pseudoexfoliation was diagnosed in the presence of dandruff such as deposits or radial pigments on the lens capsule or other ocular structures such as pupil, cornea, or conjunctiva. Those with exfoliation deposits with normal intraocular pressure, disc, and visual field were diagnosed as PXF, whereas those with raised intraocular pressure requiring medicines or with glaucomatous disc damage with corresponding visual field defect were classified as PXG.

Primary open-angle glaucoma included those >40 years with raised IOP at presentation with disc and field changes consistent with glaucoma. Those with any anterior segment pathology precluding anterior segment details such as corneal opacity, secondary forms of glaucoma, history of previous laser or surgery, and associated ocular pathologies were excluded.

Data acquisition

All patients underwent imaging with Visante anterior segment OCT (model 1000 (Carl Zeiss Meditec, Dublin, California) by the same person blinded to the clinical details of the patients before dilatation. The Visante ASOCT is a noncontact mode of measuring the anterior segment which allows acquisition of 2000 A scans per second. The subject is asked to fixate on an internally placed target after adequate adjusting of focus for refractive error of the patent for distance. The ASOCT acquires several A-scans and then computes the anterior segment in 360° and reports the angle dimensions in four quadrants. The types of scans that were acquired for each eye included enhanced depth anterior segment single scan and anterior segment quadrant scan (0°–180°, 45°–225°, 90°–270°, and 135°–315°).

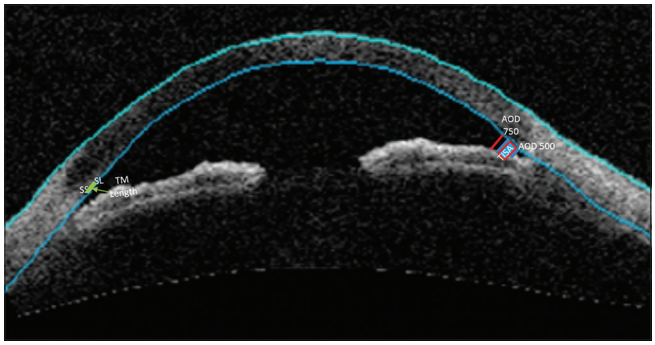

Figure 1: Measurement of common angle and iris parameters in automated fashion using ASOCT in eyes with pseudoexfoliation syndrome (PXF) pseudoexfoliation glaucoma or primary open-angle glaucoma

Image analysis

Angle parameters

All angle parameters, TM length, and iris thickness were analyzed from the EDI single scans obtained. The angle parameters were calculated automatically by the Visante OCT system, which included the angle opening distance (AOD) and angle recess area (ARA) at 500–750 mm (ARA500/750), trabecular iris angle (TIA 500/750) and 500–750 mm (AOD 500/750), trabecular-iris space area at 500–750 mm (TISA 500/750), Fig. 1. The trabecular meshwork length was measured by a method as described previously.[12] Briefly, the SS and SL marked the two boundaries of the TM, which was then measured using calipers function.

Iris parameters

The iris parameters measured and analyzed included iris volume (as detailed above) and iris thickness (defined by the distance between the anterior and posterior surfaces) at the thickest point and root of iris was measured at midpoint of the iris root and point of iridolenticular contact in the single scan image, Fig. 1. The detailed method is described in the supplemental text [Supplemental Methods], Figs. 2 and 3.

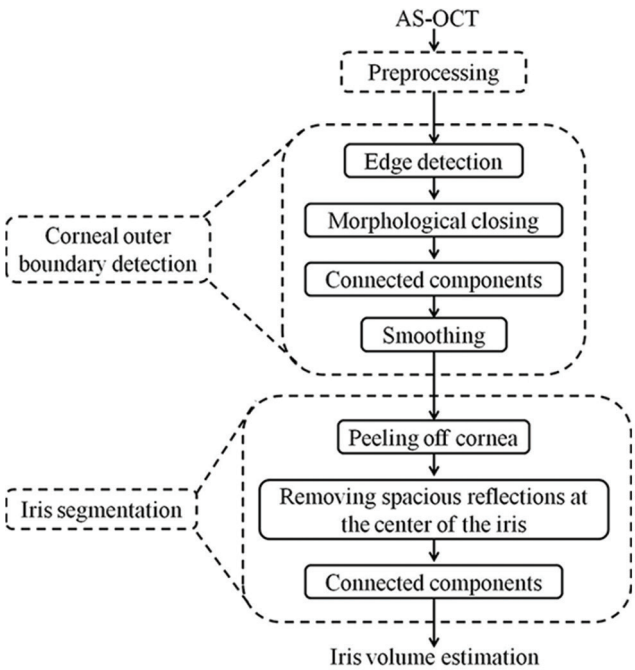

Figure 2: Schematic of the proposed methodology of automated calculation of iris volume on anterior segment optical coherence tomography

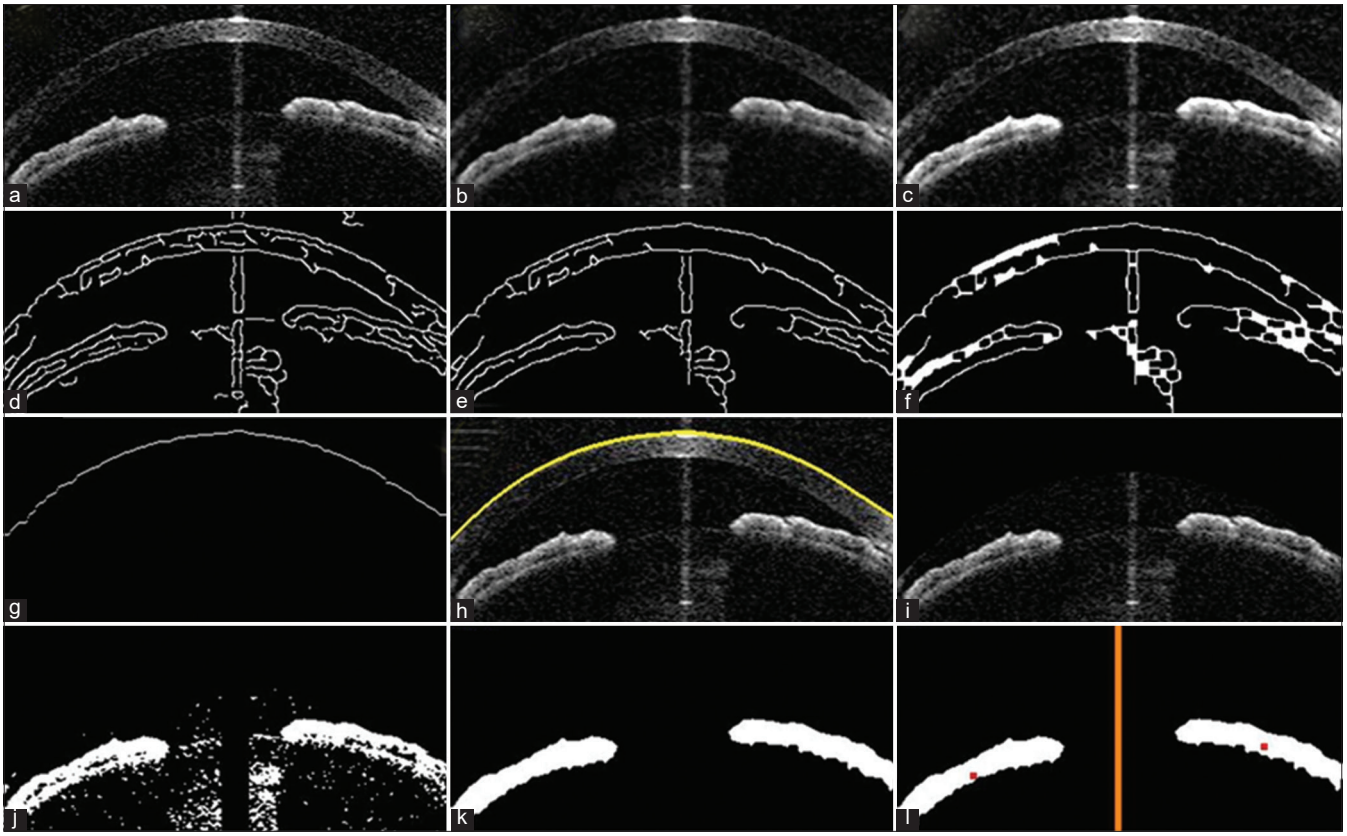

Figure 3: Graphical depiction of the proposed methodology: (a) sample AS-OCT image; (b) median filtered image; (c) contrasted adjusted image; (d) canny edge map; (e) image after removing small connected components; (f) image after morphological closing operation to remove discontinuities; (g) initial COB estimate; (h) final COB estimate in yellow overplayed on the OCT image; (i) localized iris after peeling off cornea; (j) image after removing high reflective region in the central cornea; (k) extracted iris using connected components algorithm and morphological hole filling; and (l) estimated centroids (red dots) and the axis of rotation (orange line) required for volume estimation

Results

A total of 225 eyes were recruited, which included 75 PXG and 98 PXF cases and 52 POAG with a mean age of 67 ± 9.7 years at presentation. The age at presentation and proportion of males with disease was significantly greater for PXG eyes than PXF and POAG eyes [Table 1]. Both PXF and PXG eyes had significantly worse visual field baseline indices at presentation than POAG [Table 1]. Our proposed method detected 60%–80% of the iris in 12 images and 80%–100% in remaining 18 images [Figs. S1-S5 and supplemental methods].

The iris volume was analyzed in 197 images of 225 eyes due to incomplete delineation and identification of iris boundaries (clear delineation of boundary between iris and sclera) in rest of the images on the custom built software for automated analysis of iris volume. The iris volume did not differ significantly in PXF and PXG eyes, although both had significantly greater volume (mean iris volume 51 mm^3 and 50 mm^3) as compared to POAG eyes (mean 42 mm^3) [Table 2]. The iris volume did not correlate with iris thickness or other ASOCT parameters not with clinical variables such as IOP, age or visual field indices.

The iris thickness and other ASOCT parameters such as AOD 500, AOD750, ARA 500, TISA 500, and 750 did not differ between the three groups, Table 2. The TM length was also similar in all three groups. None of the ASOCT variables correlated with visual field indices, IOP, or age.

Discussion

This study found no significant angle or iris variables which predicted a diagnosis of PXG or POAG eyes. Although PXF and PXG eyes had greater iris volume than POAG, it was not significantly different between PXF and PXG eyes. None of the angle parameters or other ASOCT variables predicted the diagnosis of glaucoma in this study. The ASOCT has evolved over the years with its uses expanding to diagnosis of many ocular conditions. Yet this study did not find any difference in angle iris or TM parameters predicting glaucoma. This could be because of either no difference existing or could be due to the methods of extrapolation used for computing iris thickness or other structural parameters which could have therefore missed some areas with morphological difference in eyes with PXG.

PXF represents a unique age-related fibrillopathy with deposition of exfoliative material over different ocular structures.[10,11,13-19] The origin of the deposits is presumed to be either the lens, ciliary epithelium or the iris.[8,10,11] The pattern of deposits over the lens with close proximity to the iris coupled with prominent iris changes makes the iris as possible source of this material which may be further swept

Table 1: Clinical characteristics in patients with pseudoexfoliation syndrome (PXF) pseudoexfoliation glaucoma or primary open-angle glaucoma

Variable	POAG *n*=52	PXG *n*=75	PXF *n*=98	*P*
Age	62±11.4	70±7.5	68±9.5	0.05
M:F	33:19	68:7	86:12	<0.0001
Refraction	0.2±1.3	–0.07±1.2	0.2±2.5	0.1
Mean deviation (dB)	–10±4.3	–15±10.1	–11±8.8	0.03
Pattern standard deviation (dB)	8±3.5	5.9±3.3	4±3.02	0.04
Visual field index (%)	80±28.9	58±35.3	72±29.8	0.001
Baseline Intraocular pressure (mm Hg)	17±8.1	25±12.1	17±7.5	<0.001

Table 2: Comparison of angle iris and trabecular meshwork parameters on anterior segment optical coherence tomography in patients with pseudoexfoliation syndrome (PXF) pseudoexfoliation glaucoma or primary open-angle glaucoma

Variable	POAG *n*	PXG *n*	PXF *n*	*P*
AOD 500 (mm)	0.5±0.1	0.5±0.1	0.5±0.1	0.06
AOD 750 (mm)	0.7±0.1	0.7±0.2	0.7±0.2	0.1
ARA500 (mm^2)	0.2±0.3	0.3±0.04	0.2±0.06	0.4
ARA750 (mm^2)	0.3±0.07	0.4±0.08	0.4±0.1	0.3
TISA 500 (mm^2)	0.1±0.03	0.2±0.04	0.2±0.04	0.01
TISA 750 (mm^2)	0.3±0.07	0.3±0.09	0.3±0.1	0.1
Iris thickness 1 (mm)	0.4±0.1	0.5±0.08	0.5±0.1	0.2
Iris thickness 2 (mm)	0.4±0.08	0.4±0.06	0.4±0.07	0.3
TM length) mm)	0.6±0.1	0.6±0.1	0.6±0.1	0.3
Iris volume (mm^3)	42±2.4	51±5.3	50±7.4	0.01

POAG=Primary open-angle glaucoma, PXG=Pseudoexfoliation glaucoma, PXF=Pseudoexfoliation syndrome. Data are expressed as mean value±SD, *P* values are obtained after one-way ANOVA with *post hoc* Bonferroni corrections. See text for method of measurement of each parameter using ASOCT

off by aqueous convention current onto other ocular structures aided by physiologic iris movements under different lighting conditions.[11] The iris is reported to be prominently involved with stromal fibrotic degeneration. Electron microscopy has revealed fibrosis involving the muscle tissue associated with disorganization and fibrillar components in the capillary basal lamina.[9,13] Marked muscular degenerative changes were reported in transmission electron microscopy study of 33 iris specimens, which also reported focal disintegration of pigment epithelial cells with unusual PXF material along the epithelial cell apices and also on endothelial cells/pericytes of vessels.[13] Such degenerative changes predominantly involving the muscular layer of the iris may be responsible for poor iris dilatation and ruff atrophy seen in eyes with this entity.

The iris volume represents a unique attribute of iris consistency or sponginess which represents its ability to lose water upon physiologic movements. Aptel *et al.* showed significant differences in eyes with APAC compared to other subtypes of angle closure.[20] Other studies have reported significant changes in dynamic iris area and other parameters in eyes with angle closure and exfoliation.[3,5,7,19-26] This is largely dependent on the intactness of the iris muscle tissue apart from different iris response in each ethnicity to physiologic conditions. As the muscle tissue is reported to undergo degenerative and fibrotic changes, it is logical to expect that the iris volume should be greater in eyes with glaucoma. The iris volume is recognized as a significant risk factor of angle closure with retention of water in dilated state accounting for crowding of the angle in predisposed eyes.[7,20,21] The exchange of fluid between the iris and the aqueous may depend on vascular permeability and other physiologic conditions such as papillary movements apart from intactness of the aqueous blood barrier. This has been found to be impaired in PXF and PXG eyes. As both iris muscular changes and impaired blood aqueous barrier are key findings in both PXF and PXG eyes, this may explain the reason for not finding any difference between the two. Further, the quadrant scan used only computes the parameters in between the scans which therefore have resulted in some areas with morphological differences to be missed. The other reason may be the exclusion of eyes with narrow angles where iris volume is supposed to play a key role in glaucoma pathogenesis. This suggests that iris related muscle tone may be important for impaired dilatation or ruff atrophy (structural changes) in PXF, altered muscular function does not play any role in PXF eyes with open angles.

The ASOCT has revolutionized glaucoma monitoring and has identified novel parameters predicting angle closure in different studies.[3,4,6,7,21-23,25,26] Yet, studies on ASOCT in PXF subtypes are scarce. One study has found no difference in angle ACA or ACV or any other angle parameter between PXF and PXG eyes using Schemiflug pentacam imaging.[19] This study did not find any significant difference in angle or iris parameter between PXF and PXG eyes under scotopic conditions. We did not study these parameters under different physiologic conditions and do not believe that there may be any difference keeping these results in mind.

The trabecular meshwork is involved with significant fibrotic changes in the juxtacanlicular area where the fibrillar deposits are found to be greatest.[13] Though gonioscopy identifies TM pigmentation IN PXF eyes, these findings are known to have no correlation with extent of damage or glaucoma.[8] ASOCT has now improved visualization of the angle structures including the TM which can be analyzed on images.[12,27-29] The TM length was first studied by Usui *et al.* which was again revisited by other studies studying its relation to various angle dimensions and age.[28] One study found no significant correlation of TM parameters with age, gonioscopy score or IOP.[12] This again suggests that structural changes in the TM may not portend parallel functional changes in eyes

with glaucoma, where, local tissue specific molecular events could be trigger to onset of glaucoma.

We only included only eyes with open angles to ensure comparisons between PXF/PXG eyes with POAG eyes. We did not compare with controls or normals as PXF/PXG eyes are known to behave differently compared to other types of glaucoma and our aim was to find out predictors of glaucoma in PXF eyes and not detection of PXF using ASOCT. We also did not study dynamic changes in iris or angle parameters as our results in scotopic conditions pointed toward nor correlation of any of these in glaucoma pathogenesis in PXF eyes. Further search for molecular events rather than structural or functional changes would through insight into the actual events responsible for onset of glaucoma in these eyes.

Conclusion

The results of our study show that the iris volume or other angle parameters including TM length do not explain pathogenesis of glaucoma in pseudoexfoliation.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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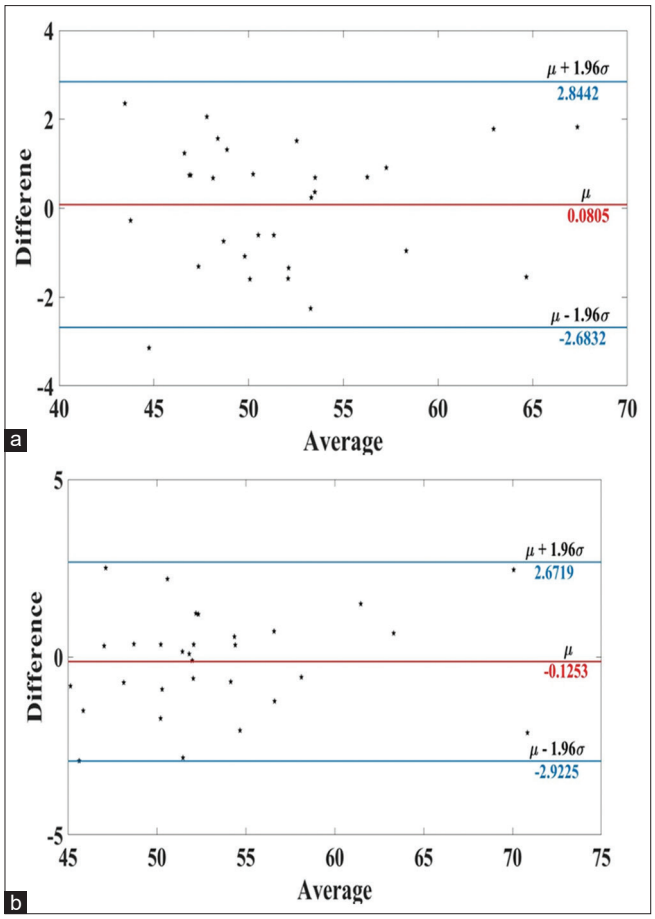

Figure S1: Bland–Altman analysis for intraobserver repeatability for running the software twice by two observers: (a) Observer-1; (b) Observer-2

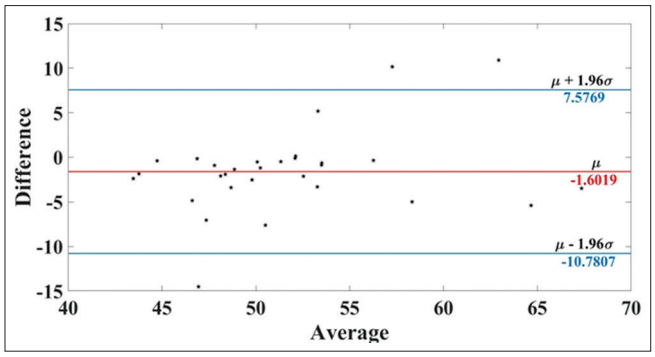

Figure S2: Bland–Altman analysis for interobserver repeatability for running the software twice by two observers

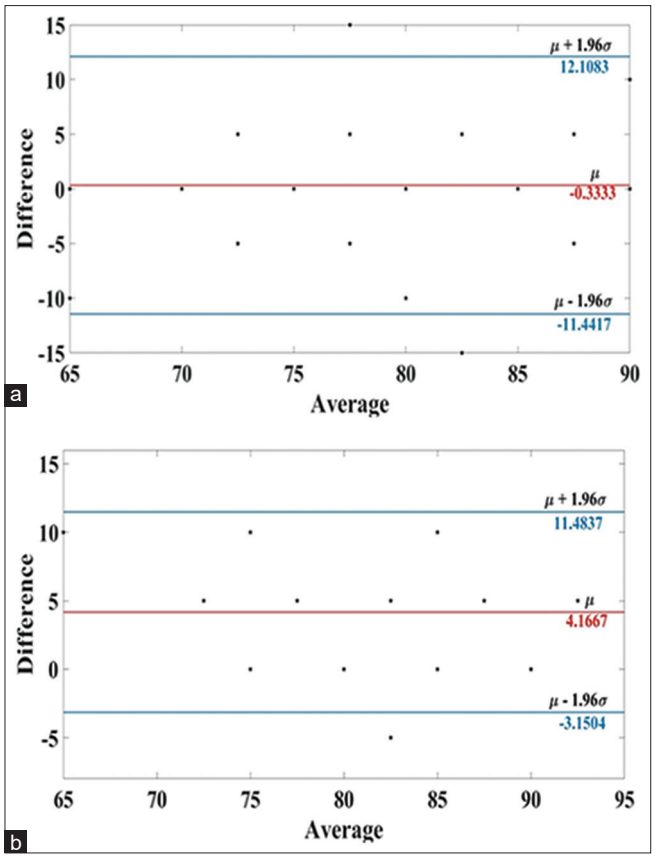

Figure S3: Bland–Altman analysis for intraobserver repeatability for grading the segmentation by software twice by two observers: (a) Observer-1; (b) Observer 2

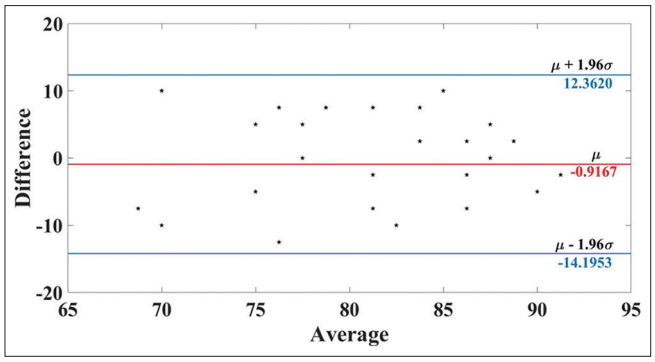

Figure S4: Bland–Altman analysis for interobserver repeatability for grading the segmentation by software twice by two observers

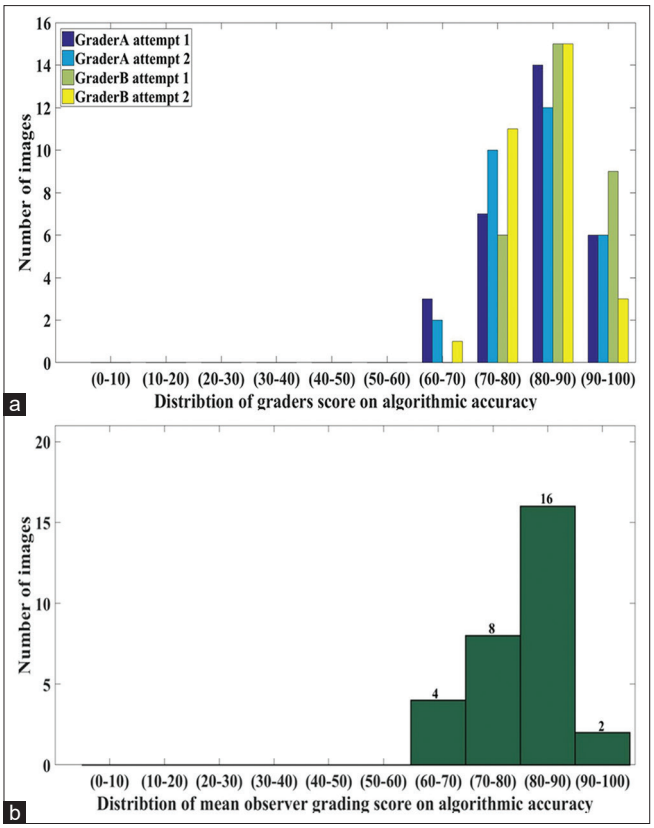

Figure S5: Statistical analysis: Distribution of grader scores performed twice by two observers: (a) Two attempts by each of the two graders, grader-A and grader-B; (b) Average of all attempts by both the graders