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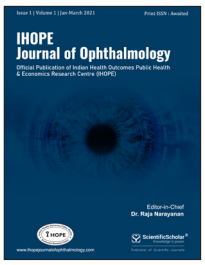

Review Article

Screening for angle-closure disease in the community: A review

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ABSTRACT

Primary angle-closure glaucoma (PACG) has a higher risk of association with blindness compared to primary open-angle glaucoma. Early determination of PAC disease (PACD) before progression to PACG can help prevent loss of vision. Although gonioscopy is the gold standard for the determination of angle status, it requires more training and experience and may not be feasible to use for screening. We reviewed the performance of other modalities of angle assessment in population studies in comparison with gonioscopy. Assessment of limbal anterior chamber depth, biometric parameters such as central anterior chamber depth, lens thickness, axial length measurements, and anterior segment optical coherence tomography were used to qualitatively and quantitatively assess the angle structures in these studies. The sensitivity, specificity, and predictive values varied widely due to the use of varying techniques and definitions. A combination of more than 1 parameter was found to give better results in comparison with gonioscopy in some studies. Individual or combination tests most appropriate for screening need to be determined and reassessed by further well-controlled studies with uniform criteria.

Keywords: Angle closure, Community, Screening test, Anterior segment optical coherence tomography, van Herick, Biometry

Primary angle-closure glaucoma (PACG) is estimated to affect about 23 million persons globally in 2020, the majority reside in Asia where it accounts for about 40% of all primary glaucoma.[1] There are a much larger number of people with primary angle closure disease (PACD), estimated at 24 million persons in India alone.[2,3] The 5-year risk of progression of primary angle closure suspect to primary angle closure (PAC) is 22% and PAC to PACG 28.5% in population-based studies.[4,5] Population-based studies have shown that fewer people with PACG in a rural setting are likely to be aware of their condition in comparison with those in an urban setting.[6] PACG has a higher risk of association with blindness in comparison to primary open-angle glaucoma (27% vs. 8.9%) with a cumulative risk ratio of 2.39% on the meta-analysis of epidemiological studies worldwide.[2] However, detection rates of PACG are poor in many parts of Asia and could contribute to the increased risk of blindness.[6,7]

The search is still ongoing for a reliable, easily available, and accessible, economically viable test for timely detection of those with early PACD in the population to prevent progression and blindness.

ASSESSMENT OF ANTERIOR CHAMBER ANGLE

Gonioscopy is the gold standard for the diagnosis of occludable angles.[8,9] Iridotrabecular contact (ITC) is present when the iris appears to touch the posterior pigmented trabecular meshwork or

anterior structures on gonioscopy. The characteristic feature in angle-closure disease on gonioscopy is the presence of ITC for at least 180° without indentation or manipulation in dark ambient light conditions and with a dim light not reaching up to the pupillary margin during the assessment.[10] However, in various community-based studies, the definition of an occludable angle varies from 180 to 270° (i.e., 2–3 quadrants) of non-visualization of the posterior trabecular meshwork. It is not feasible to use gonioscopy for screening as it is a contact, subjective test that requires considerable training, experience, and patient cooperation. The results can vary with ambient and instrument lighting and inadvertent pressure on the cornea. The lack of objective documentation of gonioscopic finding is also a problem during follow-up.

Several alternative techniques to gonioscopy for the assessment of the anterior chamber angle have been proposed in the literature including assessment of limbal anterior chamber depth (LACD), biometry including central anterior chamber depth (ACD), lens thickness, and axial length (AXL) measurements, and anterior segment optical coherence tomography (ASOCT) to qualitatively and quantitatively assess the angle structures. We reviewed the performance of these techniques in population-based studies that used gonioscopy as the reference standard. We looked at population-based studies with data available for the prevalence of occludable angles on gonioscopy as well as the sensitivity and specificity of the screening tests. The positive and negative predictive values and likelihood ratios (LR) were used, where available or calculated. As the predictive values can vary depending on the prevalence of occludable angles in a population, we felt that the LR would enable a better comparison of test results.

SCREENING FOR ANGLE-CLOSURE DISEASE IN POPULATION STUDIES WITH ASOCT

Anterior segment OCT is a non-contact and objective method of qualitative and quantitative assessment of anterior chamber angle structures. The landmark used in ASOCT imaging is the scleral spur. An angle where there is contact of the iris anterior to the scleral spur is deemed a closed-angle. Depending on the machine used, the assessment of a single cross-section of the angle or the entire 360° circumferential angle may be possible.[11] Although several ASOCT population-based studies are available, the definition of angle-closure on gonioscopy and the parameters assessed in ASOCT are variable in these studies. The sensitivity and specificity of the individual qualitative and quantitative tests in population-based studies using ASOCT are thus not directly comparable. For example, when using gonioscopic criteria of two versus three quadrants ITC for the definition of occludable angles, increased sensitivity of the screening test is seen with increasing the threshold for occludable angle by gonioscopy.[12-20] A large majority of published community-based ASOCT studies have been conducted in Singapore where the prevalence of PACG is higher than in India (1.5% vs. 0.9–1.1%).[6,7,21]

Published data include qualitative tests like the presence of ITC in one or multiple quadrants and quantitative data measuring several parameters such as lens vault, angle opening distance (AOD), trabecular iris space area (TISA), angle recess area (ARA), anterior chamber area, and volume. The sensitivity, specificity, predictive values, and LR of the individual tests and the prevalence of PACD on gonioscopy are shown in [Table 1].

Narayanaswamy *et al.* assessed several parameters using a time-domain OCT (Visante; Carl Zeiss Meditec, Dublin, California, USA) including AOD, TISA, and ARA at varied distances from the scleral spur in both the nasal and temporal quadrants.[19] Among these, the AOD at 750 μ from the scleral spur was found to be the most useful in identifying those with gonioscopically narrow angles (temporal quadrant AOD750 sensitivity – 90.2%, specificity – 77.4%, and likelihood ratio: Positive – 3.99 and negative – 0.13).

A higher sensitivity (96%) and better LR (positive – 8.09 and negative – 0.12) were obtained by Nongpiur *et al.* using an estimated threshold calculated using multiple parameters including anterior chamber volume, area, width, lens vault, iris thickness, and area.[16]

Quantitative data to measure 360° angle like the ITC index (extent of angle-closure across 360° of the angle measured as a percentage) have also been used.[11] When a cutoff of ≥35% ITC was used, the sensitivity and specificity ranged from 82.1 to 84.7% and 77 to 78.4%, respectively.[13,14] Increasing the threshold of ASOCT ITC to ≥50 or 75% increased the specificity of the test; however, the sensitivity decreased [Table 1]. The positive and negative LRs increased on increasing the ITC threshold on ASOCT.

SCREENING FOR ANGLE-CLOSURE DISEASE IN POPULATION-BASED STUDIES USING SLIT-LAMP ASSESSMENT AND BIOMETRY

The van Herick (vH) grading and LACD measure the limbal peripheral ACD using the peripheral cornea as reference.[22,23] Biometric parameters assessed in population-based studies include AXL, ACD, and lens thickness. [Table 2] shows the results of these studies in comparison to gonioscopy as the reference standard. Both ultrasound and optical biometry were used in the studies reviewed. Ultrasound biometry is a contact procedure and requires more expertise. However, in denser cataracts and posterior subcapsular cataracts, optical biometry is less accurate.[24,25]

Foster *et al.* evaluated the LACD as a percentage of peripheral corneal thickness in a community-based evaluation in a Mongolian population.[23] The LACD was graded into seven

Table 1: Sensitivity, specificity, predictive values, and likelihood ratio of ASOCT in comparison with gonioscopy.

No.	Author	Year	Country	Eyes	Setting	Gonioscopic criteria	Occluded angles by gonioscopy (%)	ASOCT criteria	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	PLR (95% CI)	NLR (95% CI)
1	Porporato	2019	Singapore	1865	Community	PTM not visible in≥2 quadrants	7.5	ITC index ≥35%[a]	82.1 (74.8–88.1)	78.4 (76.4–80.4)	23.6 (21.5–25.8)	98.2 (97.4–98.7)	3.8 (3.38–4.28)	0.23 (0.16–0.33)
								ITC index ≥50%[a]	75.7 (67.8–82.6)	84.2 (82.4–85.9)	28 (25.2–31.0)	97.7 (97.0–98.3)	4.79 (4.15–5.53)	0.29 (0.22–0.39)
								ITC index ≥75%[a]	60.7 (52.1–68.9)	90.8 (89.3–92.1)	34.8 (30.5–39.5)	96.6 (95.9–97.2)	6.6 (5.41–8.05)	0.43 (0.35–0.53)
2	Porporato	2018	Singapore	1857	Community	PTM not visible in≥3 quadrants	5.17	ITC index ≥35%[a]	84.7 (76.0–91.2)	77 (75.0–78.0)	16.7 (15.1–18.4)	98.9 (98.3–99.3)	3.68 (3.26–4.15)	0.2 (0.12–0.32)
								ITC index ≥50%[a]	84.7 (76.0–91.2)	77.1 (75.0–78.0)	16.7 (15.1–18.4)	98.9 (98.3–99.3)	3.7 (3.28–4.27)	0.2 (0.12–0.32)
								ITC index ≥75%[a]	61.2 (50.8–70.7)	89.7 (88.2–91.0)	24.3 (19.2–30.2)	97.7 (96.8–98.4)	5.94 (4.81–7.33)	0.43 (0.34–0.56)
3	Campbell	2015	UK	78	Community	PTM visible for<270◦	15	Iridotrabecular touch in nasal or temporal quadrant[b]	46 (17–77)	87 (76–94)	36	90	3.54 (1.47–8.53)	0.62 (0.36–1.06)
4	Nongpiur	2013	Singapore	1368	Community	PTM not visible in≥180◦	21.6	0.5% estimated probablity threshold[c,d]	96	75	51	99	3.84 (3.45–4.27)	0.05 (0.03–0.09)
								0.26% estimated probablity threshold[c,d]	89	89	69	97	8.09 (6.75–9.64)	0.12 (0.09–0.17)
5	Tan	2012	Singapore	1465	Community	PTM not visible in≥180◦	21.5	Lens vault >576μ[c]	85.7	77.5	51	95.2	3.81 (3.39–4.28)	0.18 (0.14–0.24)
6	Chang	2011	Singapore	2047	Community	Shaffer grade≤1 in≥2 quadrants	19.3	AOD 750 <0.258 mm[c]	83 (78.9–86.5)	78.2 (76.1–80.2)	48.4 (44.6–52.3)	94.9 (93.6–96.0)	3.81 (3.44–4.21)	0.22 (0.17–0.27)
7	Narayana swamy	2010	Singapore	1465	Community	PTM not visible in≥180◦	21.5	Temporal AOD 750 <0.258 mm[c]	90.2 (86.9–93.4)	77.4 (74.9–79.8)	49.9 (45.6–54.2)	96.9 (95.8–98.0)	3.99 (3.56–4.47)	0.13 (0.09–0.18)

(Contd...)

Table 1: *(Continued)*.

No.	Author	Year	Country	Eyes	Setting	Gonioscopic criteria	Occluded angles by gonioscopy (%)	ASOCT criteria	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	PLR (95% CI)	NLR (95% CI)
8	Khor	2010	Singapore	1853	Community	PTM not visible in≥2 quadrants	20.5	Quadrant closed on ASOCT imaging of inferior angle	83.9	68.8	41	94.3	2.69 (2.46–2.94)	0.23 (0.19–0.30)
						PTM not visible in≥3 quadrants	16.4	Quadrant closed on ASOCT imaging of inferior angle	87.8	67	34.3	96.6	2.66 (2.45–2.89)	0.18 (0.13–0.25)

ASOCT: Anterior segment optical coherence tomography, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value, PLR: Positive likelihood ratio, NLR: Negative likelihood ration, PTM: Posterior trabecular meshwork, ITC: Iridotrabecular contact, AOD: Angle opening distance. (a) Using swept source OCT (CASIA SS-1000; Tomey, Nagoya, Japan), (b) using spectral domain Topcon OCT-2000 (Topcon Europe Medical B.V, Netherlands), (c) using time domain OCT Visante (Carl Zeiss Meditec, Dublin, California, USA), (d) estimated probability threshold calculated using several anterior chamber parameter measurements

categories (0%, 5%, 15%, 25%, 40%, 75%, and >100%). A high sensitivity of 99.2% was obtained when using a cutoff of 25% or vH Grade 2 in the population. The gonioscopic threshold for diagnosis of occludable angles in this study was set as trabecular meshwork not visible in <90°. This may be one of the reasons for the lower values obtained in other population-based studies.[17,18,23,26-28]

Choudhari *et al.* calculated the sensitivity and specificity of teleophthalmic photography of vH grading ≤2 (sensitivity – 52.5% and specificity – 92.8%), ocular biometry parameters including central ACD < first quartile (sensitivity – 73.3% and specificity – 77.9%), and lens thickness > 3rd quartile (sensitivity – 54.5% and specificity – 75.1%) with gonioscopy as the gold standard.[27] They also reported better results on the use of combined parameters such as vH grading and ACD for better sensitivity (82.2%) and the use of combined vH or ACD grading for improved specificity (97.1%). This combination also had the best LRs (positive – 15 and negative – 0.24) in comparison with all the other studies using slit-lamp assessment or biometry to screen for occludable angles.

PERFORMANCE OF ASOCT VERSUS SLIT LAMP OR BIOMETRY WITH GONIOSCOPY AS REFERENCE

ASOCT is a non-contact procedure and the newer machines can assess the 360° circumferential angle structure characteristics in eyes.[11] However, it is expensive and requires more skill to obtain and assess the data obtained.[27] Among all the studies assessed, the optimum LRs were obtained by Nongpiur *et al.* (positive – 8.09 and negative – 0.12) using multiple ASOCT parameters and Choudhari *et al.* (positive – 15 and negative – 0.24) using slit-lamp photography for vH grading and ultrasound biometry for the central ACD.[16,27] The ASOCT technique is a non-contact technique whereas ultrasound biometry is a contact procedure, which can be replaced by non-contact biometry for screening purposes. However, the overall acquisition and assessment using slit lamp and biometry for screening is simpler and requires lesser time and expertise.

Anterior segment imaging did not offer substantial improvements over the vH test or biometry. [Figures 1 and 2] compare the sensitivity, specificity, and LRs obtained, with the criteria used, among studies using ASOCT and vH grading. The use of relatively inexpensive, widely available, and familiar techniques such as the vH and biometry will be more feasible in remote areas with relatively lesser resources where targeted screening of the population can be done before assessment by a specialist. This may also be integrated with currently conducted cataract and refraction or other camps for wider coverage. Proponents of ASOCT in the detection of occludable angles argue that the use of visible light in

Table 2: Sensitivity, specificity, predictive values, and likelihood ratio of slit lamp and ocular biometry in comparison with gonioscopy.

No	Author	Year	Country	Eyes	Setting	Gonioscopic criteria	Occluded angles by gonioscopy (%)	Screening criteria	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	PLR (95% CI)	NLR (95% CI)
1	Choudhari	2020	India	1965	Community	PTM not visualized in≥180°	5.1	≤VH 2	52.5 (42.3–62.5)	92.8 (91.5–93.9)	28.2 (21.9–35.2)	97.3 (96.4–98)	7.29 (5.69–9.34)	0.51 (0.42–0.63)
								Central ACD≤1st quartile (2.89 mm)	73.3 (63.5–81.6)	77.9 (75.9–79.8)	15.2 (12.1–18.7)	98.2 (97.4–98.8)	3.32 (2.87–3.84)	0.34 (0.25–0.47)
								Combined VH and/or ACD	82.2 (73.3–89.1)	97.1 (96.2–97.8)	44.9 (34.8–55.3)	98.7 (98–99.2)	15 (10.7–21.2)	0.24 (0.15–0.36)
2	Choudhari	2019	India	111	A. rural clinic	PTM not visualized in>180°	62.1	≤VH 2	75.4 (63.5–84.9)	90.5 (77.4–97.3)	46.8 (25.5–69.3)	97.1 (95.6–98.1)	7.94 (3.09–20)	0.27 (0.18–0.42)
				888	B. rural population based	PTM not visualized in>180°	30.5	≤VH 2	70.8 (65–76.2)	91.9 (89.5–93.9)	49.3 (42.4–56.2)	96.9 (95.9–97.2)	8.74 (6.63–12)	0.32 (0.26–0.38)
3	Tan	2012	Singapore	1465	Community	PTM not visible in≥180◦	21.5	AXL≤23.5 mm	74.3	63.6	35.8	90.1	2.04 (1.85–2.26)	0.4 (0.33–0.49)
								CACD≤2.9 mm	84.4	80.3	53.9	95	4.28 (3.78–4.86)	0.19 (0.15–0.25)
4	Chang	2011	Singapore	2047	Community	Shaffer grade≤1 in≥2 quadrants	19.3	ACD at 750 µ from SS, <240 µ	89.9 (86.5–92.7)	75.6 (73.5–77.7)	47 (43.4–50.6)	96.9 (95.8–97.8)	3.68 (3.36–4.04)	0.13 (0.10–0.18)
5	Nolan	2006	Singapore	1090	Community	TM not visible in<90◦	6.5	LCD≤15% CT	83 (80.7– 85.2)	88.1 (86.2–90)	32.7	98.7	6.97 (5.72–8.50)	0.19 (0.12–0.32)
								ACD<2.53 mm	75.6 (73.1– 78.2)	73.7 (71.1–76.3)	16.7	97.7	2.87 (2.43–3.40)	0.33 (0.22-0.50)
6	Foster	2000	Mongolia	1717	Community	TM not visible in<90°	8.1	≤VH 2/LCD 25% CT	99.2	65.5	20.2	99.9	2.88 (2.68-3.08)	0.01 (0.00-0.08)

CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value, PLR: Positive likelihood ratio, NLR: Negative likelihood ratio, PTM: Posterior trabecular meshwork, VH: van Herick, ACD: Anterior chamber depth, AXL: Axial length, CACD: Central anterior chamber depth, LCD: Limbal anterior chamber depth, CT: Corneal thickness

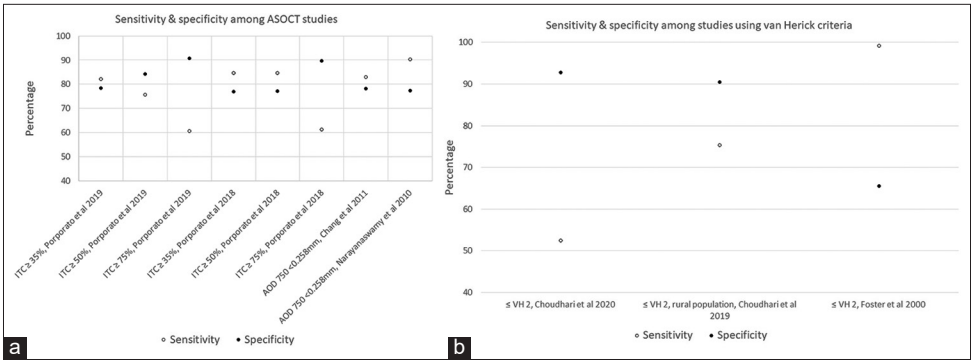

Figure 1: Graph showing the sensitivity and specificity using different characteristics assessed by studies using (a) ASOCT and (b) slit-lamp evaluation (van Herick grading).

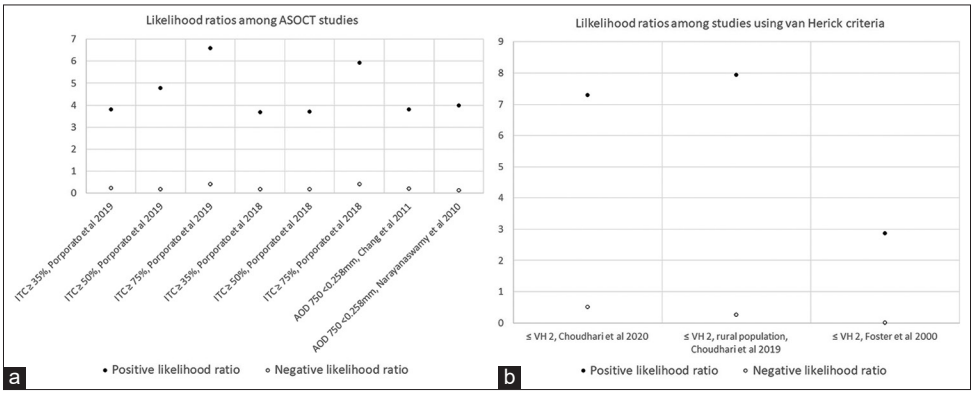

Figure 2: Likelihood ratios when using different characteristics assessed by studies using (a) ASOCT and (b) slit-lamp evaluation (van Herick grading).

gonioscopy versus infrared light in ASOCT may change the diagnosis. Most studies have detected more occludable angles with ASOCT.[29] About a fifth of these eyes were found to be occludable on gonioscopy at follow-up.[29,30] However, it is yet to be clear whether the delay in the diagnosis leads to a worse prognosis as the studies have mainly focused on the development of gonioscopic closure of angles on follow-up and not on the incidence of angle-closure glaucoma. The available evidence from two randomized control trials the Zhongshan angle-closure prevention trial (ZAP – follow-up of 6 years) and the Singapore asymptomatic narrow angles laser iridotomy study (ANALIS – follow-up of 5 years) shows a low rate of progression of PACS to angle-closure disease in untreated eyes (7.97 per thousand eye years and 9.4% over 5 years, respectively).[31,32] Most of the eyes progressing were secondary to the development of peripheral anterior synechiae (ZAP – 6.64 per thousand eye years and ANALIS – 4.9% over 5 years). The rates of acute angle-closure and the number of those with elevated IOP were also not significantly different among untreated eyes and those treated with laser iridotomy in these eyes during the follow-up period. Large well-controlled longitudinal studies are needed to establish if there is a difference in the long-term prognosis of eyes by earlier detection of occludable angles with ASOCT when compared to gonioscopy.

Since most studies have used different diagnostic cutoffs for both imaging and biometry, it is difficult to identify a single cutoff applicable across different populations.[13-20,23,26-28] Biometric differences exist between different racial groups and in rates of acute angle closure.[33,34] This would explain the different cutoffs in these studies but may necessitate the need for individualized cutoffs in different populations.

Most of the studies have looked at identifying angle closure and not PACG.[13-20,23,26-28] Incorporating these in screening programs could overwhelm healthcare systems in resource-constrained areas. It would also need a clear policy about the need for a laser iridotomy in all eyes with PACS. However, these tests in combination with other evidence of PACG such as raised IOP or a glaucomatous disc would be helpful in appropriate referral.

CONCLUSION

A review of the population-based studies shows that both ASOCT and slit-lamp examination combined with biometry yield favorable results in the target population when screening

for angle closure. A combination of tested parameters yielded better results. The feasibility of individual techniques used in different populations may be determined by multiple factors including invasiveness of the procedures, expertise in the use of, and analysis of the individual methods and the resources available.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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