Early Detection of Glaucomatous Visual Field Progression Using Pointwise Linear Regression With Binomial Test in the Central 10 Degrees

SHOTARO ASANO, HIROSHI MURATA, MASATO MATSUURA, YURI FUJINO, AND RYO ASAOKA

• PURPOSE: **We previously reported that it was beneficial to apply binomial pointwise linear regression (PLR) to detect 24-2 glaucomatous visual field (VF) progression, compared to mean deviation (MD) trend analysis and permutation analysis of PLR (PoPLR). The purpose of the current study was to validate the usefulness of the binomial PLR method to detect VF progression in the central 10 degrees in glaucoma patients.**

• DESIGN: **Reliability assessment.**

• METHODS: **A series of 15 VFs (Humphrey Field Analyzer 10-2 SITA-standard) from 97 eyes in 69 primary open-angle glaucoma patients, obtained over 8.5 ± 1.3 years (mean ± SD), were investigated. PLR was performed by regressing the total deviation of all test points on the series of 15 VFs. VF progression was determined from the analyses of VF test points using the binomial test (1-sided, $P < .025$). The time needed to detect VF progression was also investigated. The results were compared with PoPLR and MD trend analyses.**

• RESULTS: **The binomial PLR was comparable to PoPLR and MD trend analyses in the positive predictive value (0.19 to 0.80), the negative predictive value (0.86 to 1.0), and the false positive rate (0.0 to 0.13) to evaluate glaucomatous VF progression. The time needed to detect VF progression (4.2 ± 1.8 years) was significantly shorter with the binomial PLR method compared with PoPLR and MD trend analysis ($P = .04$, $P = .012$, respectively).**

• CONCLUSIONS: **The binomial PLR method detected glaucomatous VF progression in the central 10 degrees significantly earlier than PoPLR and MD trend analyses. (Am J Ophthalmol 2019;199:140–149.**

Accepted for publication Nov 10, 2018.

From the Department of Ophthalmology, Graduate School of Medicine and Faculty of Medicine, The University of Tokyo, Tokyo, Japan (S.A., H.M., M.M., Y.F., R.A.); and Department of Ophthalmology, Graduate School of Medical Sciences, Kitasato University, Kanagawa, Japan (M.M., Y.F.).

Inquiries to Ryo Asaoka, Department of Ophthalmology, Graduate School of Medicine and Faculty of Medicine, The University of Tokyo, Tokyo 113-8655, Japan; e-mail: rasaoka-tky@umin.ac.jp

GLAUCOMA IS ONE OF THE LEADING CAUSES OF blindness in the world.[1] Because glaucomatous visual field (VF) deterioration is progressive and irreversible,[2] early and accurate detection of progression of VF defect is essential.[3] VF progression can be halted by applying medical and/or surgical intraocular pressure (IOP)-reduction treatments, as shown in many previous randomized controlled trial studies[4-8]; however, such treatments can be associated with serious complications[9-14] and also a decrease in patients' quality of life,[15,16] and hence, excessive treatment must be avoided. Thus, accurate assessment and early detection of VF progression is essential in the management of glaucoma.

The mean deviation (MD) trend analysis of the Humphrey Field Analyzer (HFA; Carl Zeiss Meditec, Dublin, California, USA) 24-2 VF is one of the most frequently used methods to clinically assess the speed of glaucomatous VF progression. However, the MD value is the average of VF damage in the entire VF, and as a result, this approach is not sensitive to detect focal VF progression. Such information can be well assessed using the pointwise trend analysis or pointwise linear regression (PLR),[17-19] as in the VF progression analysis software of PROGRESSOR (Medisoft ltd, Leeds, UK).[20] As a result, as shown in many previous reports, PLR is more useful than MD trend analysis to achieve early detection of VF progression.[21-25] Despite this advantage, there is a drawback in PLR: the assessment of progression speed in the entire VF cannot be obtained.[26] O'Leary and associates established an approach to overcome this problem by applying the permutation test analysis to PLR (PoPLR), and they proposed that the PoPLR method surpassed MD trend analysis to detect progression of VF damage.[27] In addition, we have also previously reported that applying the binomial test to PLR (binomial PLR), instead of the permutation test, enabled an even more reliable and sensitive detection of progression than PoPLR.[26] To the best of our knowledge, there has not been any other report that suggested such a method with a better ability for early detection of progression in whole VF using PLR.

Recent studies have revealed that HFA 24-2 VF is not optimal to assess the damage in the central VF and is recommended to measure HFA 10-2 VF.[28-33] Furthermore, the central VF is clinically very important, because it is more directly associated with the patients' vision related to the

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2018.11.004

quality of life[34,35] and also more directly related to visual acuity than HFA 24-2 VF.[36] Indeed, the early use of trabeculectomy is often clinically performed in eyes with progression in the central VF area, irrespective of the progression status in more peripheral areas. Thus, an accurate assessment of progression in the central VF area is directly related to the treatment decision, and hence it is very important to detect progression in the HFA 10-2 VF accurately.

In the current study, we investigated the usefulness of the binomial PLR to evaluate the VF progression in the central 10 degrees, in comparison to PoPLR and MD trend analyses.

METHODS

THE CURRENT STUDY IS A COHORT STUDY. THE STUDY WAS approved by the Institutional Review Board of the University of Tokyo and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients.

All of the VF data of primary open-angle glaucoma (POAG) patients who underwent VF measurements at least 16 times at the glaucoma clinic in the Tokyo University Hospital and Matsuo Eye Clinic during the period from January 2000 to December 2015 were retrospectively enrolled. As a result, VF data from 97 eyes of 69 patients with POAG were collected.

Criteria for inclusion were visual acuity better than 6/20, refraction error between ±6.0 diopters, no previous ocular surgery (except for cataract extraction and intraocular lens implantation prior to the first VF measurement), open anterior chamber angle, and no other posterior segment eye disease. All VFs were recorded using the 10-2 test pattern and the SITA standard strategy with a Goldmann size III target. The reliability criteria applied were fixation losses less than 20% and false-positive responses less than 15%, following the criteria used by the HFA software. The false-negative rate was not used.[37]

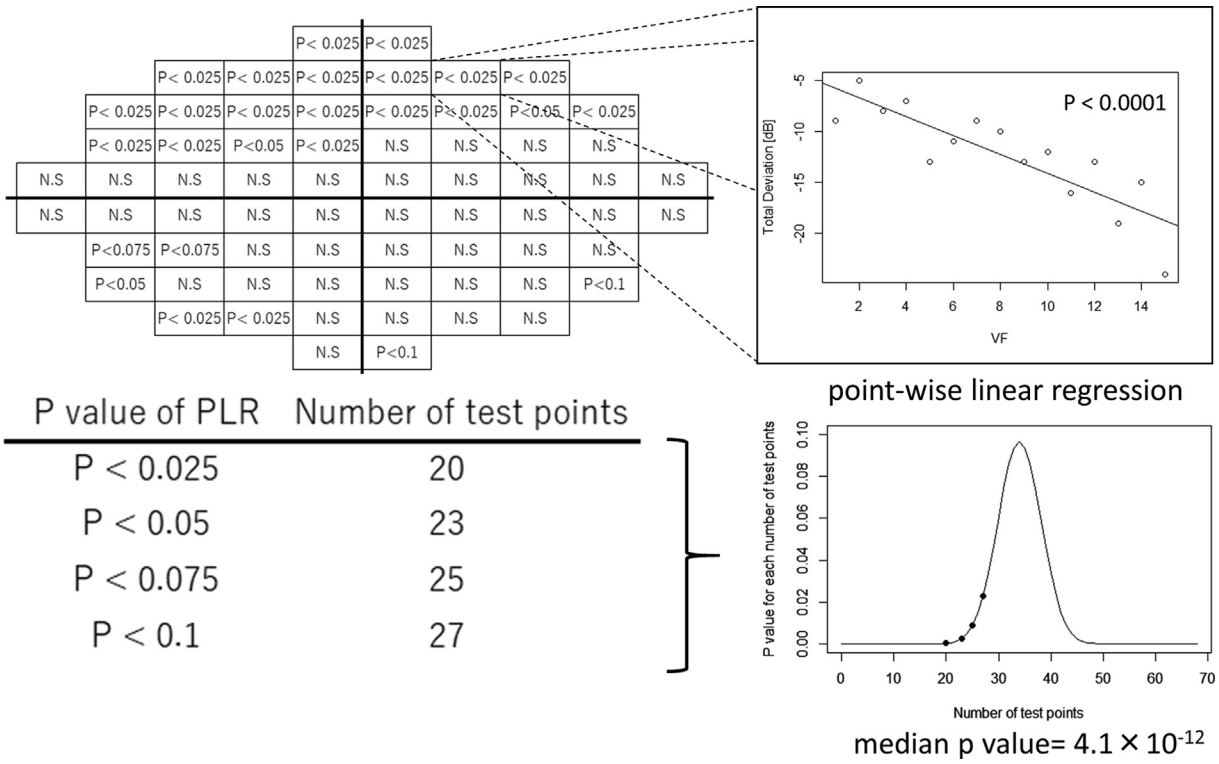
• **MEAN DEVIATION TREND ANALYSIS:** First, the initial VF was excluded to avoid the learning effect, and the remaining 15 VFs (VF_1 to VF_{15}) were used in all of the analyses. In the MD trend analysis, the MD value was linearly regressed against the time, using 15 VFs ($VF_{1\text{-}15}$), and then from $VF_{1\text{-}14}$ to $VF_{1\text{-}5}$. In the current study, the progression assessment with $VF_{1\text{-}15}$ was regarded as a surrogate for the absolute true progression, and the reliability of the MD trend analysis was evaluated using the following consistency measures: (1) the proportion of both progressing (PBP) as a surrogate measure for the true-positive rate, (2) the proportion of both not progressing (PBNP) as a surrogate measure for the true-negative rate, and (3) the proportion of inconsistent progression (PIP) as a surrogate measure for the false-positive rate. More specifically, these values were calculated as follows: (1) PBP: probability the MD trend analysis based on the complete series of VFs ($VF_{1\text{-}15}$) was "significant" in eyes with a "significant" progression with the MD trend analysis using shorter subsets of VFs (from $VF_{1\text{-}14}$ to $VF_{1\text{-}5}$); (2) PBNP: probability the MD trend analysis based on the complete series of VFs ($VF_{1\text{-}15}$) was "not significant" in eyes and progression was "not significant" with the MD trend analysis using shorter subsets of VFs (from $VF_{1\text{-}14}$ to $VF_{1\text{-}5}$); and (3) PIP: trend analysis based on the shorter series of VFs (from $VF_{1\text{-}14}$ to $VF_{1\text{-}5}$) was "significant" but the complete series of VFs ($VF_{1\text{-}15}$) was "not significant." In addition, the time required for the MD trend analysis to first detect a significant progression was calculated.

• **BINOMIAL PLR_{ALL} (FIGURE 1):** Figure 1 illustrates the calculation of binomial PLR_{all} in a sample case.

The detailed calculation of the binomial PLR method is described in our previous report.[26] The assumption in PLR is that VF damage progresses linearly over time, as a standard assumption for the VF trend analyses, including the MD trend analysis.[38-40] Here, the null hypothesis was that the slope of VF progression was equal to 0. Using this null hypothesis, slope coefficient *P* values from linear regression are distributed between 0 and 1, and consequently, the numbers of test points with *P* values less than .025, .05, .075, and .1 would follow the binomial distribution. If the null hypothesis was accepted, the numbers of test points would follow a binomial distribution, whereas if the null hypothesis was rejected, a slope coefficient of zero would be considered unlikely to be the result of random chance. Thus, the significance of the entire VF progression was assessed using these 4 cut-off *P* values, and then the median value was used to determine progression to merge the 4 *P* values.[41,42] We defined that a series of VF tests was "significant" if the *P* value calculated by binomial PLR was less than .025; otherwise, it was "not significant." Therefore, PBP, PBNP, PIP, and the time to first detect a significant progression were calculated, similarly to the MD trend analysis.

• **BINOMIAL $PLR_{4POINTS}$:** To identify the usefulness of HFA 24-2 VF to detect VF progression with the HFA 10-2 VF, the binomial PLR analysis was also applied to the test locations overlapping with a 24-2 program [4 points: (X, Y) = (3, 3), (3, −3), (−3, 3), and (−3, −3)]. Then, PBP, PBNP, PIP, and the time to first detect a significant progression were calculated.

• **PERMUTATION ANALYSIS OF POINTWISE LINEAR REGRESSION:** The PoPLR method was carried out using the R package "visualFields" modified to deal with HFA 10-2 VF, and then PBP, PBNP, PIP, and the time to first detect a significant progression were calculated.



P value of PLR	Number of test points
P < 0.025	20
P < 0.05	23
P < 0.075	25
P < 0.1	27

FIGURE 1. Calculation of binomial PLR_{all} in a sample case (male patient, aged 42 years) using first to 15th visual fields (VFs). (Top) The *P* value for each test point with linear regression was evaluated, and (Bottom left) the number of $P < .025$, $P < .05$, $P < .075$, and $P < .1$ were counted. (Bottom right) *P* values of each number of test points with binomial tests were calculated, and median value for those for *P* values (4.1×10^{-12}) were estimated. MD = mean deviation; PLR = pointwise linear regression; VF = visual field.

These PBP, PBNP, and PIP values of each VF series (from $VF_{1\text{-}14}$ to $VF_{1\text{-}5}$) were compared among the binomial PLR_{all}, $PLR_{4points}$, PoPLR method, and MD trend analysis, using a linear mixed model. The linear mixed model is equivalent to ordinary linear regression in that the model describes the relationship between the predictor variables and a single outcome variable. However, standard linear regression analysis makes the assumption that all observations are independent of each other. In the current study, measurements are nested within subjects and thus dependent of each other. Ignoring this grouping of the measurements will result in the underestimation of standard errors of regression coefficients. The linear mixed model adjusts for the hierarchical structure of the data, modeling in a way in which measurements are grouped within subjects.[43] The sensitivity of each method to detect a significant progression was assessed using the Kaplan-Meier survival analysis and compared using the log-rank test. *P* values in multiple comparisons were corrected using the Holm's multiple comparison method.[44]

All statistical analyses were carried out using the statistical program R software (version 3.4.4 http://www.r-project.org/).

RESULTS

DEMOGRAPHICS OF THE EYES ARE SHOWN IN THE TABLE. The average baseline MD was −19.7 (standard deviation [SD], 8.0) dB, and the initial age of the patients was 57.6 ± 12 years. Mean observation period between the VF_1 and VF_{15} was 8.5 ± 1.3 years. Average rate of VF progression was −0.38 ± 0.50 dB/y with $VF_{1\text{-}15}$.

Figure 2 shows the PBP with the binomial PLR_{all}, binomial $PLR_{4points}$, PoPLR, and MD trend analysis. These values varied between 0.19 with $VF_{1\text{-}5}$ and 0.80 with $VF_{1\text{-}14}$ (binomial PLR_{all}), 0.10 with $VF_{1\text{-}5}$ and 0.93 with $VF_{1\text{-}5}$ (binomial $PLR_{4points}$), 0.11 with $VF_{1\text{-}5}$ and 0.92 with $VF_{1\text{-}13}$ (PoPLR), and 0.13 with $VF_{1\text{-}5}$ and 0.96 with $VF_{1\text{-}14}$ (MD trend analysis), respectively. There was no significant difference among the PBP values with the 4 methods ($P = .83$, linear mixed model).

Figure 3 shows the PBNP calculated with binomial PLR_{all}, binomial $PLR_{4points}$, PoPLR method, and MD trend analysis. These values were between 0.86 with $VF_{1\text{-}8}$ and 1.0 with $VF_{1\text{-}14}$ (binomial PLR_{all}), 0.96 with $VF_{1\text{-}13}$ and 1.0 with $VF_{1\text{-}14}$ (binomial $PLR_{4points}$), 0.86 with $VF_{1\text{-}7}$ and 0.97 with $VF_{1\text{-}12}$ (PoPLR), and 0.90 with $VF_{1\text{-}6}$ and 1.0 with $VF_{1\text{-}9}$ (MD trend analysis), respectively. There was

TABLE. Demographics of the Study Eyes

Demographic	Result
Eyes, n	97
Subjects, n	69
Type of glaucoma, n	
Primary open-angle glaucoma	46
Normal tension glaucoma	41
Secondary glaucoma	6
Angle closure glaucoma	2
Exfoliation glaucoma	2
Age, y	57.6 ± 12
Sex (male/female)	34/63
Eye laterality (right/left)	46/51
Follow-up, y	8.5 ± 1.3
MD in the first VF, dB	−19.7 ± 8.0
MD in the final VF, dB	−22.9 ± 7.5
MD progression rate, dB/y	−0.38 ± 0.5

MD = mean deviation; VF = visual field.
Results are n or mean (SD).

no significant difference among the PBNP values with the 4 methods ($P = .18$, linear mixed model).

Figure 4 indicates the PIP for binomial PLR_{all}, binomial $PLR_{4points}$, PoPLR method, and MD trend analysis. The values ranged from 0.0 with $VF_{1\text{-}14}$ to 0.13 with $VF_{1\text{-}5}$ (binomial PLR_{all}), from 0.0 with $VF_{1\text{-}14}$ to 0.17 with $VF_{1\text{-}6}$ (binomial $PLR_{4points}$), from 0.02 with $VF_{1\text{-}12}$ to 0.30 with $VF_{1\text{-}5}$ (PoPLR), and from 0.0 with $VF_{1\text{-}9}$ to 0.30 with $VF_{1\text{-}5}$ (MD trend analysis), respectively. There was no significant difference among the PIP values with the 4 methods ($P = .14$, linear mixed model).

Figure 5 (Left) shows the relationship among the diagnoses of "progressive" with binomial PLR_{all}, PoPLR, and MD trend analysis, using the complete VF series ($VF_{1\text{-}15}$). Seventy-five eyes were assigned the diagnosis of "progressive" with binomial PLR_{all}, whereas this value was 61 eyes with PoPLR, and 55 eyes with MD trend analysis. In the 55 progressive eyes with the MD trend analysis, 54 eyes (98.2%) were also diagnosed as progressive with binomial PLR_{all}. However, 21 eyes were diagnosed as progressive by binomial PLR_{all}, but not using MD trend analysis. Eleven of these 21 eyes (52.4%) were progressive with PoPLR as well; however, the remaining 10 eyes were not progressive with PoPLR. As shown in Figure 5 (Right), 30 eyes were assigned the diagnosis of "progressive" with binomial $PLR_{4points}$. With binomial $PLR_{4points}$, 45 of 75 (60%) of the progressive eyes with binomial PLR_{all} were not diagnosed as progressive.

Figure 6 shows the results of Kaplan-Meier survival analyses. Log-rank test results indicated that the binomial PLR_{all} method detected more progressions than the other methods of binomial $PLR_{4points}$, PoPLR, and MD trend analysis ($P < .001$, $P < .04$, and $P < .012$, respectively; log-rank tests were adjusted for multiple comparisons using the Holm method). PoPLR and MD trend analyses showed no significant difference ($P = .5$; log-rank tests adjusted for multiple comparisons using the Holm method). The mean time to reach the diagnosis of progression with each method was as follows: 4.2 ± 1.8 (mean ± SD) years with binomial PLR_{all}, 4.9 ± 2.0 years with binomial $PLR_{4points}$, 4.8 ± 2.2 years with PoPLR, and 4.6 ± 2.0 years with MD trend analysis.

DISCUSSION

IN THE CURRENT STUDY, USING VARIOUS HFA 10-2 VF SERIES (from $VF_{1\text{-}5}$ to $VF_{1\text{-}15}$) of 97 eyes of 69 POAG patients, VF progression was analyzed using PLR, and the binomial test was applied to detect progression in the entire VF. This approach contrasted with the standard method of MD trend analysis and the PoPLR method. Almost all of the eyes (54 of 55 eyes; 98.2%) with a significant progression with the MD trend analysis were detected with the binomial PLR_{all} method, whereas the latter detected 21 additional progressive eyes. The consistency or reliability of each method was compared using the PBP, PBNP, and PIP measures. As a result, these values were not significantly different across the method analyses. The sensitivity of detecting progression was also evaluated, and as a result it was suggested that binomial PLR_{all} detected VF progression significantly earlier among the methods. These results were not observed when the binomial test method was applied to only 4 test points, which overlapped with the HFA 24-2 VF.

In our previous report, we evaluated PBP, PBNP, and PIP among binomial PLR, PoPLR, and MD trend analyses, using HFA 24-2 VF.[26] As a result, PBP of the binomial PLR (from 0.14 to 0.86) was significantly higher than those of the MD trend analysis and PoPLR, PIP of the binomial PLR (from 0.0 to 0.17) was significantly lower than those of the MD trend analysis and PoPLR, and PBNS (from 0.90 to 1.0) was not significantly different among the 3 methods. The previous study dealt with only 52 test points, because the number of test points was 52 in the HFA 24-2 VF test, whereas there were 16 more test points (68 test points in total) in the current study, which may be advantageous for methods based on PLR.[45] In the current study, all of the PBP (from 0.10 to 0.93), PBNP (0.86 to 1.0), and PIP (from 0.0 to 0.17) values (Figures 2-4) of binomial PLR_{all} were not significantly different than those of the MD trend analysis and PoPLR, in contrast to our previous study with HFA 24-2 VF.[26] This may be because the variance of VF sensitivity in the central area was much smaller than that in the peripheral area,[46] and the better consistency or reliability of binomial PLR was canceled out. Those results confirmed the reliability of

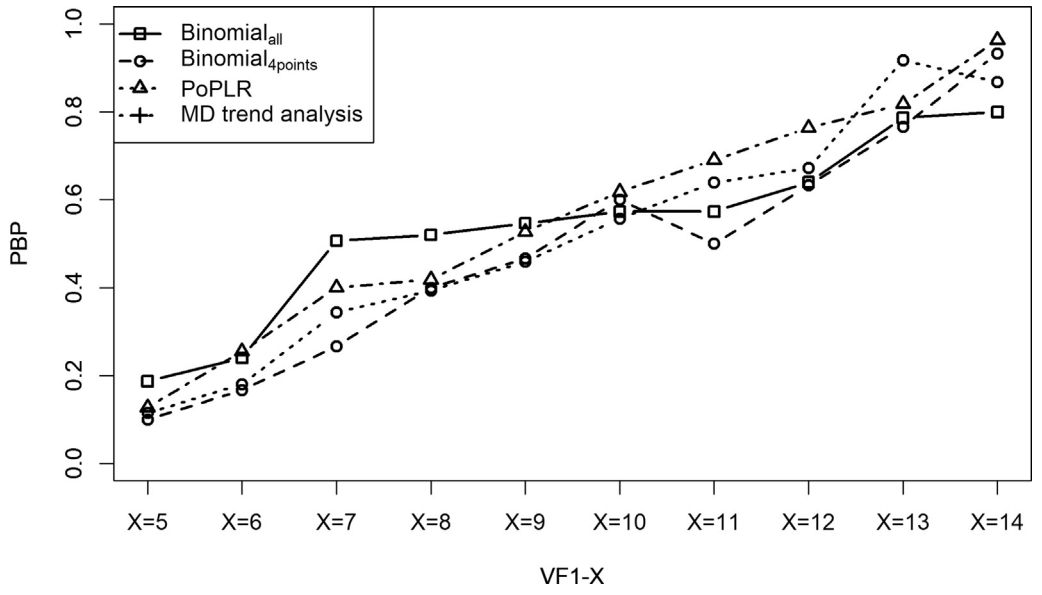


FIGURE 2. The rates of proportion of both progressing (PBP) with binomial PLR_{all}, binomial $PLR_{4points}$, PoPLR, and MD trend analysis. The rates of PBP were compared across binomial PLR_{all}, binomial $PLR_{4points}$, PoPLR, and MD trend analysis. There was no significant difference between the PBP of the 4 methods ($P = 0.83$, linear mixed model). MD = mean deviation; PLR = pointwise linear regression; PoPLR = permutation test analysis to PLR; VF = visual field.

binomial PLR in evaluating VF progression in the central 10 degrees. Kaplan-Meier survival analyses (Figure 6) indicated that the binomial PLR was better in detecting more progression compared with PoPLR and MD trend analyses. This suggested that binomial PLR detected VF progression earlier than the other 2 methods.

In our previous study with HFA 24-2 VF, the MD progression rate was −0.37 ± 0.48 dB/year and 51.0% of the eyes were diagnosed as progressive with the MD trend analysis.[26] A very similar MD progression rate (−0.38 ± 0.50 dB/year) was observed in the current study and a similar proportion (56.7%) of eyes were diagnosed as progressive with the MD trend analysis. There are other previous studies that reported the progression rate of HFA 10-2 VF.[47,48] These studies have also reported very similar progression rates of MD around −0.4 dB/year. We previously investigated 149 eyes of 110 open-angle glaucoma patients and the MD slope was −0.4 ± 1.0 dB/year. Likewise, Igor and associates[47] examined 34 eyes of open-angle glaucoma and the MD slope was −0.48 ± 2.2 dB/year within eyes having IOP ≥16 mm Hg. Age is an established risk factor for the progression of glaucoma[49-54] and previous studies have suggested that VF damage at baseline is a risk factor for progression.[49,52,54] The age (57.6 years old) and MD value in the initial VF (−19.7 dB) were very similar to those (mean age: from 58 to 60 years old; and MD: from −19.8 to −19.7 dB) in these previous studies.

The binomial PLR is similar to PoPLR in that the progression of the entire VF is estimated using the results of PLR, aiming for an earlier detection of progression than that of MD trend analysis. The benefit of PoPLR over the MD trend analysis has been reported using the HFA 24-2 VF[26,27]; however, our results suggested that the benefit of PoPLR was not observed when HFA 10-2 VF was used. In contrast, the currently proposed method of binomial PLR suggested a significantly earlier detection of progression than with PoPLR, when HFA 10-2 VF was evaluated. Previous studies with HFA 24-2 VF have suggested that exponential regression may better fit pointwise progression of VF damage,[55] and episodic progression can also sometimes occur (estimated as 7% in their study population),[56] although our recent study resulted in contrasting results; linear regression performed better than nonlinear regression in predicting a future VF,[57] similarly to previous studies.[21,58,59] This issue has not been investigated in many studies using HFA 10-2 VF. Our recent study compared the usefulness of linear and nonlinear regression models in HFA 10-2 VF, and it was suggested that there was no merit in using nonlinear regression models over the linear regression model.[48] This implies it would be most advantageous to apply binomial tests to PLR, although binominal tests can be applied to summarize the results of any pointwise analysis, as long as a P value is obtained at each location. Another possible benefit of the binomial PLR approach, in comparison to PoPLR in particular, is that the binomial test is much more computationally efficient, which is important when implemented in diagnosis support software to be used in real-world clinics.

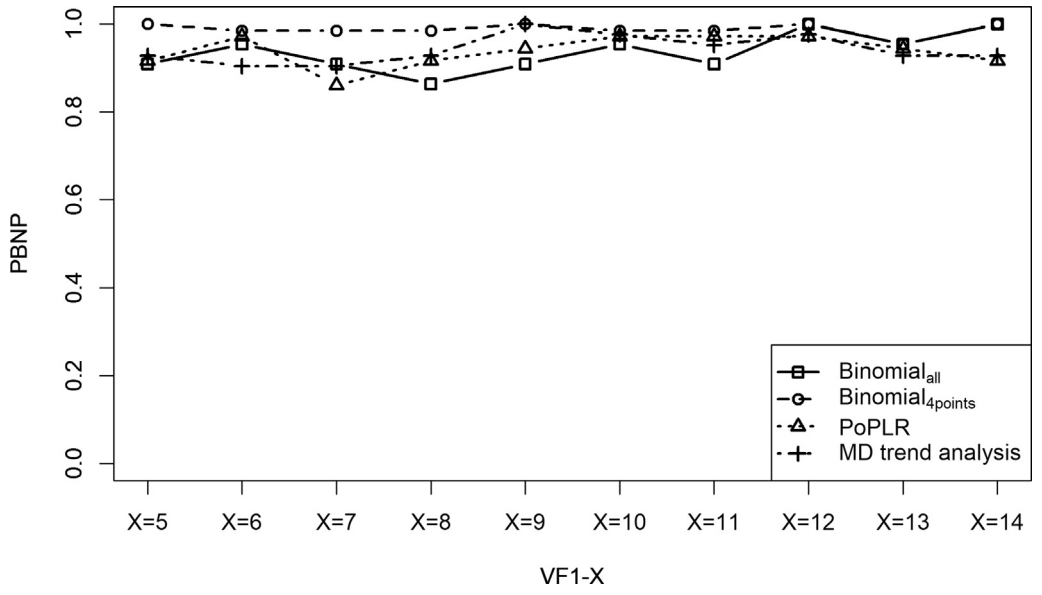


FIGURE 3. The rates of proportion of both not progressing (PBNP) with binomial PLR_{all}, binomial $PLR_{4points}$, PoPLR, and MD trend analysis. The rates of PBNP were compared across binomial PLR_{all}, binomial $PLR_{4points}$, PoPLR, and MD trend analysis. There was no significant difference between the PBNP of the 4 methods ($P = .18$, linear mixed model). MD = mean deviation; PLR = pointwise linear regression; PoPLR = permutation test analysis to PLR; VF = visual field.

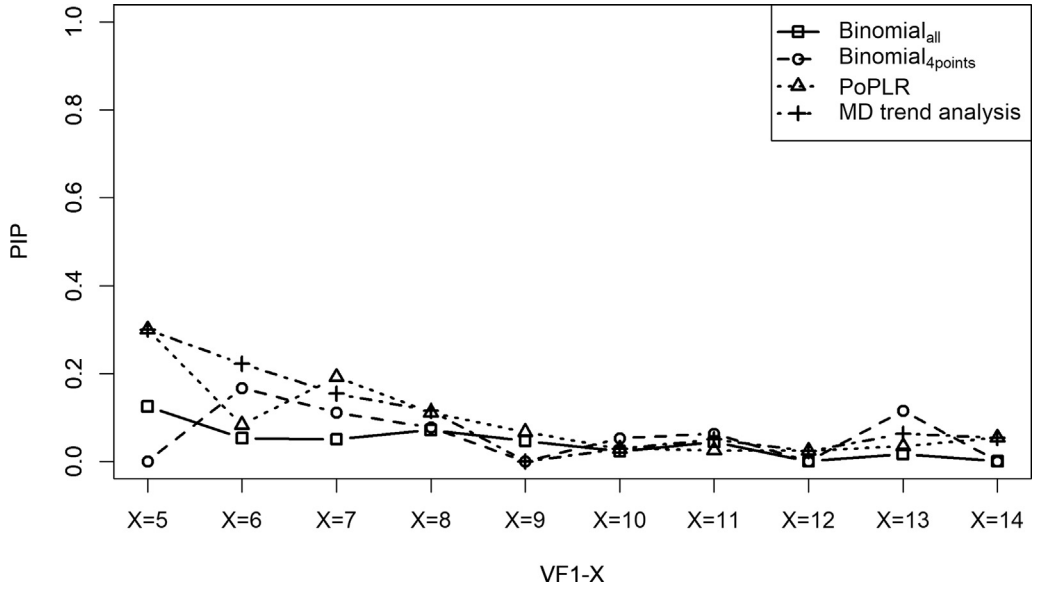


FIGURE 4. The rates of proportion inconsistent progressing (PIP) with binomial PLR_{all}, binomial $PLR_{4points}$, PoPLR, and MD trend analysis. The rates of PIP were compared across binomial PLR_{all}, binomial $PLR_{4points}$, PoPLR, and MD trend analysis. There was no significant difference between the PIP of the 4 methods ($P = .14$, linear mixed model). MD = mean deviation; PLR = pointwise linear regression; PoPLR = permutation test analysis to PLR; VF = visual field.

The results of binomial $PLR_{4points}$ suggested that significantly longer time was needed to detect progression compared to binomial PLR_{all}, although PBP, PBNP, and PIP values were not significantly different. This is probably because central VF could not be assessed accurately with HFA 24-2 VF and without HFA 10-2 VF. Park and associates indicated that HFA 10-2 detected more progressing eyes than HFA 24-2 in initial parafoveal scotoma.[33] Grillo and associates reported that glaucomatous central macular damage detected by optical coherence tomography was

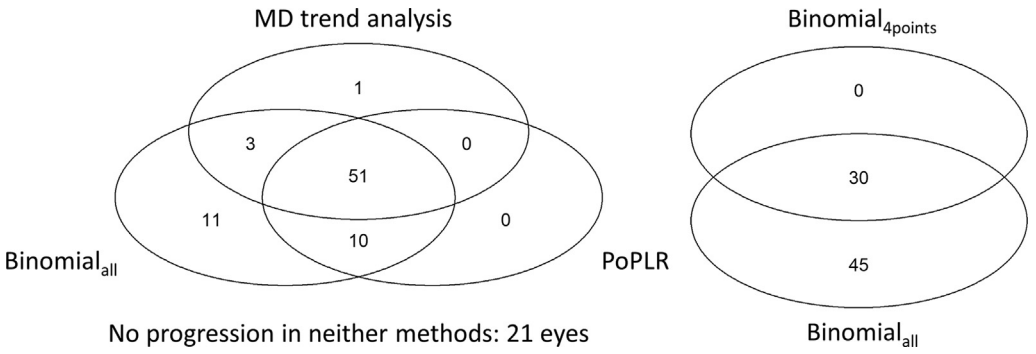


FIGURE 5. The relationship among the diagnosis of progression with binomial PLR_{all}, PoPLR, MD trend analysis, and binomial $PLR_{4points}$ using the complete series of 15 VFs. (Left) The relationship among the diagnosis of "progressive" with binomial PLR_{all}, PoPLR, and MD trend analysis, using the complete VF series. Seventy-five eyes were given the diagnosis of "progressive" with binomial PLR_{all}, whereas this value was 61 eyes with PoPLR, and 55 eyes with MD trend analysis. In the 55 progressive eyes with the MD trend analysis, 54 (98.2%) eyes were also diagnosed as progressive with binomial PLR_{all}. However, 21 eyes were diagnosed as progressive by binomial PLR_{all}, but not with MD trend analysis. Eleven of these 21 eyes (52.4%) were progressive with PoPLR as well; however, the remaining 10 eyes were not progressive with PoPLR. (Right) Thirty eyes were assigned the diagnosis of "progressive" with binomial $PLR_{4points}$. With binomial $PLR_{4points}$, 45 of 75 (60%) progressive eyes with binomial PLR_{all} were not diagnosed as progressive. MD = mean deviation; PLR = pointwise linear regression; PoPLR = permutation test analysis to PLR.

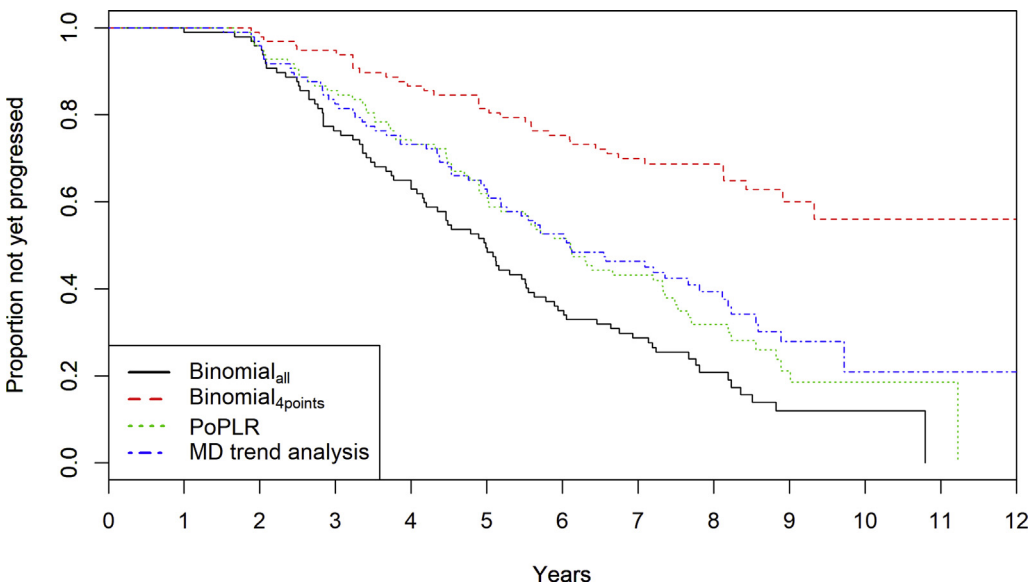


FIGURE 6. The results of the Kaplan-Meier survival analysis with binomial PLR_{all}, binomial $PLR_{4points}$, PoPLR, and MD trend analysis are shown. Log-rank tests indicated that the binomial PLR_{all} method detected progression significantly earlier than the other methods of binomial $PLR_{4points}$, PoPLR, and MD trend analysis ($P < .001$, $P < .04$, and $P < .012$, respectively; log-rank test adjusted for multiple comparisons using the Holm's method). PoPLR and MD trend analyses showed no significant difference ($P = .5$; log-rank tests adjusted for multiple comparisons using the Holm method). MD = mean deviation; PLR = pointwise linear regression; PoPLR = permutation test analysis to PLR.

missed with the HFA 24-2 VF and without the HFA 10-2 VF.[29] In addition, Hood and associates[60] traced the RNFL stream, and the corresponding angle on the optic disc was identified. As a result, it was suggested that a more vulnerable region of the optic nerve head (between 40 and 67.5 degrees inferior to the papillomacular bundle on the retina) corresponds to an area of the HFA 10-2 VF; in contrast, there are very few test points in HFA 24-2 VF. Also, conducting the binomial test using small numbers of variables (4 in the current study) could lead to acceptance of a false null hypothesis.[45] These results would encourage clinicians to perform HFA 10-2 VF when following up glaucoma

patients. However, it may not be practical to carry out HFA 10-2 VF frequently, because even performing only HFA 24-2 VF in sufficient frequency, such as every 6 months, is already too heavy a physical and economic burden to our real-world clinics.[61,62] Asaoka and associates indicated that deriving 10-2 VF MD values from 24-2 VFs using least absolute shrinkage and selection operator (Lasso) regression improved the prediction accuracy of glaucomatous VF progression.[63] Thus, supplementing information from HFA 24-2 VF in the progression analysis of HFA 10-2 VF may enable reliable and early detection of progression in central VF areas.

As a limitation of this study, PBP, PBNP, and PIP were calculated regarding the progression assessment with $VF_{1\text{-}15}$ as a surrogate for the absolute true progression, which may not be absolutely valid. As the absolute true progression cannot be known, the current study may need to be validated again, using a simulation dataset, although any simulated data can be artificial and the results may not be 100% clinically applicable. However, using $VF_{1\text{-}15}$, 98.2% (54 of 55 eyes) and 100% (61 of 61 eyes) of the eyes progressive with the MD trend analysis and PoPLR, respectively, were also diagnosed as progressive with binomial PLR_{all}, respectively. In addition, only 1 in 22 eyes not progressive with PLR_{all} was progressive with the MD trend analysis. These findings support the reliability of diagnosis with the binomial PLR_{all} method, which implies that it is valid to regard the diagnosis as a surrogate measure of the absolute true progression.

In conclusion, we applied the binomial test to the pointwise linear regression analysis to HFA 10-2 VF, to evaluate VF progression. This method achieved reliable detection of progression with a significantly earlier detection of progression.

FUNDING/SUPPORT: SUPPORTED BY GRANTS FROM THE JAPAN SCIENCE AND TECHNOLOGY AGENCY (JST)-CREST, GRANT 17K11418 from the Ministry of Education, Culture, Sports, Science and Technology of Japan, Research grant from the Suzuken Memorial Foundation and Mitsui Life Social Welfare Foundation. Financial Disclosures: The following authors have no financial disclosures: Shotaro Asano, Hiroshi Murata, Masato Matsuura, Yuri Fujino, and Ryo Asaoka. All authors attest that they meet the current ICMJE criteria for authorship.

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