Detection of primary angle closure suspect with different mechanisms of angle closure using multivariate prediction models

Ye Zhang,† Zhe Dong,† Qing Zhang, Lei Li, Ravi Thomas, Si Zhen Li, Ming Guang He and Ning Li Wang

ABSTRACT.

Purpose: We had found that a multivariate prediction model used for the detection of primary angle-closure suspects (PACS) by combining multiple static and dynamic anterior segment optical coherence tomography (ASOCT) parameters had an area under the receiver operating characteristic curve (AUC) of 0.844. We undertook this study to evaluate this method in screening of PACS with different dominant mechanisms of angle closure (AC).

Methods: The right eyes of subjects aged ≥40 years who participated in the 5-year follow-up of the Handan Eye Study and had undergone gonioscopy and ASOCT examinations under light and dark conditions were included. All ASOCT images were analysed by the Zhongshan Angle Assessment Program. The dominant AC mechanism in each eye was determined to be pupillary block (PB), plateau iris configuration (PIC) or thick peripheral iris roll (TPIR). Backward logistic regression (LR) was used for inclusion of variables in the prediction models. LR, Naïve Bayes’ classification (NBC) and neural network (NN) were evaluated and compared using the AUC.

Results: Data from 796 subjects (413 PACS and 383 normal eyes) were analysed. The AUCs of LR, NBC and NN in the PB group were 0.920, 0.918 and 0.917. The AUCs of LR, NBC and NN in the PIC group were 0.715, 0.708 and 0.707. The AUCs of LR, NBC and NN in TPIR group were 0.867, 0.833 and 0.886.

Conclusions: Prediction models showed the best performance for detection of PACS with PB mechanism for AC and have potential for screening of PACS.

Key words: primary angle-closure suspect – screening – angle-closure mechanisms – static and dynamic ASOCT parameters – prediction models

Introduction

Glaucoma is a leading cause of irreversible blindness worldwide, and primary angle-closure glaucoma (PACG) is a major cause of visual impairment in Asia, especially in China (Quigley et al. 2006; Tham et al. 2014). With 10 million people estimated to be affected with PACG in China by 2020 (about 48% of the total worldwide), the disease will be a serious challenge for healthcare systems in our country (Quigley et al. 2006).

The definition of primary angle-closure disease (PACD) and the diagnosis of primary angle-closure suspect (PACS), primary angle closure (PAC) and primary angle-closure glaucoma (PACG) were based on the criteria established by the International Society of Geographic and Epidemiologic Ophthalmology (ISGEO) (Foster et al. 2002).

Vision loss resulting from PACG cannot be reversed; it is therefore essential to detect the early asymptomatic stage of the disease (PACS) and perform prophylactic laser iridotomy to prevent damage to the optic nerve and irreversible visual impairment (Weinreb et al. 2006; Tham et al. 2014).

Gonioscopy is the gold standard examination for opportunistic case
identification of eyes with gonioscopic PACS. While this is a good AUC, it is still not ideal for population-based screening. A possible reason for this was considered to be different angle-closure mechanisms of PACS eyes enrolled in that study.

The aim of this investigation was to evaluate three prediction models to detect PACS with different dominant AC mechanisms including pupillary block (PB), plateau iris configuration (PIC) and thick peripheral iris roll (TPIR), based on static and dynamic ASOCT parameters.

**Methods**

This was a cross-sectional observational study conducted with the approval of the Ethics committee of the Beijing Tongren Hospital. We adhered to the tenets of Declaration of Helsinki, and informed consent was obtained from all participants.

Subjects aged ≥40 years who participated in the five-year follow-up examination of the Handan Eye Study (HES) between June 2012 and May 2013, with limbal anterior chamber depth ≤40%, and had undergone gonioscopic examination and ASOCT imaging under light and dark conditions were eligible for inclusion.

Patients were excluded if they had a history of use of eyedrops that could influence the anterior chamber angle, intraocular surgery, laser treatment, eye trauma and ocular surface disorders, such as corneal opacity, pterygium or other abnormalities that precluded ASOCT imaging. Eyes with peripheral anterior synchia (PAS), raised intraocular pressure (IOP), cup-disc ratio ≥0.6 or presence of typical glaucomatous optic neuropathy (GON), secondary AC, and past history of acute angle-closure (AAC) attack were also excluded. Other exclusion criteria were inability to fixate on the target, or general physical or mental impairment that precluded participation in the testing.

All participants underwent a comprehensive ophthalmic examination including presenting visual acuity (PVA) and best-corrected visual acuity (BCVA) measurement using a logarithm of minimum-angle-of-resolution chart (LogMAR E chart), auto-refraction (Topcon KR-8800, Topcon Corporation, Tokyo, Japan), slit-lamp examination, IOP using Kowa applanation tonometry, A-scan ultrasound biomicroscopy using an OcuScan RxP (Alcon, Inc., Fort Worth, TX, USA) and stereoscopic optic-disc examination with a 90-dioptre lens (Volk Optical Inc., Mentor, OH, USA).

**Gonioscopy**

Gonioscopy was performed in the dark in all enrolled subjects by one of two glaucoma specialists (ZP and YSH) who were masked to imaging findings. Static gonioscopy was performed using a Goldmann one-mirror lens at a magnification of ×16 with the eye in the primary position of gaze. Care was taken to avoid light falling on the pupil and to avoid inadvertent indentation during examination. Dynamic examination (manipulation) then was performed using the same lens. Primary angle-closure suspects (PACS) was diagnosed if ≥180° of the posterior trabecular meshwork was not visible on static gonioscopy.

**ASOCT imaging and measurement**

The Visante ASOCT (Carl Zeiss Meditec Inc., Dublin, CA, USA) obtains scans at a rate of 2000 A-scans per second, with an axial and transverse resolution of 18 and 60 µm, respectively (Quek et al. 2011).

Subjects underwent ASOCT imaging first under dark conditions (~3 lux, to induce physiologic mydriasis) after allowing dark adaptation for at least 3 min prior to examination without the use of any mydriatics followed by imaging under light conditions (~200 lux). The scans were performed by a single trained examiner who was masked to the gonioscopy results. During ASOCT scanning, an internal fixation target was used with the subjects’ refractive correction in place to perform the measurements in an unaccommodated state.

All images were obtained in the ‘anterior segment quadrant’ mode at 0°–180°, 45°–225°, 90°–270°, and 135°–315° meridians. Due to interference from the eyelids with image acquisition of the ACA at 6 and 12 o’clock, the lower lid was gently retracted by the operator to image the inferior angle and the upper lid was elevated gently to image the superior angle; care was taken to avoid pressure on the globe.
Acta Ophthalmologica 2021

Imaging was repeated if the scleral spur visibility was poor.

A customized software, the Zhongshan Angle Assessment Program (ZAAP, Guangzhou, China), was used to process the ASOCT images (Console et al. 2008). For each image, one ophthalmologist (ZY) determined the location of the 2 scleral spurs, described as the inward protrusion of the sclera with a change in curvature of its inner surface (Sakata et al. 2008). The algorithm then automatically calculated parameters, including angle opening distance at 500 μm (AOD500), trabecular-iris space area at 500 μm (TISA500), angle recess area at 750 μm (ARA750), anterior chamber depth (ACD), anterior chamber area (ACA), anterior chamber volume (ACV), anterior chamber width (ACW), iris thickness at 750 μm (IT750), iris curvature (IC) and iris cross-sectional area (IA), lens vault (LV), and pupil diameter (PD) (Console et al. 2008).

The AOD500 was measured as the perpendicular distance between anterior iris surface and a point at trabecular meshwork at 500 μm anterior to the scleral spur (Salim 2012). The TISA500 was measured as an area bounded anteriorly by the AOD500, posteriorly by a line drawn from the scleral spur perpendicular to the plane of the inner scleral wall to the opposing iris, superiorly by the inner corneoscleral wall and inferiorly by the iris surface (Salim 2012). The ARA750 is the area of the angle recess bounded anteriorly by the anterior iris surface, corneal endothelium and a line perpendicular to the corneal endothelium drawn to the iris surface from a point at 750 μm anterior to the scleral spur (Salim 2012).

The ACD was measured as the perpendicular distance from the corneal endothelium at the corneal apex to the anterior lens surface (Salim 2012). The ACA was defined as the cross-sectional area of anterior segment bounded by the corneal endothelium, the anterior surface of the iris and the anterior surface of the lens (within the pupil) (Wang et al. 2012). The algorithm plots a vertical axis through the midpoint (centre) of the anterior chamber area, and by rotating the anterior chamber area 360 degrees around this vertical axis, calculates the ACV (Wang et al. 2012). The ACW was defined as the horizontal scleral spur–to-spur distance (Nongpiur et al. 2010).

The IT750 was the iris thickness measured at 750 μm from the scleral spur, and the IC was determined by measuring the maximum distance between the posterior iris surface and a line from the iris root to the first point of contact between the iris and lens (Wang et al. 2013). The LV was the perpendicular distance between the anterior pole of the crystalline lens and the horizontal line joining the 2 scleral spurs (Nongpiur et al., 2011a).

The IA was calculated as the cross-sectional area of the full length (from spur to pupil) of the iris (Sun et al. 2012). Iris cross-sectional area (IA) change was calculated as IA in light minus IA in dark, and PD change was calculated as PD in dark minus PD in light. Iris cross-sectional area (IA) change/PD change was calculated as IA change divided by PD change.

Categories of angle-closure mechanisms

Four ASOCT images from each PACS eye obtained in the dark with clearly discernible scleral spurs were analysed qualitatively and categorized into one of three AC mechanisms: PB, PIC and TPIR (Figs 1, 2 and 3). Where the image suggested more than one mechanism for AC, a forced choice was made to select the dominant mechanism without the benefit of other information. The AC mechanism that was identified in at least two ASOCT images of each PACS eye was determined to be predominant AC mechanism of that eye. The detailed guidelines of the three AC mechanism categorizations based on ASOCT images and the reproducibility of AC mechanism categories based on ASOCT and ultrasound biomicroscopy (UBM) images are described elsewhere (Zhang et al. 2015; Zhang et al. 2016).

Statistical analysis

Data from right eyes of all the enrolled subjects were analysed using the Statistical Analysis System (SAS) version 9.4 (SAS Institute, Cary, NC, USA). For continuous variables, data were first examined by Kolmogorov–Smirnov test for the normality of distribution. Variables demonstrating a normal distribution were presented as mean (standard deviation, SD), while variables failing to achieve a normal distribution were presented as median (percentiles). For those variables with a normal distribution, analysis of variance (ANOVA) was used to compare the
The difference between four groups: normal subjects and PACS patients with the three different AC mechanisms. Bonferroni correction was used to adjust p-values for multiple pair-wise comparisons of normally distributed variables. The Kruskal–Wallis test for unpaired data was used to compare variables which were not normally distributed and to determine differences between the four groups. The Mann–Whitney U-test was used to compare the normal group and PACS groups with PB, PIC or TPIR, respectively. A p value < 0.05 was considered statistically significant.

**Variable selection**

Normal subjects were classified as negative outcomes. For each PACS group with PB, PIC or TPIR, logistic regression (LR) analysis (Backward) was used for inclusion of variables in the prediction models from the following 12 parameters under dark and light conditions: AOD500, TISA500, ARA750, IT750, IC, LV, ACD, ACW, ACA, ACV, IA and PD. And plus two calculated parameters of changes in dark and light conditions including IA change and IA change/ PD change, there were a total of 26 candidate parameters for inclusion of variables in the prediction models. First of all, we used the univariate LR analysis (Backward) on the 26 ASOCT parameters and excluded the variables with a p value more than 0.1. Then, in order to avoid the obvious correlations between the independent variables, we designed four combinations of variables for multivariate LR analysis (Backward) to build the models for each PACS group with different...

**Table 1.** Demographic and ocular bircometric data of PACS subjects with different angle-closure mechanisms and normal subjects.

| Parameter                | 1 = PB (n = 141) | 2 = PIC (n = 147) | 3 = TPIR (n = 125) | 0 = Normal Subjects (n = 383) |
|--------------------------|------------------|-------------------|--------------------|--------------------------------|
| Age, median (IR), years  | 64.0 (59.0, 70.0)| 60.0 (55.0, 64.0)| 62.0 (57.0, 66.5)| 61.0 (56.0, 66.0) |
| Male (%)                 | 36 (25.5)        | 48 (32.7)         | 43 (34.4)          | 145 (37.9) |
| Female (%)               | 105 (74.5)       | 99 (67.3)         | 82 (65.6)          | 238 (62.1)  |
| PVA, median (IR)         | 0.34 (0.20, 0.50)| 0.20 (0.08, 0.40)| 0.30 (0.14, 0.44)| 0.20 (0.10, 0.32)|
| BCVA, median (IR)        | 0.10 (0.00, 0.21)| 0.00 (0.00, 0.15)| 0.10 (0.00, 0.17)| 0.00 (0.00, 0.16)|
| SE, median (IR), dioptre | 1.00 (0.13, 1.75)| 0.75 (0.00, 1.50)| 0.63 (0.00, 1.50)| 0.50 (0.13, 1.13)|
| IOP, median (IR), mmHg   | 11.3 (10.0, 13.0)| 12.0 (10.0, 13.5)| 12.0 (10.0, 13.0)| 12.0 (10.0, 13.5)|
| CCT, median (IR), μm     | 527 (512, 544)   | 528 (514, 552)   | 530 (514, 548)    | 528 (513, 546)  |
| Central ACD, median (IR), mm | 2.44 (2.30, 2.68)| 2.58 (2.43, 2.84)| 2.47 (2.31, 2.71)| 2.71 (2.49, 2.92) |
| LT, median (IR), mm      | 4.97 (4.69, 5.16)| 4.73 (4.39, 4.94)| 4.90 (4.48, 5.15)| 4.78 (4.48, 5.07) |
| AL, median (IR), mm      | 22.19 (21.81, 22.75)| 22.29 (21.89, 23.15)| 22.23 (21.61, 22.80)| 22.73 (22.22, 23.25) |

ACD = anterior chamber depth, AL = axial length, BCVA = best-corrected visual acuity, CCT = central corneal thickness, IOP = intraocular pressure, IR = interquartile range, LT = lens thickness, PB = pupillary block, PIC = plateau iris configuration, PVA = presenting visual acuity, SE = spherical equivalent, TPIR = thick peripheral iris roll.

† Kruskal–Wallis test.
‡ χ² test.
§ Mann–Whitney test (<0.05/4 = 0.0125 = significant different).
### Table 2. ASOCT data of PACS subjects with different angle-closure mechanisms and normal subjects.

| Conditions | Parameter          | 1 = PB (n = 141) | 2 = PIC (n = 147) | 3 = TPIR (n = 125) | 0 = Normal Subjects (n = 383) | p value | p value (0 & 1) | p value (0 & 2) | p value (0 & 3) |
|------------|--------------------|------------------|-------------------|--------------------|-------------------------------|---------|----------------|----------------|----------------|
| Light      | AOD500, median (IR), mm | 0.210 (0.158, 0.281) | 0.285 (0.232, 0.363) | 0.217 (0.156, 0.292) | 0.339 (0.276, 0.434) | <0.001† | <0.001† | <0.001† | <0.001† |
|            | TISA500, median (IR), mm² | 0.095 (0.074, 0.118) | 0.090 (0.065, 0.122) | 0.142 (0.116, 0.177) | 0.320 (0.264, 0.374) | <0.001† | <0.001† | <0.001† | <0.001† |
|            | ARA750, median (IR), mm² | 0.262 (0.189, 0.344) | 0.309 (0.250, 0.378) | 0.227 (0.164, 0.310) | 0.390 (0.311, 0.475) | <0.001† | <0.001† | <0.001† | <0.001† |
|            | ACD, median (IR), mm    | 2.113 (1.964, 2.249) | 2.378 (2.243, 2.545) | 2.264 (2.104, 2.393) | 2.488 (2.325, 2.642) | <0.001† | <0.001† | <0.001† | <0.001† |
|            | ACW, median (IR), mm    | 10.79 (10.47, 11.06) | 11.02 (10.79, 11.28) | 10.85 (10.60, 11.10) | 11.12 (10.82, 11.43) | <0.001† | <0.001† | <0.001† | <0.001† |
|            | ACA, median (IR), mm²   | 14.72 (13.19, 15.92) | 17.13 (15.97, 17.84) | 15.84 (14.16, 17.08) | 18.27 (16.60, 19.82) | <0.001† | <0.001† | <0.001† | <0.001† |
|            | ACV, median (IR), mm³   | 56.25 (48.64, 63.11) | 67.83 (61.96, 75.40) | 59.49 (52.44, 66.87) | 73.89 (65.25, 82.40) | <0.001† | <0.001† | <0.001† | <0.001† |
|            | IT750, median (IR), mm  | 0.44 (0.39, 0.47)   | 0.45 (0.42, 0.48)   | 0.50 (0.47, 0.55)   | 0.44 (0.39, 0.48)   | <0.001† | <0.001† | <0.001† | <0.001† |
|            | IC, mean (SD), mm       | 0.30 (0.06)        | 0.24 (0.07)        | 0.25 (0.06)        | 0.24 (0.07)        | <0.001† | <0.001† | <0.001† | <0.001† |
| Dark       | AOD500, median (IR), mm | 0.176 (0.124, 0.231) | 0.258 (0.204, 0.328) | 0.178 (0.110, 0.260) | 0.307 (0.242, 0.383) | <0.001† | <0.001† | <0.001† | <0.001† |
|            | TISA500, median (IR), mm² | 0.075 (0.055, 0.099) | 0.103 (0.076, 0.128) | 0.068 (0.045, 0.101) | 0.127 (0.100, 0.156) | <0.001† | <0.001† | <0.001† | <0.001† |
|            | ARA750, median (IR), mm² | 0.191 (0.140, 0.256) | 0.257 (0.181, 0.327) | 0.168 (0.109, 0.256) | 0.322 (0.253, 0.405) | <0.001† | <0.001† | <0.001† | <0.001† |
|            | ACD, median (IR), mm    | 2.123 (1.967, 2.246) | 2.385 (2.255, 2.547) | 2.258 (2.080, 2.399) | 2.483 (2.329, 2.636) | <0.001† | <0.001† | <0.001† | <0.001† |
|            | ACW, median (IR), mm    | 10.93 (10.65, 11.19) | 11.03 (10.79, 11.30) | 10.91 (10.59, 11.14) | 11.11 (10.84, 11.39) | <0.001† | <0.001† | <0.001† | <0.001† |
|            | ACA, median (IR), mm²   | 15.16 (13.8, 16.43) | 17.54 (16.52, 18.99) | 15.97 (14.46, 17.45) | 18.61 (16.89, 20.27) | <0.001† | <0.001† | <0.001† | <0.001† |
|            | ACV, median (IR), mm³   | 58.01 (49.91, 64.93) | 69.70 (63.62, 77.25) | 60.14 (52.42, 69.20) | 74.57 (66.57, 83.86) | <0.001† | <0.001† | <0.001† | <0.001† |
|            | IT750, median (IR), mm  | 0.47 (0.41, 0.50)   | 0.48 (0.40, 0.51)   | 0.53 (0.50, 0.57)   | 0.47 (0.42, 0.51)   | <0.001† | <0.001† | <0.001† | <0.001† |
|            | IC, median (IR), mm     | 0.29 (0.25, 0.32)   | 0.23 (0.19, 0.28)   | 0.24 (0.21, 0.28)   | 0.24 (0.20, 0.28)   | <0.001† | <0.001† | <0.001† | <0.001† |
|            | LV, median (IR), mm     | 552.7 (422.0, 684.6) | 341.7 (204.6, 446.0) | 412.4 (276.2, 530.8) | 285.9 (18.5, 401.6) | 0.003† | <0.001† | <0.001† | <0.001† |

ACA = anterior chamber area, ACD = anterior chamber depth, ACV = anterior chamber volume, ACW = anterior chamber width, AOD500 = angle opening distance at 500 µm, ARA750 = angle recess area at 750 µm, IC = iris thickness at 750 µm, IR = interquartile range, IT750 = iris thickness at 750 µm, LV = lens vault, PB = pupillary block, PIC = plateau iris configuration, SD = standard deviation, TISA500 = trabecular-iris space at 500 µm, TPIR = thickness peripheral iris roll.

* One-way analysis of variance.
† Kruskal–Wallis test.
‡ Bonferroni.
§ Mann–Whitney test (<0.05/4 = 0.0125 = significant different).
detection of PACS with different AC mechanisms were developed by SAS 9.4 using the significant variables.

Neural network mimics the brain’s information processing system, which involves complex neuron connections and complex computations (Hassoun 1995). Neural network (NN) consists of multiple linear regression models are advantageous when there is a large number of variables with complex relations among them (Dreiseitl et al. 2002). For each PACS group, significant variables selected were used as inputs and 1 binary variable (PACS or normal) was used as output. Our NN models, which were built by the Statistical Package for Social Sciences (SPSS) version 25.0 (SPSS, Chicago, IL, USA), consisted of one input layer, a hidden layer and an output layer.

The ROC curve was used as a metric to measure prediction model performance. Each model was assessed for its ability to classify PACS cases versus controls using the AUCs. The optimal operating point was determined at the point at which the Youden index was maximized and was used as the diagnostic threshold to calculate sensitivity and specificity (Fluss et al. 2005). The estimates of AUC (95% confidence interval [CI]), sensitivity and specificity were obtained using the SPSS 25.0. Comparisons of AUCs of the three different models for each PACS group with PB, PIC or TPIR were performed using ANOVA.

The testing dataset was used to validate models’ ability to discriminate between PACS patients versus normal subjects. Overall model accuracy which is the correct classification ratio for each model was the key indicator of model validation in our study.

Results

Subjects characteristics

A total of 989 subjects age ≥40 years who attended the 5-year HES follow-up and completed ocular examinations as well as gonioscopy and ASOCT measurements under light and dark conditions were eligible for inclusion. A total of 132 eyes (13.3%) were excluded due to poor quality ASOCT images or inability to accurately identify the scleral spur.

We excluded 5 PACS eyes considered to have an exaggerated lens vault

Table 3. Changes in IA, IV and PD from light to dark conditions in PACS subjects with different angle-closure mechanisms.

| Parameter | 1 = PB (n = 141) | 2 = PIC (n = 147) | 3 = TPIR (n = 125) | 0 = Normal Subjects (n = 383) |
|-----------|------------------|------------------|------------------|-----------------------------|
| IA; L, mean (SD), mm | 2.76 (0.30) | 2.89 (0.40) | 3.45 (0.59) | 2.84 (0.37) |
| PD; L, median (IR), mm | 3.89 (3.39, 4.34) | 3.90 (3.41, 4.33) | 3.95 (3.55, 4.42) | 3.89 (3.41, 4.34) |
| IA Change, median (IR), mm | 0.13 (-0.02, 0.29) | 0.22 (0.07, 0.37) | 0.21 (0.03, 0.39) | 0.24 (0.06, 0.37) |
| PD Change, median (IR), mm | 0.64 (0.51, 0.96) | 0.81 (0.58, 1.16) | 0.70 (0.53, 1.03) | 0.79 (0.55, 1.15) |
| IA Change/ PD Change, median (IR), mm | 0.15 (-0.03, 0.33) | 0.25 (0.10, 0.39) | 0.24 (0.15, 0.36) | 0.26 (0.15, 0.36) |

IA = iris area; L = light; PB = pupillary block; PD = pupil diameter; PIC = plateau iris configuration; SD = standard deviation; TPIR = thick peripheral iris roll.

- One-way analysis of variance.
- Kruskal-Wallis test.
- Bonferroni.
- Mann-Whitney test (p < 0.05 = significant different).
In Table 4, Nagelkerke $R^2$ squares of different combinations of variables through backward logistic regression analysis are shown. The Multivariate prediction models for PACS group with PB, the Nagelkerke $R^2$ of the four combinations of variables selected through multivariate LR analysis are shown in Table 4, with the best one being 0.563. For PACS group with PIC, the parameter IA change was excluded through univariate LR analysis because of a $p$ value of less than 0.1. Hence, there were only two combinations of variables, with the Nagelkerke $R^2$ being 0.178 and 0.157 (Table 4). Finally, for PACS group with TPIR, two parameters including IA change and IA change/PD change were both excluded through univariate LR analysis. There were also two combinations of variables left through multivariate LR analysis, with the Nagelkerke $R^2$ being 0.358 and 0.441 (Table 4).

Table 5 details the variables included as the best combinations using LR analysis. In the PB group, ACV in light ($p < 0.001$), LV in light ($p < 0.001$), and IA change/PD change ($p < 0.001$) were included. In the PIC group, significant variables were IA change in light and dark ($p < 0.001$), changes in PD’s ($p = 0.012$) and IA changes/PD changes ($p < 0.001$) in dark and light conditions were observed between the four groups. The PB group was found to have the smallest IA changes ($p < 0.001$ between PB and normal groups, $p = 0.001$ between PB and PIC groups, $p = 0.005$ between PB and TPIR groups) and IA changes/PD changes ($p < 0.001$ between PB and normal groups, $p = 0.007$ between PB and PIC groups, $p = 0.009$ between PB and TPIR groups).

Table 4. Nagelkerke $R^2$ squares of different combinations of variables through backward logistic regression analysis

| Angle-Closure Mechanisms | Logistic Models | Parameter | Nagelkerke $R^2$ |
|--------------------------|----------------|-----------|-----------------|
| Pupillary Block          | 1              | ACV (L), LV (L), IA Change | 0.553           |
|                          | 2              | ACV (L), LV (L), IA Change/PD Change | 0.563           |
|                          | 3              | IC (D), ACV (D), LV (D), IA Change | 0.554           |
|                          | 4              | IC (D), ACV (D), LV (D), IA Change/PD Change | 0.557           |
| Plateau Iris Configuration| 1              | AOD500 (L), ARA750 (L), IA Change/PD Change | 0.178           |
|                          | 2              | ARA750 (D), ACV (D), LV (D), IA Change/PD Change | 0.157           |
| Thick Peripheral Iris Roll| 1              | ARA750 (L), IA (L), ACV (L) | 0.358           |
|                          | 2              | ARA750 (D), IT750 (D), ACV (D) | 0.441           |

($\text{IA Change} = \text{IA in light} – \text{IA in dark}; \text{PD Change} = \text{PD in dark} – \text{PD in light}$. \text{ACV} = \text{anterior chamber volume}; \text{AOD500} = \text{angle opening distance at 500 $\mu m$}; \text{ARA750} = \text{angle recess area at 750 $\mu m$}; \text{D} = \text{dark}; \text{IA} = \text{iris cross-sectional area}; \text{IT750} = \text{iris thickness at 750 $\mu m$}; \text{L} = \text{light}; \text{LV} = \text{lens vault}; \text{PD} = \text{pupil diameter}.$)

Table 5. Variables included in the best combinations through backward logistic regression analysis

| Angle-Closure Mechanisms | Parameter | Estimated regression coefficient | Standard error | $\chi^2$ | $p$ value | OR (95% CI) |
|--------------------------|-----------|---------------------------------|----------------|---------|----------|-------------|
| Pupillary Block          | ACV; L, $\text{mm}^3$ | $-0.121$ | 0.018 | 47.072 | $<0.001$ | 0.886 (0.856, 0.917) |
|                          | LV; L, mm | 0.005 | 0.001 | 24.450 | $<0.001$ | 1.005 (1.003, 1.007) |
| Plateau Iris Configuration| AOD500; L, mm | $-1.987$ | 0.520 | 14.582 | $<0.001$ | 0.137 (0.049, 0.380) |
|                          | ARA750; L, $\text{mm}^2$ | $-10.113$ | 2.232 | 4.971 | 0.026 | 144.963 (1.825, 11512.382) |
|                          | IA Change/PD Change, mm | $-0.803$ | 0.368 | 4.770 | 0.029 | 0.448 (0.218, 0.921) |
| Thick Peripheral Iris Roll| ARA750; D, $\text{mm}^2$ | $-8.507$ | 1.987 | 18.339 | $<0.001$ | 0.000 (0.000, 0.010) |
|                          | IT750; D, mm | 12.039 | 2.862 | 17.698 | $<0.001$ | 169282.464 (620.373, 46192469.33) |
|                          | ACV; D, $\text{mm}^3$ | $-0.033$ | 0.015 | 4.684 | 0.030 | 0.967 (0.939, 0.997) |

($\text{IA Change} = \text{IA in light} – \text{IA in dark}; \text{PD Change} = \text{PD in dark} – \text{PD in light}$. \text{ACV} = \text{anterior chamber volume}; \text{AOD500} = \text{angle opening distance at 500 $\mu m$}; \text{ARA750} = \text{angle recess area at 750 $\mu m$}; \text{D} = \text{dark}; \text{IA} = \text{iris cross-sectional area}; \text{IT750} = \text{iris thickness at 750 $\mu m$}; \text{L} = \text{light}; \text{LV} = \text{lens vault}; \text{PD} = \text{pupil diameter}.$)
determined as AOD500 in light 
(p = 0.026), ARA750 in light 
(p < 0.001) and IA change/PD change 
(p = 0.029). In the TPIR group, the 
following three variables were selected: 
ARA750 in dark (p < 0.001), IT750 in 
dark (p < 0.001) and ACA in dark 
(p = 0.030). No significant collinearity 
among the input variables of each 
group was detected.

Figures 5, 6 and 7 show the ROC 
curves of the 3 algorithms in PB, PIC 
and TPIR groups, respectively. Table 6 
shows the AUCs and 95% CIs of BLR, 
NBC and NN: in the PB group, these 
were 0.920, (95% CI, 0.890–0.950), 
0.918 (95% CI, 0.889–0.947) and 
0.917 (95% CI, 0.887–0.946), with no 
significant statistical differences 
(p = 0.990). The AUCs and 95% CIs 
of BLR, NBC and NN in TPIR group 
were 0.867, (95% CI, 0.823–0.912), 
0.833 (95% CI, 0.784–0.882) and 
0.886 (95% CI, 0.849–0.922), respectively, 
with no significant statistical 
differences (p = 0.240). The sensitivity, 
specificity and the validation results 
(overall accuracy) of the three algo-

Discussion

In a previous study, we had investi-
gated algorithms for detection of 
PACS by combining static and 
dynamic ASOCT parameters and 
found that the three algorithms includ-
ing BLR, NBC and NN failed to meet 
the requirements for population-based 
screening of PACS; NN had the largest 
AUC of 0.844 (Zhang et al. 2020). The 
current investigation shows potential 
for the development of an image-based 
non-contact method to screen for 
PACS, which is the ASOCT examina-
tions under both light and dark condi-
tions.

There are different AC mechanisms 
for PACD (Wang et al. 2000; Li et al. 
2009). Pure pupillary block, pure non-
pupillary block and combination of 
multiple mechanisms have been 
reported to underlie AC in Chinese 
eyes with PACD (Wang et al. 2000). In 
our previous study, we found that there 
were significant differences in ASOCT 
parameters between PACD eyes with 
different dominant AC mechanisms 
(Zhang et al. 2015). In another study, 
we also showed that the contribution of 
dynamic iris behaviour to the patho-
genesis of PACD varies among those 
with different AC mechanisms (Zhang 
et al. 2015). Accordingly, we felt that 
using a single algorithm in detection of 
all PACS eyes might not be the best 
way to screen.

In this study, we categorized 
enrolled PACS eyes into three groups 
including PB, PIC and TPIR according 
to their dominant AC mechanisms as 
determined by ASOCT images. Among 
the three groups, PB group had the 
smallest IA change and IA change/PD change, suggesting that dynamic iris change has a more important role in angle closure where PB is the dominant AC mechanism; this is what we had found in our earlier study (Zhang et al. 2015). The reason for that may be the pressure gradient between the anterior
and posterior chambers in the PB group created by three forces including sphincter and dilator muscles as well as iris elasticity which affect the iris structure and change the capacity for free fluid movement (Nongpiur et al., 2011b; Zhang et al. 2015).

The three algorithms demonstrated good AUCs in the PB group, moderate AUCs in TPIR group and relatively poor AUCs in PIC group. In our previous study, the largest AUC (0.844) was for NN for detection of all PACS eyes; this is less than that for the PB and TPIR groups and better than that for the PIC group. We evaluated the performance of three prediction models in detection of PACS as a new method of screening for PACD based on different AC mechanisms. This method performed best in detection of PACS with PB as the dominant AC mechanism.

Early diagnosis of PACD can be achieved by population-based screening or case detection (opportunistic screening) (Thomas et al. 2002). Our findings suggest that this new method (prediction models using variables obtained through ASOCT measurements in both dark and light conditions) was suitable for population-based screening as well as in case detection of PACS eyes with PB as the dominant AC mechanism. And this method (prediction models using variables obtained through ASOCT measurements in dark conditions) may have potential use in case detection of PACS eyes with TPIR as the dominant AC mechanism. The algorithm was not suitable for population-based screening or case detection in PACS eyes with PIC as the dominant AC mechanism.

The Zhongshan Angle-Closure Prevention (ZAP) trial reported a low incidence of development of PAC or PACG in PACS subjects over 6 years and also suggested that performing LPI on a population basis may not be the best strategy for preventing visual impairment in PACS (He et al. 2019). Hence, population-based screening of PACS may seem insignificant based on those findings. However, the ZAP trial fails to provide sufficient information referring to the risk which is especially important in determining whether an individual PACS is with higher possibility of a sight-threatening acute attack and should undergo a prophylactic LPI (He et al. 2019).

We believe that early screening for PACS is not useless; identifying and targeting which PACS are at higher risk of developing angle closure or vision-impairing acute attack are essential and also the most powerful tool for preventing blindness and low vision caused by PACD.

The ultimate goal of our study is looking for an ideal screening method for all stages of PACD, not only for PACS. However, as our study was based on a population-based research (follow-up of the Handan Eye Study), the number of PAC or PACG was very limited. We intended to establish and evaluate this new method first in PACS cases; in a future study, we will further evaluate the performance of this method in PAC/PACG cases.

Previous studies have reported that the AC mechanism involved in most AAC eyes and fellow eyes of AAC is predominantly PB, while non-pupillary block or multiple mechanisms have a greater role in non-acute presentations (Barkan 1954; Zhou et al. 1993; Moghimi et al. 2018). Acute angle-closure (AAC) is a subtype of PACD and an ocular emergency which in the

Table 6. AUC, sensitivity and specificity of algorithms.

| Angle-closure mechanisms | Prediction algorithm | Overall accuracy (%) | 95% CI of AUC | Sensitivity | 95% CI of sensitivity | Specificity | 95% CI of specificity |
|--------------------------|----------------------|----------------------|---------------|-------------|----------------------|------------|----------------------|
| Pupillary Block          | LR                   | 80.9                 | 0.920         | 0.890, 0.950| 86.87%               | 84.81%, 88.93%| 86.57%               | 83.14%, 89.99% |
|                          | NBC                  | 77.7                 | 0.918         | 0.889, 0.947| 87.88%               | 85.89%, 89.87%| 83.96%               | 80.27%, 87.64% |
|                          | NN                   | 82.1                 | 0.917         | 0.887, 0.946| 88.89%               | 86.97%, 90.81%| 83.96%               | 80.27%, 87.64% |
| Plateau Iris Configuration| LR                   | 66.0                 | 0.715         | 0.659, 0.771| 77.67%               | 75.13%, 80.21%| 54.85%               | 49.95%, 59.75% |
|                          | NBC                  | 68.6                 | 0.708         | 0.651, 0.764| 68.93%               | 66.11%, 71.76%| 62.69%               | 57.92%, 67.45% |
|                          | NN                   | 74.7                 | 0.707         | 0.650, 0.764| 68.93%               | 66.11%, 71.76%| 60.45%               | 55.63%, 65.27% |
| Thick Peripheral Iris Roll| LR                   | 79.6                 | 0.867         | 0.823, 0.912| 78.41%               | 75.90%, 80.92%| 82.84%               | 78.82%, 86.86% |
|                          | NBC                  | 73.7                 | 0.833         | 0.784, 0.882| 86.36%               | 84.27%, 88.46%| 67.54%               | 62.55%, 72.53% |
|                          | NN                   | 86.8                 | 0.886         | 0.849, 0.922| 87.50%               | 85.48%, 89.52%| 77.24%               | 72.77%, 81.71% |

AUC = area under the receiver operator characteristic curve, CI = confidence interval, LR = logistic regression, NBC = Naive Bayes’ classification, NN = neural network.
absence of timely treatment causes permanent visual loss (Ha et al. 2019). Early screening for AAC would be beneficial. We found that the new method which was based on algorithms and combination of anatomical and dynamic ASOCT parameters performed well in detection of PACS with PB as the dominant AC mechanism and may be helpful in screening eyes which are at risk of AAC. This would require confirmation by a prospective study.

Gonioscopy certainly remains the primary method for angle assessment and the gold standard for the diagnosis of PACD and is essential when the decision of how to manage an individual with PACD is made. However, even in the clinics, gonioscopy is not performed half of the time probably due to lack of experience, potential discomfort and lack of time (Chansangpetch et al. 2018). And its fair inter- and intra-observer reproducibility, situations such as corneal pathologies or uncooperative patients prevents it from being an ideal screening, detecting and monitoring method for angle closure (Chansangpetch et al. 2018).

The anterior segment imaging machines such as ASOCT are now already commonly available in more developed areas. In developing areas and countries such as China, ASOCT will become more and more common with the development of economics and medical resources, which makes it a preferable option for early screening of PACD. For underdeveloped countries and areas where ASOCT is not practical for screening for its high costs, gonioscopy is still more suitable for its characteristics of being cost-effective and portable (Chansangpetch et al. 2018).

Our study has several strengths. To the best of our knowledge, it is the first study to establish and evaluate a novel method for detection of PACS with different AC mechanisms by combining multiple static and dynamic anterior segment parameters on the basis of three prediction algorithms. Our analysis used the ISGEO classification system for PACD. Anterior segment optical coherence tomography (ASOCT), which is non-contact, eliminates patient discomfort and inadvertent compression of the globe and has the advantages of ease of operation, rapidity of image acquisition, less inter-operator variability and angle viewing in its natural state because of the use of infrared light (Angmo et al. 2016).

The study has several limitations. Firstly, we included only PACS eyes but not those with established primary angle closure because the decision to treat is evident in the latter. This makes it difficult to estimate how eyes with confirmed angle closure would respond. Secondly, our subjects were Chinese and caution is warranted in extrapolating the findings to other ethnic groups. Thirdly, subjects with limbal anterior chamber depth ≤40% and had undergone gonioscopic examination and ASOCT imaging under light and dark conditions were enrolled in our study, which may cause some bias when drawing a conclusion. In the future, we would further assess this screening method in general population. Fourthly, the main disadvantage of ASOCT is the inability to image structures posterior to the iris such as the posterior chamber of the eye, zonules and the ciliary body (Nongpiur et al. 2020). Therefore, mechanisms of angle closure effected by ciliary body components such as plateau iris may not be wholly elucidated with ASOCT (Nongpiur et al. 2020). Our earlier study did find a good kappa (0.870) with the UBM for the same observer in determination of the AC mechanism (Zhang et al. 2016). Also, the Visante ASOCT could not perform the 360-degree imaging of the entire anterior chamber, which may miss some information. Also, currently available software-analysis programmes are semiautomated and require manual localisation of the scleral spur (Quek et al. 2011). This can be difficult especially in closed angles or where there is a smooth transition from cornea to sclera (Quek et al. 2011). We are planning a study to investigate fully automated image analysis software for angle-closure detection. Finally, external validation which requires evaluation of the performance of these models in other participant data is needed.

Conclusions

In summary, we compared three prediction models derived from static and dynamic ASOCT-based parameters obtained under both light and dark conditions for the detection of PACS with different dominant AC mechanisms. This new method showed the best performance for detection of PACS with pupillary block mechanism with potential for use in population-based screening as well as in case detection. In a future study, we plan to enrol PACD patients from clinics at our hospital and further evaluate the performance of these models in screening of PACD in the real world.

References

Angmo D, Nongpiur ME, Sharma R, Sidhu T, Shiota R & Dada T (2016): Clinical utility of anterior segment swept-source optical coherence tomography in glaucoma. Oman J Ophthalmol 9: 3–10.

Barkan O (1954): Narrow-angle glaucoma; pupillary block and the narrow-angle mechanism. Am J Ophthalmol 37: 332–350.

Chansangpetch S, Rojanapongpun P & Lin SC (2018): Anterior segment imaging for angle closure. Am J Ophthalmol 188: xvi–xxix.

Console JW, Sakata LM, Aung T, Friedman DS & He M (2008): Quantitative analysis of anterior segment optical coherence tomography images: the Zhongshan Angle Assessment Program. Br J Ophthalmol 92: 1612–1616.

Cox DR (1958): The regression analysis of binary sequences (with discussion). J Roy Stat Soc B 20: 215–242.

Dorairaj S, Tsai JC & Grippo TM (2012): Changing trends of imaging in angle closure evaluation. ISRN Ophthalmol 2012: 597124.

Dreisell S & Ohno-Machado L (2002): Logistic regression and artificial neural network classification models: a methodology review. J Biomed Inform 35: 352–359.

Flurin F, Faraggi D & Reiser B (2005): Estimation of the Youden Index and its associated cutoff point. Biom J 47: 485–472.

Ford E, Rooney P, Oliver S, Hoile R, Hurley P, Banerjee S, van Marwijk H & Cassell J (2019): Identifying undetected dementia in UK primary care patients: a retrospective case control study comparing machine-learning and standard epidemiological approaches. BMC Med Inform Decis Mak 19: 248.

Foster PJ, Buhrmann R, Quigley HA & Johnson GJ (2002): The definition and classification of glaucoma in prevalence surveys. Br J Ophthalmol 86: 238–242.

Friedman DS & He M (2008): Anterior chamber angle assessment techniques. Surv Ophthalmol 53: 250–273.

Fu H, Xu Y, Lin S, Wong DWK, Baskaran M, Mahesh M, Aung T & Liu J (2019): Angle-closure detection in anterior segment OCT based on multilevel deep network. IEEE Trans Cybern 50: 3358–3366. https://doi.org/10.1109/TCYB.2019.2907162.

Ha JY, Sung MS, Heo H & Park SW (2019): Trends in the characteristics of acute
primary angle closure in Korea over the past 10 years. PLoS One 14: e0223527.

Hassoun MH (1995): Fundamentals of artificial neural networks. Cambridge, MA: The MIT Press.

Hastie T, Tibshirani R & Friedman J (2009): The Elements of Statistical Learning: Data Mining, Inference, and Prediction, 2nd edn. New York: Springer.

He M, Jiang Y, Huang S, Chang DS, Munoz B, Aung T, Foster PJ & Friedman DS (2019): Laser peripheral iridotomy for the prevention of angle closure: a single-centre, randomised controlled trial. Lancet 393: 1609–1618.

Jamal S, Khubaib M, Grover S, Grover A & Hasnain SE (2020): Artificial Intelligence and Machine learning based prediction of resistant and susceptible mutations in Mycobacterium tuberculosis. Sci Rep 10: 5487.

Lavanya R, Foster PJ, Sakata LM et al. (2008): Screening for narrow angles in the Singapore population: evaluation of new noncontact screening methods. Ophthalmology 115: 1720–1727.

Li SZ, Liang YB, Fan SJ et al. (2009): IEEE Workshop on Learning for Text Categorization 41: 48.

Moghimi S, Torkashvand A, Mohammadi M, Moghimi S, Vahedian Z, Fakhraie G et al. (2012): The role of anterior segment optical coherence tomography in glaucoma. J Ophthalmol 2012: 476801.

Nongpiur M, Tun TA & Aung T (2020): Angle closure and angle closure glaucoma. The Hauge, The Netherlands: Kugler Publications.

Zhang Y, Li SZ, Li L, He MG, Thomas R & Wang NL (2015): Quantitative analysis of iris changes following mydriasis in subjects with different mechanisms of angle closure. Invest Ophthalmol Vis Sci 56: 563–570.

Zhang Y, Li SZ, Li L, Thomas R & Wang NL (2014): The handan eye study: comparison of screening methods for primary angle closure suspects in a rural Chinese population. Ophthalmic Epidemiol 21: 268–275.

Yazdanfar S, Westphal V, Bardenstein DS & Izatt JA (2001): Real time optical coherence tomography of the anterior segment at 1310 nm. Arch Ophthalmol 119: 1179–1185.

Zhang Y, Li SZ, Li L, Thomas R & Wang NL (2020): Establishment and comparison of algorithms for detection of primary angle closure suspect based on static and dynamic anterior segment parameters. Trans Vis Sci Tech 9: 16. (Accepted).

Zhou WB, Li MY & Wang ZH (1993): Advances in the Glaucoma Research. Shandong: Qingdao Ocean Press, pp. 43–45.

Weinreb N, Friedman D & authors, (2006): Angle closure and angle closure glaucoma. The Hauge, The Netherlands: Kugler Publications.