

# Asymmetric Patterns of Visual Field Defect in Primary Open-Angle and Primary Angle-Closure Glaucoma

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**PURPOSE.** To compare the hemifield asymmetry of visual field (VF) loss in primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG) across all severity levels.

**METHODS.** A total of 522 eyes of 327 patients with POAG (mean age  $\pm$  SD, 54.1  $\pm$  12.4 years) and 375 eyes of 204 patients with PACG (67.3  $\pm$  8.9 years) were included. Subjects meeting the definitions of POAG or PACG were included. Means of the total deviation (TD) values (Humphrey 24-2 VF) in the Glaucoma Hemifield Test (GHT) regions were calculated in early ( $\geq -6$  dB), moderate ( $< -6$  dB and  $\geq -12$  dB), and advanced ( $< -12$  dB) stages of POAG and PACG eyes. Then the differences of the TD values between superior and inferior hemifield GHT regions of POAG and PACG eyes were calculated. Also, the relationship between the values of pattern SD (PSD) and mean TD (mTD) was compared between POAG and PACG.

**RESULTS.** In POAG eyes in the early stage, three regions (central, paracentral, and peripheral) in the superior hemifield had greater loss than their inferior counterparts; in moderate and advanced stages, all GHT regions in the superior hemifield had greater loss than their inferior counterparts. In PACG eyes, significantly fewer regions in the superior hemifield were significantly worse than their inferior counterpart, compared with POAG: one region (central) in early stage, two regions (central and peripheral) in moderate stage, and one region (central) in advanced stage. POAG eyes had greater PSD values than PACG eyes for given mean of TD values.

**CONCLUSIONS.** In both POAG and PACG eyes, VF damage was more pronounced in superior hemifield than inferior hemifield; however, this tendency was more obvious in POAG eyes than in PACG eyes.

**Keywords:** angle-closure glaucoma, open-angle glaucoma, visual field, patterns of defect

Glaucoma is the second leading cause of blindness worldwide after cataract.<sup>1-3</sup> Primary glaucoma is categorized into disease types with respect to the status of the iridocorneal angle: primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG). The prevalence of POAG and PACG varies across the world.<sup>2,4,5</sup> POAG is more predominant in most populations, with a prevalence of approximately 3.5% in those between 40 and 80 years old,<sup>6</sup> whereas the prevalence of PACG is approximately 0.9%.<sup>2</sup> Although the prevalence of POAG is higher, patients with PACG have a 3-fold greater risk of developing blindness compared with POAG.<sup>2,6-8</sup> As a result, it is estimated that 4.5 million people are bilaterally blind due to POAG, whereas that number is 3.9 million people with PACG, worldwide.<sup>2</sup> This is problematic in specific areas. A high prevalence of PACG has been reported in Alaskan natives,<sup>9</sup> Asia,<sup>6,9</sup> Myanmar,<sup>10</sup> and Mongolia.<sup>11,12</sup>

It is well documented that the major risk factor for developing glaucoma is raised IOP; however, in POAG, there

are other proposed non-IOP risk factors, including low systemic blood pressure, myopia, and also vulnerability at the optic disc.<sup>13-15</sup> On the other hand, in PACG, elevated IOP secondary to angle closure is the fundamental disease mechanism.<sup>12</sup> Reflecting this, hyperopia is a risk factor for the development of PACG,<sup>16-18</sup> although contradicting results have also been reported,<sup>19-21</sup> whereas myopia is a risk factor for POAG.<sup>15</sup> The difference in disease mechanisms is also supported by different genetic associations; single nucleotide polymorphisms identified in PACG, such as PLEKHA7 and COL11A1,<sup>22,23</sup> are different from those in POAG, although the detailed pathogenic function of these genes is still unknown.

The clinical course of the disease is also very different between POAG and PACG eyes. The development of PACG requires elevated IOP, which is usually preventable if the angle-closure process is resolved before irreversible trabecular damage occurs, usually through laser peripheral iridotomy and/or cataract extraction, although it has been reported that the visual field (VF) can continue to deteriorate, despite well-



controlled pressure.<sup>24</sup> On the other hand, in POAG, although IOP lowering slows the rate of VF progression, individuals can continue to progress.<sup>25-29</sup> Furthermore, when there is fast VF progression in POAG, trabeculectomy is often performed even if IOP is in the normal range with medical treatments, aiming for a further reduction of IOP. Probably reflecting these differences in pathogenesis, the optic discs often show different characteristics between POAG and PACG eyes. For instance, it has been reported that the prevalence of peripapillary atrophy is higher and the peripapillary atrophy-to-disc area ratio is significantly larger in the POAG group compared with the chronic PACG group with no evidence of an acute attack.<sup>30</sup> Also, PACG eyes can have a pale disc; although optic disc pallor is usually a feature of acute angle closure, there is evidence that the optic disc may be pale in chronic PACG eyes.<sup>30</sup>

All of these findings suggest different disease mechanisms for POAG and PACG, which may be reflected on the patterns of VF damage. Although both in POAG<sup>31,32</sup> and PACG,<sup>33</sup> VF damage is more pronounced in the superior than the inferior hemifield, the pattern of VF defects in POAG and PACG may differ. There are several previous studies that reported that PACG eyes had diffuse VF damage compared with POAG<sup>34-36</sup>; however, these studies included a relatively small number of eyes; fewer than 110 POAG eyes and fewer than 50 PACG eyes. There is just one previous report analyzing more than 100 eyes both in POAG and PACG groups<sup>37</sup>; however, the comparison of VF damage was carried out in each of early, moderate, and advanced stages, so the comparison was made using no more than 30 eyes at each severity level. Thus, these findings need confirmation in a further study with larger sample sizes in both glaucoma groups. There are other studies that investigated the pattern(s) of VF loss in POAG and PACG eyes from large cohorts; however, these studies included only one of the disease types.<sup>34,38</sup> Thus, the purpose of the current study was to compare the patterns of VF loss in a large number of POAG (522 eyes) and PACG eyes (375 eyes).

## METHODS

The VFs collected from POAG and PACG patients were analyzed. The eyes were stratified to three severity levels: early, moderate, and advanced. The VF asymmetry for each POAG and PACG eye was calculated pointwise and in the GHT regions. VF asymmetry was defined as the sensitivity difference between the superior and inferior hemifields; the total deviation (TD) values in the inferior hemifield (pointwise or regionwise) were subtracted from the corresponding TD values at the superior hemifield. The superior-inferior VF asymmetry of POAG eyes and PACG eyes were calculated and the patterns of VF asymmetry in each severity level in POAG and PACG were determined and their statistical significance was established.

## POAG and PACG Subjects

The review boards of both institutes of the Tokyo University Hospital and the Ryukyus University Hospital reviewed and approved the study protocol. This study complied with the tenets of the Declaration of Helsinki. Written consent was given by patients for their information to be stored in the hospital database and used for research; otherwise, based on the regulations of the Japanese Guidelines for Epidemiologic Study 2008 issued by the Japanese Government, the study protocols did not require each patient to provide written informed consent, instead the protocol was posted at the outpatient clinic to notify participants about the study.

All of the VF records were retrospectively obtained from medical records of participants who visited either the Tokyo University Hospital or Ryukyus University Hospital between 1998 and 2016. Using the electronic records of both institutes, all patients with POAG and PACG who satisfied the following criteria were identified: (1) glaucoma was the only disease causing VF damage, (2) at least two reliable VF measurements with the Humphrey Field Analyzer II (HFA; Carl Zeiss Meditec, Inc., Dublin, CA, USA) using either the 24-2 or 30-2 pattern and the SITA standard program, and (3) presence of an abnormal VF following Anderson-Patella's criteria.<sup>39</sup>

We included eyes with best-corrected visual acuity (VA) better than than 0.5 logMAR (Snellen equivalent approximately 6/18). POAG was defined as (1) the presence of typical glaucomatous changes in the optic nerve head, such as a rim notch with a rim width  $\leq 0.1$  disc diameter or a vertical cup-to-disc ratio of  $>0.7$  and/or a retinal nerve fiber layer defect with its width at the optic nerve head margin greater than a major retinal vessel, diverging in an arcuate or wedge shape, with a VF defect suggestive of glaucoma<sup>40</sup>; and (2) as gonioscopic wide open angles of grade 3 or 4 based on the Shaffer classification; IOP was not a diagnostic criterion. Exclusion criteria were being younger than 20 years, and (2) having possible secondary ocular hypertension in either eye. PACG was defined as the presence of angle closure (at least 180 degree of the posterior pigmented trabecular meshwork not visible on gonioscopy in the primary position of gaze with no indentation) with glaucomatous optic neuropathy (defined as loss of neuroretinal rim with a vertical cup-to-disc ratio of greater than 0.7 or between-eye vertical cup-to-disc ratio asymmetry of greater than 0.2, focal notching of the neuroretinal rim) with a VF defect suggestive of glaucoma.<sup>40</sup> Eyes with a history of IOL surgery or acute angle closure or IOP greater than 30 mm Hg were excluded. All of the IOP records before the VF measurements were collected from medical record, and the maximum IOP was calculated accordingly (maximum IOP).

## Visual Fields

The first VFs were excluded from the analysis (due to learning effect), and only reliable VF tests were included. Reliable VF was defined as  $\leq 33\%$  fixation losses and  $\leq 15\%$  false-positive results, following a previous study that performed similar analyses. When VFs were obtained with the 30-2 test pattern, only the central 52 test locations corresponding to the 24-2 test pattern were used in the analysis. Then the mean of TD (mTD) of the 52 test points was calculated.

Both for POAG and PACG, eyes were stratified into three groups according to the severity of the average of TD values: early glaucoma (mTD value equal to or better than  $-6$  dB), moderate glaucoma (mTD value worse than  $-6$  dB and better than  $-12$  dB) and advanced glaucoma (mTD value equal or worse than  $-12$  dB).<sup>41</sup> Then the entire VF was divided into 10 regions: a central, a paracentral, a nasal, and two peripheral (arcuate 1 and arcuate 2) regions in each of superior and inferior hemifields, derived from the Glaucoma Hemifield Test (GHT) and also following previous studies (see Fig. 1).<sup>37,38</sup> The average of TD values in each of these 10 clusters was calculated, as well as those in the entire superior and inferior hemifields.

## Statistical Analysis

Demographics of the groups were compared using the generalized estimating equation (GEE) model with Gaussian function for continuous variables, and with binomial function for categorical (binary) variables. Essentially, the GEE model is

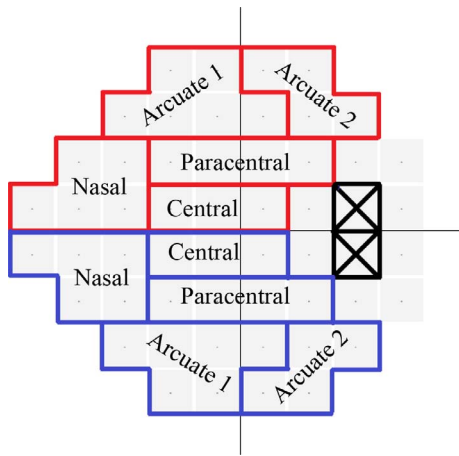


FIGURE 1. GHT VF regions. Five GHT regions at the superior hemifield and their corresponding five GHT regions at the inferior hemifield.

very similar to ordinary linear regression (OLR) in describing the relationship between the predictor variables and an outcome variable. However, OLR analysis makes the general assumption that all observations are independent of each other. In the current study, measurements are nested within subjects (both eyes from some subjects) and, thus, dependent on each other. Ignoring this grouping of the measurements will result in the underestimation of standard errors of regression coefficients. The GEE adjusts for the hierarchical structure of the data, modeling in a way in which measurements are grouped within subjects. In addition, the confounding variables of mean TD and sex were also controlled in the GEE model to minimize their effects on the outcome.

**Within-Group and Between-Group Comparisons**

In the pointwise analysis, each VF test location in the superior hemifield was compared with its counterpart (symmetrical over the horizontal line) location in the inferior hemifield, and the VF superior-inferior asymmetry was calculated (as TD value in the inferior hemifield minus TD value in the superior

hemifield) for POAG and PACG eyes using the GEE model controlling for the nested structure of two eyes in a patient and mTD. The between-group comparison was carried out by comparing the VF asymmetry patterns in POAG and PACG groups using the GEE model, accounting for sex, refractive error, maximum IOP, and visual acuity.

Likewise, in the regionwise analysis, the average of TD values in the central, paracentral, nasal, and peripheral (arcuate 1 and 2) regions (see Fig. 1) in the superior hemifield were compared with their corresponding regions in the inferior hemifield for POAG and PACG eyes at all severity levels using the GEE model. The between-group comparison was carried out by comparing the VF asymmetry patterns in POAG and PACG groups, using the GEE model, accounting for gender, refractive error, maximum IOP, and visual acuity.

**Relationship Between mTD and PSD**

To analyze whether the dominant pattern in the VFs was generalized or localized loss, the relationship between mTD and PSD was analyzed using a quadratic regression and the relationship was compared between POAG and PACG groups using the GEE model.

All statistical analyses were performed using the statistical programming language R (R version 3.3.1; The Foundation for Statistical Computing, Vienna, Austria, <http://www.r-project.org>).

**RESULTS**

Demographic characteristics of POAG and PACG patients are shown in Table 1. Within-group demographics: In POAG eyes, the best-corrected VAs were significantly different across early, moderate, and advanced severity levels ( $P = 0.001$ , GEE model). Similarly, the best-corrected VAs were significantly different across early, moderate, and advanced severity levels for PACG eyes ( $P < 0.001$ , GEE model). Although there was no significant difference in refractive error among different severity levels in POAG eyes, the difference was significant ( $P = 0.01$ , GEE model) among different severity levels in PACG eyes. Thirty-seven eyes of 29 POAG patients had a history of IOL surgery. When these eyes were excluded, the refractive

TABLE 1. Demographic Information of Patients

Characteristics	Total	Early	Moderate	Advanced	P*
POAG patients					
Subjects	327	207	124	80	-
Eyes	522	290	139	93	-
Age, y	54.1 (12.4)	53.1 (12.5)	55.1 (12.1)	55.9 (12.1)	0.72
Sex, % female	50.0	52.0	47.0	46.0	0.63
BCVA, logMAR	-0.07 (0.08)	-0.08 (0.08)	-0.06 (0.08)	-0.05 (0.09)	0.001
Refractive error, Diopters	-4.3 (3.9)	-4.1 (3.8)	-4.5 (4.2)	-4.4 (3.6)	0.37
Maximum IOP	16.0 (4.0)	16.4 (4.4)	15.7 (3.6)	15.3 (3.1)	0.03
mTD, dB	-6.7 dB (6.2)	-2.4 (1.9)	-8.8 (2.1)	-16.9 (4.2)	< 0.001
PACG patients					
Subjects	204	138	59	84	-
Eyes	375	198	68	109	-
Age, y	67.3 (8.9)	66.8 (8.4)	66.7 (9.2)	68.7 (9.5)	0.32
Sex, % female	60.7%	59.0%	68.0%	60.0%	0.64
BCVA, logMAR	-0.01 (0.08)	-0.03 (0.07)	-0.01 (0.07)	0.02 (0.1)	< 0.001
Refractive error, Diopters	-0.35 (1.7)	-0.08 (1.5)	-0.53 (1.9)	-0.70 (1.8)	0.01
Maximum IOP	15.6 (3.6)	15.7 (5.2)	15.6 (5.5)	15.4 (6.7)	0.96
mTD, dB	-8.8 dB (8.7)	-2.4 (2.0)	-8.5 (1.7)	-20.7 (5.9)	< 0.001

Data represent mean (SD).

\* P values calculated by applying ANOVA on GEE models comparing subgroups (severity) within each disease type.

TABLE 2. Between-Hemifield Comparison of GHT Regions

Region	Subregion	Early, n = 290		Moderate, n = 139		Advanced, n = 93	
		Average TD Values, dB	P*	Average TD Values, dB	P*	Average TD Values, dB	P*
POAG, n = 522							
Central	Superior	-3.1	< 0.001	-11.0	< 0.001	-19.8	< 0.001
	Inferior	-1.7		-5.9		-11.3	
Paracentral	Superior	-3.3	0.002	-12.4	< 0.001	-24.4	< 0.001
	Inferior	-2.2		-8.1		-15.8	
Nasal	Superior	-4.2	0.22	-16.1	< 0.001	-26.6	< 0.001
	Inferior	-3.6		-11.8		-21.3	
Peripheral, arcuate 1	Superior	-2.2	0.96	-10.7	< 0.001	-20.9	0.001
	Inferior	-2.2		-6.8		-14.6	
Peripheral, arcuate 2	Superior	-1.6	0.04	-7.2	< 0.001	-16.0	< 0.001
	Inferior	-1.1		-3.7		-9.3	
Region	Subregion	Early, n = 198		Moderate, n = 68		Advanced, n = 109	
		Average TD Values, dB	P*	Average TD Values, dB	P*	Average TD Values, dB	P*
PACG, n = 375							
Central	Superior	-2.5	0.02	-10.1	0.03	-21.7	< 0.001
	Inferior	-1.6		-7.3		-16.6	
Paracentral	Superior	-2.6	0.40	-10.3	0.46	-23.7	0.21
	Inferior	-2.3		-9.3		-21.9	
Nasal	Superior	-3.5	0.54	-11.9	0.85	-25.7	0.39
	Inferior	-3.2		-12.2		-24.8	
Peripheral, arcuate 1	Superior	-2.3	0.38	-8.7	0.22	-22.5	0.27
	Inferior	-2.6		-7.4		-21.1	
Peripheral, arcuate 2	Superior	-1.9	0.98	-7.5	0.02	-19.4	0.09
	Inferior	-1.9		-5.2		-17.2	

\* P values from GEE model that compares each GHT region asymmetry with corresponding test-retest GHT region asymmetry.

error in POAG eyes was -4.4 (SD 3.9), -4.2 (SD 3.8), and -4.6 (SD 4.1) Diopter in early, moderate, and advanced stages, respectively; there was no significant difference in refractive error across severity levels. There was no significant difference in age, sex, and maximum IOP across severity levels both in POAG and PACG eyes.

**Between-Group Demographics**

The mTD of PACG eyes at the advanced stage of glaucoma was significantly worse than the mTD of the POAG eyes (P < 0.001, GEE model). On average, the PACG patients were significantly older than POAG patients (67.3 vs. 54.1 years, P < 0.001, GEE model). The PACG group also had a larger number of females compared with the POAG group (P = 0.005, GEE model). The refractive error in the POAG eyes was significantly smaller (more negative) than that in the PACG eyes (P < 0.001, GEE model). The maximum IOP in the POAG group was similar to PACG group except in eyes at the early stage of glaucoma (P = 0.04, GEE model). The best-corrected VA was significantly different at all severity levels between POAG and PACG groups.

**Regionwise Comparison of Hemifields**

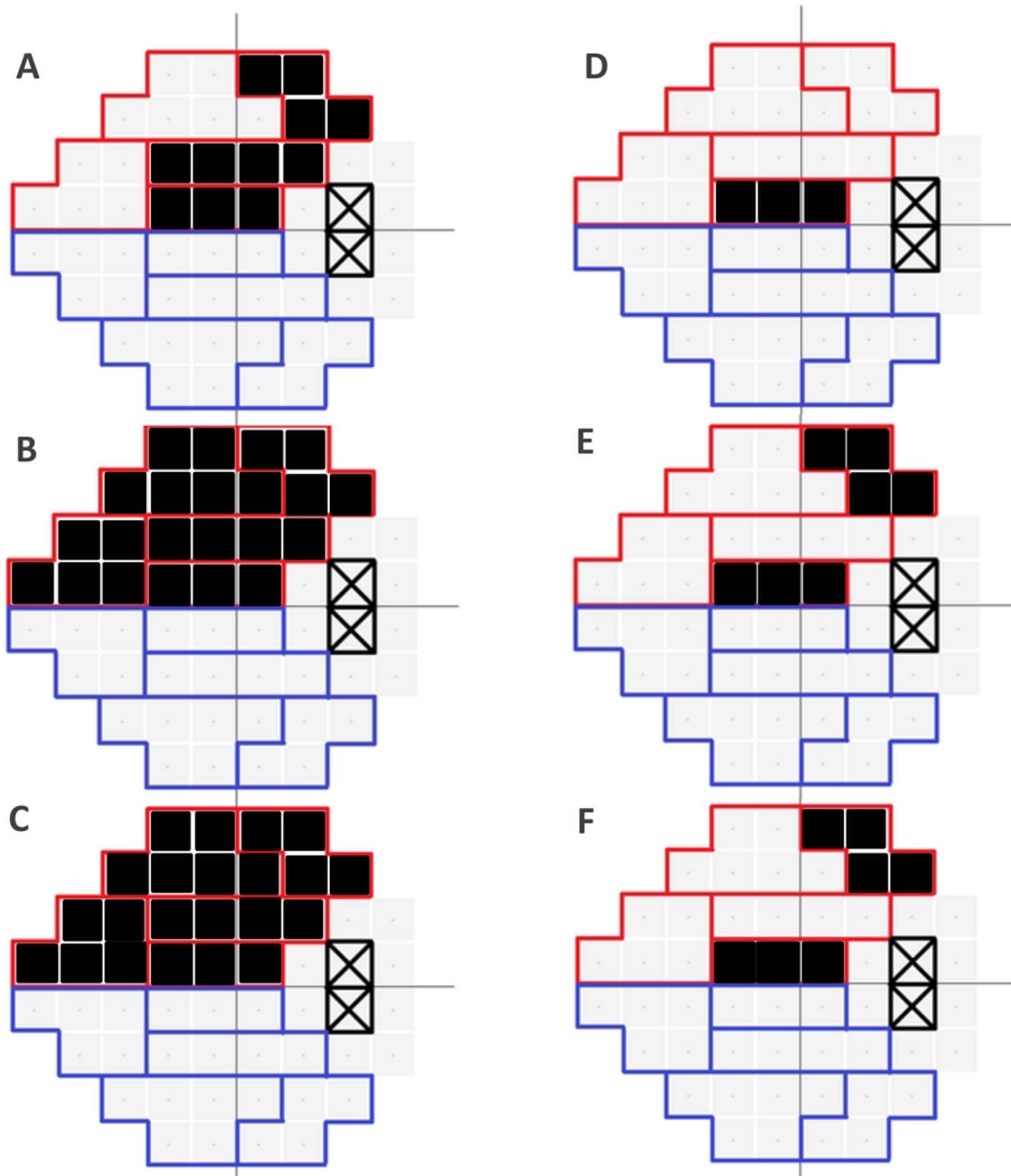
Table 2 demonstrates the regionwise superior-inferior hemifield asymmetry in POAG (top part) and PACG eyes (bottom part). In POAG eyes, in the early stage, the average TD values in the central, paracentral, and peripheral (arcuate 2) regions in the superior hemifield were significantly worse compared with corresponding regions in the inferior hemifield (P values < 0.001, 0.002, and 0.046, respectively; GEE models); however, there was no significant difference in the remaining two regions (P values were 0.22 and 0.96). In POAG eyes in the moderate and advanced stages, all five GHT regions in the

superior hemifield had worse average TD values than those in corresponding regions in the inferior hemifield (all P < 0.001) (Figs. 2A-C; Table 2).

In PACG eyes in the early stage, the average TD value in the central region of the superior hemifield was significantly worse than its counterpart region in the inferior hemifield (P = 0.014, GEE model); however, there was no significant difference in the average TD values of the remaining four regions (P values: 0.37, 0.55, 0.43, and 0.98). In the moderate-stage PACG eyes, the average TD values in both central and peripheral (arcuate 2) regions of the superior hemifield were significantly worse than those in the corresponding regions in the inferior hemifield (P values: 0.028 and 0.019, respectively). There was no significant difference in the average TD values in the remaining three regions (P values: 0.47, 0.71, and 0.26, respectively). In advanced-stage PACG eyes, the average TD values in the central regions of the superior hemifield were significantly worse than the average TD values in the corresponding region in the inferior hemifield (P < 0.001), whereas there was no significant difference in these values in the remaining four regions (P values: 0.11, 0.42, 0.27, and 0.14, respectively) (Figs. 2D-F).

**Pointwise Comparison of Hemifields**

Figure 3 shows the pointwise superior-inferior hemifield asymmetry in POAG eyes (Figs. 3A-C) and PACG eyes (Figs. 3D-F). In early POAG eyes, all of the TD points in the central region and a subset of TD points in the nasal, paracentral, and peripheral (arcuate 1) regions in superior hemifield were significantly worse than their counterparts in the inferior hemifield (TD and P values are shown in Fig. 3A). In moderate POAG eyes, the TD points in all GHT regions were significantly worse than their counterparts in the inferior hemifield (TD and



**FIGURE 2.** Between-hemifield comparison of GHT regions. (A-C) represent the patterns of VF defect of the POAG group and (D-F) show the superior-inferior asymmetric patterns of defect of the PACG group. (A) and (D) represent early stage, (B) and (E) represent moderate stage, and (C) and (F) represent advanced stage, respectively. *Black areas* show significant superior-inferior VF asymmetry; regional TD values in the superior hemifield are significantly worse than their counterpart in the inferior hemifield ( $P \leq 0.05$ ).

*P* values are shown in Fig. 3B). In advanced POAG eyes, the TD values of all TD points in all GHT regions were significantly worse than their counterparts in the inferior hemifield (TD and *P* values are shown in Fig. 3C).

In early PACG eyes, a subset of TD points in the central and paracentral regions in the superior hemifield had significantly lower values than their counterparts in the inferior hemifield (TD and *P* values are shown in Fig. 3D). In moderate PACG eyes, a subset of TD points in the central, paracentral, and peripheral (arcuate 1 and arcuate 2) regions in the superior hemifield had significantly lower values than their counterparts in the inferior hemifield (TD and *P* values are shown in Fig. 3E). In advanced PACG eyes, a subset of TD points in the central, paracentral, and peripheral (arcuate 1 and arcuate 2) regions in

the superior hemifield were significantly lower than their counterparts in the inferior hemifield (TD and *P* values are shown in Fig. 3F).

**POAG and PACG Comparison**

Figure 4 (panels from left to right: central, paracentral, nasal, arcuate 1, and arcuate 2, respectively) shows the relationship between the superior-inferior hemifield asymmetry plotted against mTD in POAG eyes (presented in blue) and PACG eyes (presented in orange). The best-fit quadratic curves for POAG and PACG groups follow a U-shape characteristic (except for the nasal region of PACG eyes), suggesting in all GHT regions, superior VF loss tended to be more pronounced than inferior

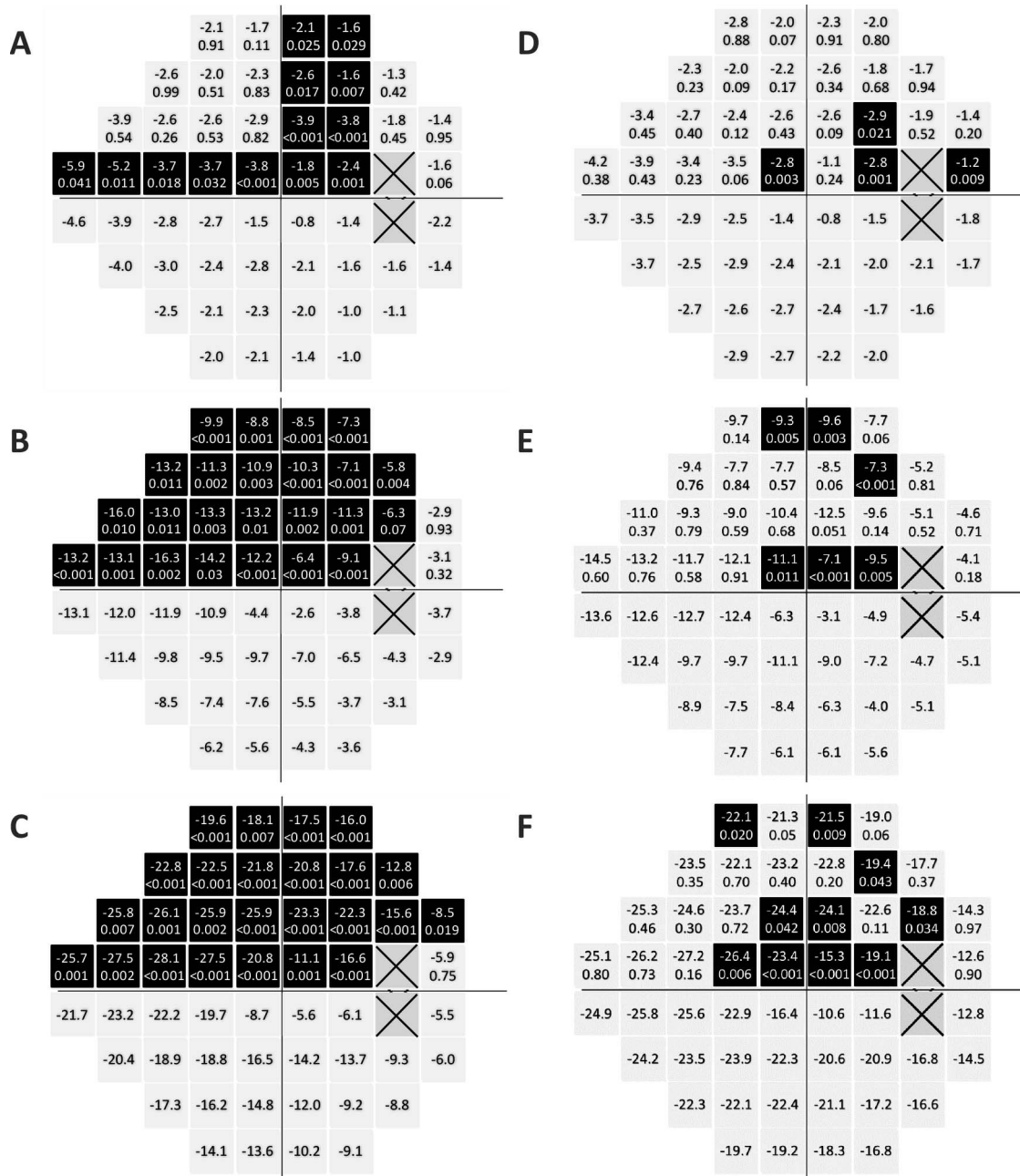


FIGURE 3. Comparison of TD values between superior and inferior hemifields. (A–C) belong to the POAG group and represent eyes in the early, moderate, and advanced stages of glaucoma, respectively. (D–F) show the patterns of defect of the PACG group corresponding to eyes in the early, moderate, and advanced stages of glaucoma, respectively. Black areas show TD values in superior hemifield test locations were significantly worse than their corresponding locations in the inferior hemifield ( $P \leq 0.05$ ). Shown at each superior location: mTD value at the top and  $P$  value at the bottom.  $P$  value reflects the significance of the difference between the mTD of the superior location and the inferior location. Shown at each inferior location: mTD value at that location.

region. Moreover, this tendency is more pronounced in POAG eyes than in PACG eyes, in the moderate stage of the disease in particular, as suggested by the greater distance between the curves of POAG and PACG.

The hemifield asymmetry (superior was worse than inferior hemifield) in all POAG eyes was significantly larger than that in all PACG eyes in central, paracentral, and nasal regions ( $P$  values: 0.041, 0.049, 0.035, GEE models), whereas the asymmetry was not significant in peripheral regions (arcuate 1 and arcuate 2  $P$  values: 0.09 and 0.07, respectively) when adjusted for sex, mTD, maximum IOP, and refractive error.

Figure 5 shows the comparison of the relationships between PSD and mTD, between POAG and PACG eyes. As was expected, the PSD and mTD followed quadratic relationship; PSD worsened as mTD worsened up to the point mTD reaches approximately  $-17.5$  dB and the PSD returns to fall beyond this point. The best-fit quadratic curves for the POAG and PACG groups demonstrated that the PACG group had lower PSD values for given mTD values. We further analyzed this finding by fitting a GEE model with PSD as the dependent variable and diagnosis as the primary independent variable while controlling for sex, maximum IOP, refractive error, and  $(mTD)^2$  to account for the quartic characteristic of the

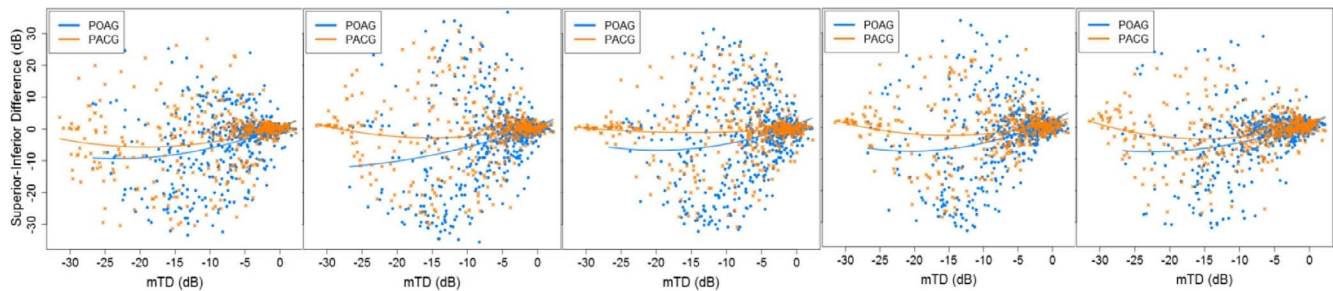


FIGURE 4. Scatterplot and second-order polynomial fitting the difference between the superior and inferior hemifields of the POAG (blue color) and PACG eyes (orange color) across all severity levels. From left to right: central, paracentral, nasal, peripheral (arcuate 1), and peripheral (arcuate 2) regions.

model. The model suggested that POAG eyes had significantly greater PSD values for a given mTD than the PACG eyes ( $P < 0.001$ , GEE model) which further emphasizes that POAG eyes had more localized patterns of defect compared with PACG eyes or in other words, PACG eyes had more generalized or diffuse loss compared with POAG eyes.

## DISCUSSION

In this study, we compared the superior-inferior asymmetric patterns of VF loss in POAG and PACG eyes. In early-stage POAG eyes, the hemifield asymmetry (superior worse than inferior) was significant in central, paracentral, and peripheral (arcuate 2) regions. In POAG eyes in moderate and advanced stages, all five GHT regions had significant hemifield asymmetry. In PACG eyes, in contrast, this finding was observed in fewer regions; only one region (central) in early and advanced stages, and two regions (central and peripheral) in moderate stage. In addition, POAG eyes tended to have more localized loss than PACG eyes, suggested by higher PSD values for given mTD values accounting for all covariates.

Among the comparisons of demographic parameters between POAG and PACG eyes, a larger number of females was observed in PACG than in POAG (see Table 1). This is in agreement with previous studies that suggested that females are more likely to develop PACG<sup>35,36,42,43</sup> and sex is even an independent risk factor for developing PACG.<sup>12</sup> We also observed that myopia was more associated with POAG,

whereas hyperopia was more associated with PACG, agreeing with previous reports.<sup>16,44</sup>

Gazzard and colleagues<sup>37</sup> reported that the paracentral and peripheral (arcuate 2) regions in the superior hemifield were more damaged than their counterpart regions in the inferior hemifield in early POAG eyes, whereas in moderately damaged eyes, all GHT regions in superior hemifield were significantly more damaged than their counterpart regions in the inferior hemifield. This is in agreement with the current results (see Figs. 2A-C). In advanced POAG eyes in the same study, only the central region in the superior hemifield was more damaged than the corresponding region in the inferior hemifield, whereas all GHT regions in the superior hemifield were significantly worse than the corresponding regions in the inferior hemifield in our study. One possible reason for this disagreement would be the different cutoff values adopted to define the severity levels. In the previous study, the advanced group was defined as mean deviation (MD)  $< -20$  dB, which is much more advanced than that in the current study ( $-12$  dB). As a result, in the previous study, the VF damage reached into the inferior hemifield, except for the central area which usually is preserved until the very late stage of glaucoma.

Gazzard and colleagues<sup>37</sup> reported that no region showed significant superior-inferior asymmetry in early PACG eyes, whereas our study showed a significant superior-inferior asymmetry in the central region. In that study, all GHT regions except the nasal region showed significant asymmetry in moderately glaucomatous eyes, whereas we observed just central and peripheral (arcuate 2) regions with significant superior-inferior asymmetry. Finally, both studies are in agreement that the central region of the advanced PACG eyes has a significant superior-inferior asymmetry (see Figs. 2D-F). On the other hand, Atalay and associates<sup>38</sup> reported that there is significant superior-inferior asymmetry in the paracentral region in the early stage, central, and paracentral regions in the moderate stage, and all GHT regions in the advanced stage of PACG eyes. Different criteria used in defining stages of the disease could be one reason for the differences in the patterns of VF defect among these studies. However, all studies are in agreement that the central region of the moderate and advanced PACG eyes is more severely damaged in the superior hemifield compared with the inferior hemifield.

In the current study, POAG eyes had a higher PSD than that in PACG eyes for given MD values, which suggests more localized patterns of loss in POAG eyes compared with PACG eyes and more diffuse VF damage in PACG eyes compared with POAG eyes. This finding is consistent with other previous reports, despite the difference of ethnicity: Gazzard et al.<sup>37</sup> (mainly Chinese subjects), Rhee et al.<sup>34</sup> (mainly Korean subjects), and Boland and associates (mainly Caucasian subjects).<sup>35</sup> Ngo et al. (mainly Chinese subjects) also reported

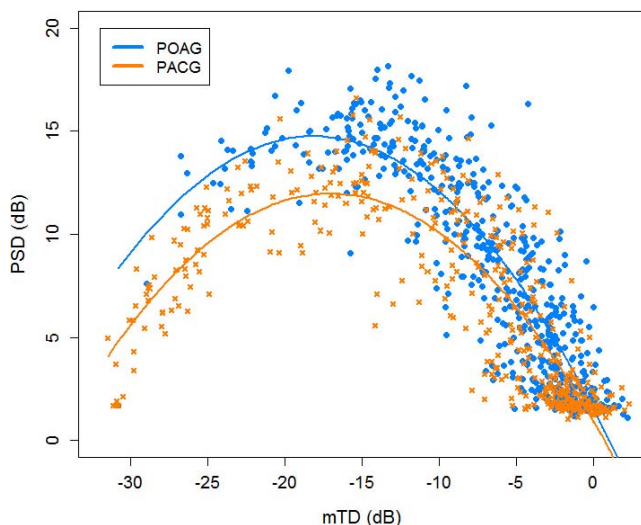


FIGURE 5. Scatterplot of PSD versus mTD for eyes with POAG (in blue circles) and PACG (in orange crosses).

similar observations, although they reported that the difference was not statistically significant.<sup>36</sup>

The current study consisted of Japanese patients, in whom normal tension glaucoma (NTG) prevalence is high compared with Caucasians.<sup>45</sup> Therefore, in the current study, this fact may have influenced the appearance of the localized VF damage in POAG eyes and observing more diffuse VF damage in PACG eyes. Diffuse VF damage in PACG eyes may be explained by the differences in the optic disc appearance of these two groups. In PACG eyes, optic disc pallor is usually a feature of acute angle closure; however, there is a report that the optic disc may be pale in chronic PACG rather than having cupping and/or optic disc rim notching, which are characteristic of optic disc change in POAG.<sup>46</sup> It should be noted that POAG eyes with localized VF defect are more likely to be diagnosed as glaucoma than those with diffuse optic disc enlargement. On the other hand, in a group of patients with PACG, it is more likely that the initial diagnosis was based on elevated IOP and narrow angle, irrespective of the type of optic disc damage they presented. Thus, the current results may be biased in this respect. In other words, it is likely that the patients with POAG at the time of diagnosis had normal IOPs and the diagnosis was made on the basis of suspicious discs (maybe more localized losses), as opposed to the PACG group, in whom IOP was likely elevated at the time of diagnosis. The current results may be biased by these differences. However, in the current study, PACG eyes with previous angle-closure attack and IOP greater than 30 mm Hg were excluded. Moreover, the effect of this bias would be small, if any, in advanced-stage disease. Nonetheless, there was a similar/continuous VF defect pattern in POAG eyes from early to advanced stage. Thus, there may be some ascertainment bias in the current results; however, the influence of this bias would be relatively small.

Gazzard et al.<sup>47</sup> reported that IOP alone was less associated with the severity of VF loss in POAG eyes than in PACG eyes, suggesting there may be other factors attributing to the VF damage in POAG eyes.<sup>37</sup> Because the IOP is not significantly different between the two groups in our study, we also suggest that there may be other factors attributing to the difference in VF patterns of loss between POAG and PACG eyes. In particular, PACG eyes often have intermittent/irreversible (without interventions) sharp spike(s) of IOP elevation. Moreover, under highly elevated IOP, the damage may be closer to ischemia of the optic disc.<sup>12</sup> VF damage in ischemic optic neuropathy is predominant in the inferior hemifield,<sup>48</sup> and also, we have recently suggested VF damage in POAG patients who smoke tends to be in the inferior hemifield.<sup>49</sup> These findings imply that the diffuse VF damage both in superior and inferior hemifields in the PACG eyes may be caused by the elevated IOP itself and also induced ischemia. Also, as speculated in Boland et al.,<sup>35</sup> PACG may not be related to increased susceptibility in the optic disc and retina, such as abnormally compliant disc connective tissues that have greater vulnerability to IOP. On the other hand, POAG, in particular in normal-tension glaucoma, often occurs at IOP levels that are tolerated by most eyes and may have idiosyncratic defects in nerve head structure or ganglion cell susceptibility to apoptosis, which may be underlying the fact that inferotemporal rim loss is the most common optic disc change in POAG.<sup>48</sup> These factors may also have contributed to the difference of VF damage between POAG and PACG eyes, observed in the current study. Another major difference may come from the study sample size. The current study analyzed a much larger dataset of 522 POAG eyes and 375 PACG eyes to allow the conducting of a robust comparison of VF patterns of defect across several severities levels.

One of the limitations of our study is that the VF damage was investigated only in a cross-sectional manner. A follow-up

study would be needed to characterize temporal VF progression patterns. Another limitation is that axial length measurements were not obtained, because the current data were obtained from a real-world clinic where axial length is not routinely measured. Also, the IOP data without treatment were unknown. Thus, the level of IOP when the damage to the optic discs occurred is unknown, and it would be suspected that they were much higher in the PACG group. These variables may be related to the VF change, and a future study should be conducted measuring these variables.

In conclusion, the current study suggested VF damage is more pronounced in the superior hemifield than in the inferior hemifield both in POAG and PACG eyes; however, this tendency was less obvious in PACG eyes. In addition, the VF damage in PACG eyes is more diffuse than that in POAG eyes. These findings may be attributed to different underlying pathologies of POAG and PACG. This fact also implies that optimal therapeutic approaches may be different.

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