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Objective quantification of lens nuclear opacities using swept-source anterior segment optical coherence tomography

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ABSTRACT

Background/aims The primary objective is to quantify the lens nuclear opacity using swept-source anterior segment optical coherence tomography (SS-ASOCT) and to evaluate its correlations with Lens Opacities Classification System III (LOCS-III) system and surgical parameters. The secondary objective is to assess the diagnostic performance for hard nuclear cataract.

Methods This cross-sectional study included 1222 patients eligible for cataract surgery (1222 eyes). The latest SS-ASOCT (CASIA-2) was used to obtain high-resolution lens images, and the average nuclear density (AND) and maximum nuclear density (MND) were measured by a custom ImageJ software. Spearman's correlations analysis was used to assess associations of AND/MND with LOCS-III nuclear scores, visual acuity and surgical parameters. The subjects were then split randomly (9:1) into the training dataset and validating dataset. Receiver operating characteristic curves and calibration curves were constructed for the classification on hard nuclear cataract.

Results The AND and MND from SS-ASOCT images were significantly correlated with nuclear colour scores (AND: r=0.716; MND: r=0.660; p<0.001) and nuclear opalescence scores (AND: r=0.712; MND: r=0.655; p<0.001). The AND by SS-ASOCT images had the highest values of Spearman's r for preoperative corrected distance visual acuity (r=0.3131), total ultrasonic time (r=0.3481) and cumulative dissipated energy (r=0.4265). The nuclear density had good performance in classifying hard nuclear cataract, with area under the curves of 0.859 (0.831–0.886) for AND and 0.796 (0.768–0.823) for MND.

Conclusion Objective and quantitative evaluation of the lens nuclear density using SS-ASOCT images enable accurate diagnosis of hard nuclear cataract.

Classification and quantification of cataract are of vital importance for estimating its prevalence in epidemiological studies, assessing its severity and progression, and making decision in clinical practice.[1] Currently, the Lens Opacities Classification System III (LOCS-III) system is the standard and widely used protocol, in which grading is achieved by comparing the lens images under slit lamp with reference lens images. Hard nuclear cataracts with nuclear opalescence (NO) scores 5 or greater on LOCS-III system were common in developing countries, which poses substantial challenge for phacoemulsification.[2] Accurately grading the degree of lens nuclear opacity is thus essential for preparing operation.[3]

The ideal lens grading system should be objective and repeatable, but the repeatability of LOCS-III was limited as it was graded subjectively and depended on experience of the graders.[4] Furthermore, only integer scores of the scale were provided by the reference lens images, but decimal scores were assigned to the grading lens images.[5] There have been efforts to quantitatively grade the lens opacities using lens density measurement, such as Scheimpflug imaging system Pentacam and swept-source optical coherence tomography (OCT) IOL-Master 700.[6] However, the entire area of lens cannot be imaged clearly in Pentacam, and the resolution of lens images remains relatively low in these devices.[6 7]

The swept-source anterior segment OCT (SS-ASOCT) is a newly developed imaging modality with greater scanning depth and faster scanning speed, which enables the visualisation of the entire angle and lens in a single image, as well as the objective measurement of lens density.[8] However, whether it was applicable for accurately quantifying nuclear opacities remains unknown.[9–11] Therefore, the primary objective of this study was to quantify lens nuclear density using SS-ASOCT, and to evaluate the associations of lens density with LOCS-III scores, visual function and phacoemulsification parameters. The secondary objective was to assess the performance of lens density measurement in diagnosing hard nuclear cataract.

MATERIALS AND METHODS

Participants

This cross-sectional study was performed at the Zhongshan Ophthalmic Center (ZOC) affiliated Sun Yat-sen University. All participants have been given detailed explanations and signed written informed consents before entering the study. The adult patients with cataract planning for phacoemulsification were eligible for this study during the period between August 2019 and June 2020. Patients with any evidence of the following conditions were excluded: previously ocular surgery or laser treatment; history of intravitreal steroid or anti-vascular endothelial growth factor

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agents; history of ocular trauma; other ocular diseases such as keratoconus, glaucoma and retinal detachment; corneal opacities caused by leucoma, pterygium and other diseases; poor fixation leading to low image quality or inability to cooperate with examinations; failure to complete examinations in compliance with study protocol; lens dislocation or complicated cataract surgery (any complications during/after the operations). Patients were also excluded when there was evidence of glaucoma or retinal diseases during postoperative examinations.

Ocular examinations and data collection

All participants underwent comprehensively ocular examinations, including visual acuity and refraction, slit-lamp and fundus examinations, ocular biometry obtained by IOL-Master 700 (IOL-Master, Zeiss, Germany), ocular ultrasonography, lens photography and intraocular pressure (IOP). All ocular examinations were performed by experienced optometrists and ophthalmologists. All participants received phacoemulsification and intraocular lens implantation according to the standard of procedures in ZOC. The data of total ultrasonic time and cumulative dissipated energy (CDE) were collected by using standardised forms.

Lens opacities grading according to LOCS-III

The pupil of the affected eye was dilated by administrating 0.5% tropicamide plus 0.5% phenylephrine drops. After the maximumly pupil dilation, the lens photography was imaged in dark conditions using slit-lamp digital cameras. Two experienced ophthalmologists (XG, XR) who were masked with patients' information graded all the eyes according to LOCS-III criteria, and a senior expert of cataract made the final diagnosis when discrepancy existed. Under standardised conditions, the grader assigned scores to the degree of NO and nuclear colour (NC) on a scale of 0.1–6.9, and scores to cortical opacity and posterior subcapsular opacity on a scale of 0.1–5.9. In this study, only NO and NC scores were adopted to evaluate associations with SS-ASOCT measurements.

SS-ASOCT imaging and nuclear density quantification

The latest commercial SS-ASOCT (CASIA-2; Tomey Corporation, Nagoya, Japan) was used for lens imaging. An experienced technician (LW) performed the lens imaging by adopting the lens high-definition protocol. After pupil dilation, the patients seated in the dark room with eyes fixated on the external lights during the examination. The scans were focused on the central lens to obtain a clear cross-sectional image of anterior segment from the nasal quadrant to the temporal quadrant. The examiner adjusted the device during the examination to acquire the best quality images. Images with poor quality, motion artefacts and data loss due to blinking were excluded.

The SS-ASOCT nuclear density was measured by a masked grader (JZ) using ImageJ software (http://rsb.info.nih.gov/ij; National Institutes of Health, Bethesda, Maryland, USA). The procedures of nuclear density quantification by ImageJ have been described in previous studies.[7 12–15] In brief, we manually outline the lens nucleus, then the nucleus was automatically measured in pixel intensity units ranged from 0 (pure black) to 255 (pure white). The average nuclear density (AND) and maximum nuclear density (MND) were the average and the maximum pixel intensity in the entire area of nucleus, respectively.

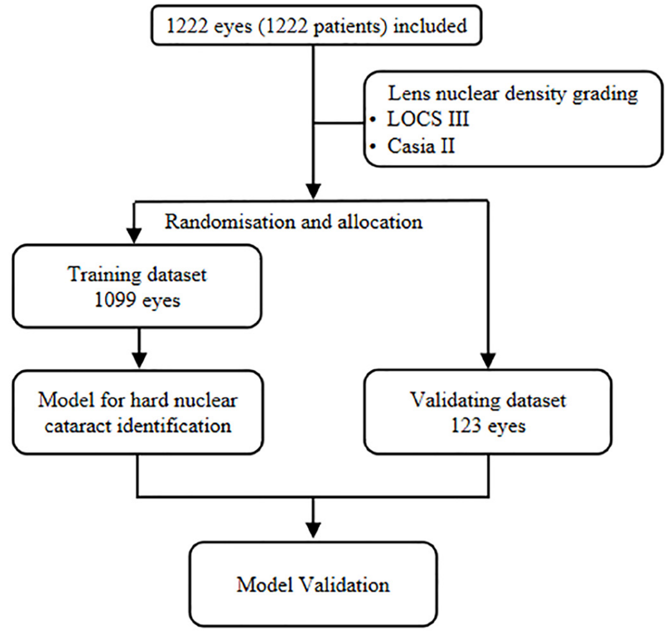

Figure 1 Flow diagram. LOCS-III, Lens Opacities Classification System III.

Statistical analyses

The participants were split randomly (9:1) into training dataset and validating dataset using random number generated by computer. All data were presented as mean (SD) or number (per cent). Kolmogorov-Smirnov was used to test the normal distribution. Spearman's correlation analysis was used to evaluate the associations of LOCS-III values with AND and MND from the SS-ASOCT images, and their associations with the visual acuity and phacoemulsification parameters in training dataset. Receiver operating characteristic curves were plotted for AND or MND in diagnosing hard nuclear cataract (NO score ≥5).[2] The Youden Index method was used to determine the cut-off threshold with optimised sensitivity and specificity. The calibration curves and Hosmer-Lemeshow test were used to evaluate the performance of calibration in diagnosing hard nuclear cataract based on AND or MND. The logistic analysis was performed to calculate the OR and 95% CI of AND or MND for hard nuclear cataract in training dataset, and a discriminant function was constructed. The discriminant function was used to predict the classification of eyes in validating dataset. For the prediction in validating dataset, the area under the curve (AUC), accuracy, sensitivity and specificity were calculated. All data analyses were done using Stata MP V.14.0 (StataCorp, College Station, Texas, USA). A value of $p<0.05$ was considered to have statistical significance.

RESULTS

Figure 1 shows the flow chart of the study. A total of 1222 patients (1222 eyes) were included in this study, with 1099 (90%) and 123 (10%) in training and validating dataset, respectively. Table 1 shows the demographic and clinical characteristics of the included patients. There were 665 women (54.38%), with a mean age of 65.2±11.7 years. Before surgery, mean corrected distance visual acuity (CDVA) and mean axial length (AL) were 0.84±0.56 logMAR (logarithmic minimal angle resolution) and 24.37±2.41 mm, respectively. At 1 week after operation, the uncorrected distance visual acuity (UDVA) and IOP were 0.30±0.57 logMAR and 14.14±4.78 mm Hg, respectively. The

Table 1 Demographic and clinical features of the included patients

Variables	All	Training set (90%)	Validating set (10%)	P value
No of subjects (eyes)	1222 (1222)	1099 (1099)	123 (123)	
Age (year)	65.25±12.75	65.28±12.66	64.92±13.64	0.799
Female (%)	665 (54.38)	604 (54.99)	60 (48.86)	0.274
Systemic hypertension (%)	403 (33.09)	366 (33.30)	38 (31.15)	0.631
CDVA preoperation (logMAR)	0.84±0.56	0.85±0.56	0.81±0.55	0.476
IOP preoperation (mm Hg)	11.75±3.15	11.72±3.16	12.03±3.05	0.302
Axial length (mm)	24.37±2.41	24.36±2.39	24.51±2.52	0.580
Anterior chamber depth (mm)	3.19±0.45	3.19±0.45	3.18±0.44	0.885
Lens thickness (mm)	4.48±0.51	4.48±0.50	4.48±0.56	0.915
Corneal diameter (mm)	11.84±0.54	11.83±0.54	11.90±0.49	0.278
Total ultrasonic time (seconds)	53.24±99.64	54.26±104.53	44.14±31.86	0.317
Cumulative dissipated energy (%-seconds)	1165.27±1885.04	1200.18±1967.23	856.26±808.25	0.072
UDVA postoperation (logMAR)	0.30±0.57	0.31±0.58	0.27±0.48	0.520
IOP postoperation (mm Hg)	14.14±4.78	14.11±4.70	14.38±5.43	0.597

Data were presented as mean±SD or number (%).
CDVA, corrected distance visual acuity; IOP, intraocular pressure; logMAR, logarithmic minimal angle resolution; UDVA, uncorrected distance visual acuity.

patients in training and validating sets had similar demographic and clinical features (all $p>0.05$).

Online supplemental table 1 shows the distribution of LOCS-III scores. The average NC and NO scores were 3.9±1.4 and 3.9±1.5 (ranging from 1.00 to 6.90), respectively. The distribution of LOCS-III scores did not differ between the training and validating dataset (all $p>0.05$). For SS-ASOCT nuclear density measurements, the AND and MND were 33.82±6.95 and 103.04±22.78, respectively. Figure 2 exhibits the large range of SS-ASOCT than LOCS-III score, with NC increase by 0.6 scores, but nuclear density can change by 7–20 pixel-unit.

Figure 2 shows the correlations of nuclear density measured by SS-ASOCT with LOCS-III scores. The AND from SS-ASOCT images was significantly correlated with NC score ($r=0.716$, $p<0.001$) and NO scores ($r=0.712$, $p<0.001$). Similarly, the MND was positively correlated with NC score ($r=0.660$, $p<0.001$) and NO scores ($r=0.655$, $p<0.001$).

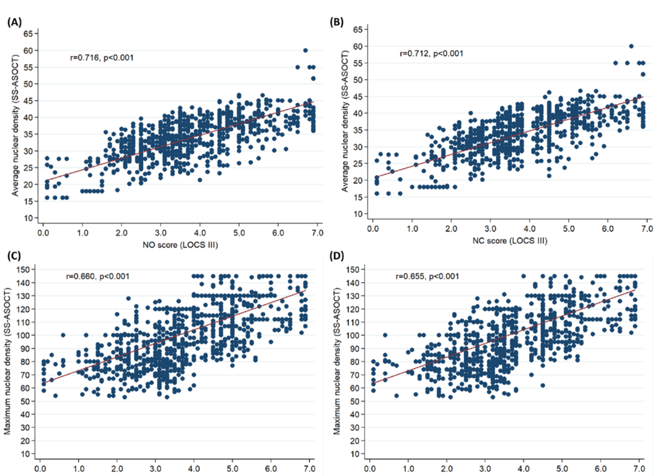

Figure 2 Scatter plots showing the correlations of SS-ASOCT nuclear density quantitated by ImageJ software in pixel intensity units with LOCS-III scores (n=1099). (A) Maximum nuclear density versus NC score; (B) maximum nuclear density versus no score; (C) average nuclear density versus NC score; (D) average nuclear density versus no score. NC, nuclear colour; NO, nuclear opalescence; LOCS-III, Lens Opacities Classification System III; SS-ASOCT, swept-source anterior segment optical coherence tomography.

Table 2 illustrates the correlations of nuclear density measured by SS-ASOCT and nuclear scales by LOCS-III system with visual acuity and phacoemulsification energy. With the exception of NC scores versus UDVA at 1 week postoperatively, both NC and NO scores were significantly associated with the CDVA preoperation, UDVA postoperation, total ultrasonic time and CDE, with the Spearman's ρ ranging from 0.0782 to 0.3784 (all $p<0.05$). Both the AND and MND by SS-ASOCT were significantly associated with all these parameters (all $p<0.05$). The AND by SS-ASOCT images had the highest values of Spearman's r for CDVA preoperative ($r=0.3131$), total ultrasonic time ($r=0.3481$) and CDE ($r=0.4265$), whereas MND had the highest correlation with UDVA at 1-week postoperation ($r=0.1945$).

Online supplemental table 2 shows the visual acuity and phacoemulsification parameters between hard cataract and non-hard cataract in training dataset (n=1099). The hard cataract group had poor visual acuity at baseline, larger phacoemulsification time and stronger CDE than non-hard cataract (all $p<0.001$). Both groups had similar visual acuity at 1 week postoperatively ($p=0.748$).

Figure 3 shows the performance of nuclear density in classifying hard nuclear cataract, with AUCs of 0.859 (0.831–0.886) for AND and 0.796 (0.768–0.823) for MND. A cut-off of 36.199 for AND distinguished patients with and without hard nuclear cataract with a sensitivity of 83.0% and a specificity of 73.0%. The calibration analysis showed good relationship between observed and predicted events (Hosmer-Lemeshow test, $p=0.706$). Regarding the MND, the optimised threshold was 111 (sensitivity 74.0%; specificity 72.0%).

By adoption of the above cut-off threshold in validating dataset, the accuracy of AND was 88.04%, with a sensitivity of 88.89% and a specificity of 85.00%. For MND over 111 unit, the accuracy for classifying hard nuclear cataract was 78.86%, with a sensitivity of 77.32% and a specificity of 84.62%. The calibration plots demonstrated good agreement in the validation sets (online supplemental figure 2).

DISCUSSION

This study demonstrated that the nuclear density measurements based on SS-ASOCT were closely correlated with LOCS-III

Table 2 Spearman's correlation analyses of LOCS-III scores and nuclear density measured by SS-ASOCT images with visual acuity and phacoemulsification parameters in training dataset (n=1099)

	NO score (LOCS-III)		NC scores (LOCS-III)		Average nuclear density (SS-OCT)		Maximum nuclear density (SS-OCT)	
	R	P value*	R	P value*	R	P value*	R	P value*
CDVA at baseline (logMAR)	0.2623	**<0.001**	0.2655	**<0.001**	0.3131	**<0.001**	0.2445	**<0.001**
UDVA at 1 week postoperatively (logMAR)	0.0782	**0.0314**	0.0605	0.096	0.1198	**0.008**	0.1945	**<0.001**
Total US time (seconds, log scale)	0.2965	**<0.001**	0.3015	**<0.001**	0.3481	**<0.001**	0.2347	**<0.001**
CDE (%-seconds, log scale)	0.3734	**<0.001**	0.3784	**<0.001**	0.4265	**<0.001**	0.2439	**<0.001**

*Bold indicates statistically significant.
CDE, cumulative dissipated energy; CDVA, corrected distance visual acuity; LOCS-III, Lens Opacities Classification System III; logMAR, logarithmic minimal angle resolution; NC, nuclear colour; NO, nuclear opalescence; SS-ASOCT, swept-source anterior segment optical coherence tomography; UDVA, uncorrected distance visual acuity; US, ultrasonic.

scores, visual acuity and phacoemulsification ultrasonic energy. In eyes with an AND ≥36.199 pixel-units, hard nuclear cataract is reasonably suspected and cautions should be given during the management of cataract. The novel nuclear density measurements on SS-ASOCT images might be used as objective and reliable indices for quantification of lens nucleus opacities.

Our results are highly consistent with previous validated methods by measuring the intensity of light scattering and lens opacity using lens images through optical densitometric method.[13 14 16] The nuclear density on Pentacam Scheimpflug images was demonstrated to be correlated with CDVA, contrast sensitivity and LOCS-III scores.[17 18] However, it is highly difficult for Scheimpflug imaging to delineate the borderline of the nucleus from the posterior cortex and posterior capsule, especially for advanced cataracts because light is absorbed.

The recent studies also reported positive association between nuclear density on IOL-Master 700 images and LOCS-III scores, but the visualisation of lens had relatively low resolution.[6 7 12] The IOL-Master 700 used a swept-source light with the centre wavelength of 1055 nm designed for biometer, which achieves an axial resolution of 22 µm in tissue at a speed of 2000 A-scans/s. Compared with IOL-Master 700, the CASIA-2 adopted a longer light (1310 nm) with greater penetration, and achieved higher resolution (≤10 µm) and quicker scan speed (50 000 A-scans/s), enables clear imaging of the posterior cortex and posterior capsule with high resolution. To the best of our knowledge, this is the first study to confirm the correlation between lens density by SS-ASOCT and LOCS-III grading scores.

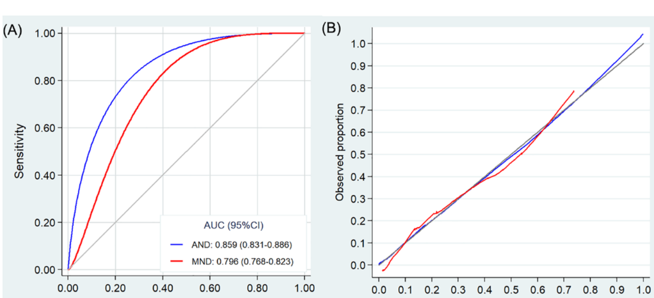

Figure 3 Receiver operating characteristic (ROC) curve and calibration curve for diagnosis of hard nuclear cataract (LOCS-III NO score ≥5.0) in training dataset (n=1099). (A) The ROC curve showing excellent discriminative power of AND and MND for diagnosing hard nuclear cataract. (B) The calibration plot showed good calibration between the observed and predicted proportion of hard nuclear cataract. AND, average nuclear density; AUC, area under the curve; LOCS-III, Lens Opacities Classification System III; MND, maximum nuclear density; NO, nuclear opalescence.

SS-ASOCT has the potential to be extensively applied in eye health examinations and effective screening of patients with cataract. It is easy and fast to evaluate lens opacity objectively and quantitatively, for which the learning curve is relatively low. This is the opposite to slit-lamp-based grading system, which is affected even by the setting of the slit lamp. In addition, neither the active involvement of the patients (as visual acuity test) nor the experience of experts (as LOCS-III grading) is required due to the relying on greyscale measurements on SS-ASOCT images. The integer scale in the LOCS-III grading system is also very difficult to use in longitudinal studies, which might neglect mild differences.[4 19] In this study, the range of the measured MND was from 50.00 to 145.00 (NO score of 1.0–6.9 correspondingly). With this larger range, SS-ASOCT can be used as a sensitive tool to detect the longitudinal changes of lens density. As shown in online supplemental figure 1, similar LOCS-III score remains had substantial variation range for SS-ASOCT measurements.

As expected, longer phacoemulsification time and greater energy are needed for harder nucleus.[3] This study was consistent with the results of previous studies based on LOCS-III grading system and Pentacam grading system.[20] It was reported that greater ultrasound energy was needed with the increase of NO and NC scores.[3] There was a linear relationship between the CDE and the MND measured by Pentacam Scheimpflug system.[21] The current study also observed a linear relationship among the total ultrasonic time, CDE and nuclear density measurements by SS-ASOCT. Interestingly, the CDE had stronger correlations with the lens density by SS-ASOCT than with the LOCS-III NO or NC scores (table 2). These findings indicate that nuclear density by SS-ASOCT might be an excellent indicator for adjusting surgical parameters at the beginning of the surgery.

Though cut-off thresholds have determined for previous objective indices such as mean Pentacam nucleus staging (PNS) and objective scatter index (OSI) in diagnosing cataract, the accurate detection of hard nuclear cataract is far established. For example, a cut-off threshold of 11% for mean was suggested to distinguish between healthy and cataract eyes. In our study, an AND of ≥36.199 pixel-units suggested the presence of hard nuclear cataract, with a sensitivity of 83.0% and a specificity of 73.0%. Our proposed cut-off threshold best accounted for the sensitivity and specificity. Only nuclear density measurement was included in the discriminant analysis, and other parameters such as visual acuity were excluded in the stepwise multivariable modelling process. The calibration analysis confirmed the good performance. Therefore, using the objective nuclear measurements on SS-ASOCT alone can effectively detect hard nuclear cataract. Future incorporation of automated calculator within the CASIA-2 device will significantly increase the clinical utility of this tool.

The strength of this study lies in the large sample size, homogeneous Chinese patients and pragmatic examinations. This study also has limitations. First, pupil dilation is required to maximise lens exposure for visualisation of the entire lens by SS-ASOCT. Second, this study was a single-centre study of only Chinese patients, the findings cannot be directly generalised to non-Chinese ethnicity. Further studies with various ethnicities are warranted. Third, the UDVA 1 week postoperatively was used in the present study. Further studies with postoperative stable CDVA are preferred.

CONCLUSIONS

In summary, the SS-ASOCT represents an excellent tool for objective and quantitative evaluation of the lens opacity, which helps to assess cataract progression in clinical and research settings and predict ultrasonic energy in phacoemulsification surgery.

Contributors WW, ZL and LL designed the research. JZ, XG, XR, XC, XT, GJ and LW collected and analysed the data. WW wrote the manuscript. JZ, MH, ZL, LL and YL critically revised the manuscript. All authors discussed the results and provided comments regarding the manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplemental information.

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