• Clinical Research •

Visual field prediction using K-means clustering in patients with primary open angle glaucoma

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Abstract

● **AIM:** To evaluate long-term visual field (VF) prediction using K-means clustering in patients with primary open angle glaucoma (POAG).

● **METHODS:** Patients who underwent 24-2 VF tests ≥10 were included in this study. Using 52 total deviation values (TDVs) from the first 10 VF tests of the training dataset, VF points were clustered into several regions using the hierarchical ordered partitioning and collapsing hybrid (HOPACH) and K-means clustering. Based on the clustering results, a linear regression analysis was applied to each clustered region of the testing dataset to predict the TDVs of the 10th VF test. Three to nine VF tests were used to predict the 10th VF test, and the prediction errors (root mean square error, RMSE) of each clustering method and pointwise linear regression (PLR) were compared.

● **RESULTS:** The training group consisted of 228 patients (mean age, 54.20±14.38y; 123 males and 105 females), and the testing group included 81 patients (mean age, 54.88±15.22y; 43 males and 38 females). All subjects were diagnosed with POAG. Fifty-two VF points were clustered into 11 and nine regions using HOPACH and K-means clustering, respectively. K-means clustering had a lower prediction error than PLR when n=1:3 and 1:4 (both P≤0.003). The prediction errors of K-means clustering were lower than those of HOPACH in all sections (n=1:4 to 1:9; all P≤0.011), except for n=1:3 (P=0.680). PLR outperformed K-means clustering only when n=1:8 and 1:9 (both P≤0.020).

● **CONCLUSION:** K-means clustering can predict long-term VF test results more accurately in patients with POAG with limited VF data.

● **KEYWORDS:** K-means clustering; hierarchical ordered partitioning and collapsing hybrid; pointwise linear regression; visual field prediction

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INTRODUCTION

Patients with glaucoma can experience progressive visual field (VF) loss as a result of the degeneration of retinal ganglion cells and their axons[1-2]. The impairment of retinal ganglion cells caused by glaucomatous damage is irreversible[3-4]. Therefore, early and adequate treatment is fundamental for glaucoma patients to prevent vision loss. In determining the treatment of glaucoma, prediction of the future progression of glaucoma could be helpful[5]. The progression of glaucoma may be predicted using machine learning models based on an initial VF test, a joint multitask learning model incorporating optical coherence tomography image, longitudinal VF data analyzed with recurrent neural networks, and deep learning model using serial optic disc photograph[6-11]. Global indices of VF tests, including the mean deviation (MD) and VF Index, are commonly used to detect overall VF progression[12-14]. However, a previous study suggested that global indices are insensitive to glaucomatous changes because they can overlook focal and spatial information[15-17].

Gardiner and Crabb[18] showed that pointwise linear regression (PLR) analysis is more sensitive than global indices in

detecting VF loss. Nouri-Mahdavi *et al*[19] suggested that the PLR may be more capable of detecting VF progression than Advanced Glaucoma Intervention Study scores. However, the PLR has poor test-retest reproducibility and a high false-positive rate[18]. To reduce the variability of each test location, Hirasawa *et al*[20] suggested a clustering method that divides VF test points into several subsectors. In fact, the hierarchical ordered partitioning and collapsing hybrid (HOPACH) clustering and Nouri-Mahdavi sectors had smaller prediction errors than the PLR with a small number of VFs[20].

HOPACH clustering, a hierarchical clustering methods, is a powerful clustering method; however, it is a complex algorithm that takes a long time to implement[21]. In contrast, K-means clustering, a popular clustering method, is based on a simple principle so that it is fast and easy to be implemented[21]. The purpose of the current study is to develop new VF clusters using the K-means clustering algorithm based on the rates of VF change and compare the performance of predicting VF with those of HOPACH and PLR methods.

PARTICIPANTS AND METHODS

Ethical Approval The study protocol was approved by the Institutional Review Board of Pusan National University Hospital (2203-018-113) and performed in accordance with the tenets of the Declaration of Helsinki. The requirement for patient consent was waived by the Institutional Review Board due to the retrospective and de-identified nature of the study.

All participants underwent a thorough ophthalmological examination, including best corrected visual acuity (BCVA), slit-lamp examination, intraocular pressure (IOP) measurement using Goldmann applanation tonometry, gonioscopy, dilated fundus examination, biometry using the IOL Master (Carl Zeiss Meditec, Dublin, CA, USA), and keratometry using an auto-kerato-refractometer (ARK-510A; NIDEK, Hiroshi, Japan).

The inclusion criteria were a diagnosis of primary open angle glaucoma (POAG) with ten or more VFs and age of >18y. The exclusion criteria included secondary glaucoma, corneal abnormalities, non-glaucomatous optic neuropathies, retinal disease affecting the VF, previous ocular trauma history, and previous ocular surgery, except for uncomplicated cataract surgery. When both eyes satisfied the inclusion criteria, one eye per individual was randomly selected.

The diagnosis of POAG was based on the following eligibility criteria: presence of glaucomatous optic nerve appearance, corresponding VF loss and open angles on gonioscopy. Glaucomatous optic nerve damage was defined as the vertical cup-to-disc ratio ≥0.7 or asymmetry between the vertical cup-to-disc ratio of both eyes >0.2 or the presence of focal neural rim notching or generalized loss of the neural rim or retinal nerve fiber layer (RNFL) defect.

VF tests were performed from November, 2006 to January 2021 using the Humphrey VF Analyzer (Carl Zeiss Meditec, Dublin, CA, USA) using the 24-2 Swedish interactive threshold algorithm standard program. Considering a learning effect of VF, patients' first and second VFs were excluded and VFs with fixation losses less than 20%, false positive responses less than 15% were included. Glaucomatous VFs were those that met at least one of the following criteria: ≥3 contiguous points with a significance level of $P<0.05$, including ≥1 point significant at the $P<0.01$ level, on the same hemifield in the pattern deviation plot and/or Glaucoma Hemifield Test outside the normal limits and/or a pattern standard deviation (SD) probability outside 95% of the normal population.

All patients were diagnosed with POAG and followed up at the Pusan National University Hospital. A total of 228 eyes from 228 patients were included as a training dataset to develop clustering regions of 24-2 VF and 81 eyes from 81 patients were included as a testing dataset to evaluate prediction error of each clustering method.

The total deviation values (TDVs) of each test location were regressed linearly with time to calculate the progression rates of each point in the training group using the first nine VF data (n=1:9). Subsequently using this data, we applied the K-means algorithm to cluster each test point. The NbClust package was used to calculate the optimal number of clusters per each index. We clustered 52 VF test points using the K-means algorithm into various regions derived by Ratkowsky, Pt-Biserial, Tau, and C-index and predicted the regional average of TDVs in the 10th VF. The prediction errors [root mean squared error (RMSE)] were calculated for each test region in the VFs. We compared the prediction errors for each cluster and evaluated the clustering model with the lowest prediction error. The optimal number of clusters for the K-means algorithm was calculated as 4, 5, and 9 using the Ratkowsky, Pt-Biserial, Tau, and C-index, respectively. We compared the absolute prediction errors of 4, 5 and 9 clusters and found that 9 clusters derived by C-index had the lowest prediction error (RMSE=5.12±2.66 dB), whereas the RMSE value of 4 and 5 clusters were 5.83±3.23 dB and 5.66±3.14 dB, respectively. We decided to use 9 clusters model to predict the VF data of the test group.

Here, we describe the C-index. Let there are K clusters exist, and each cluster C_k has $n_k(n_k\text{-}1)$ pairs of points. Let us denote N_W as the sum of the number of pairs of each cluster.

$$N_W = \sum_{k=1}^{K} \frac{n_k(n_k-1)}{2}$$

Let S_W be the sum of the N_W distances of each cluster, N_{max} the sum of the N_W largest distances of all pairs in the entire dataset, S_{min} the sum of the N_W smallest distances of all pairs in the

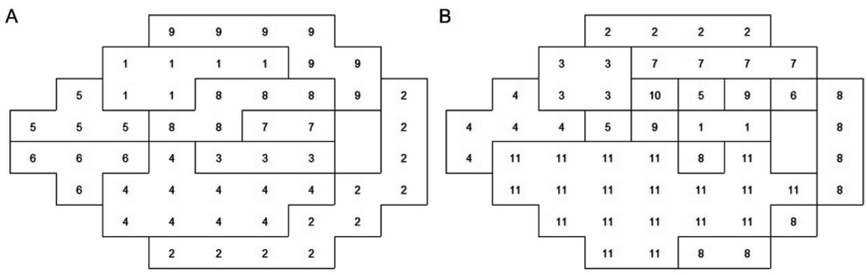

Figure 1 The 52 test points of 24-2 visual field (right eye format) clustered into 9 regions by K-means algorithm (A) and 11 regions by hierarchical ordered partitioning and collapsing hybrid algorithm (B).

entire data set. The C-index is defined as follows:

$$C = \frac{S_W - S_{min}}{S_{max} - S_{min}}$$

Consequently, the optimal number of clusters calculated using the C-index was nine, as shown in Figure 1A. The 52 VF test points were clustered into 11 regions using HOPACH algorithm, as shown in Figure 1B.

Statistical Analysis In the test group, the average TDVs for each region was calculated. Linear regression was then applied to each region to predict the regional TDV of the 10th VF. The predicted value of each VF test point in a region was regarded as the predicted regional TDV to which it belongs. Subsequently the prediction error (RMSE) was calculated for every test point and compared with the actual TDV of the 10th VF. Three to nine VF data (n=1:3 to n=1:9) were used for the prediction, and the prediction errors of K-means, HOPACH, and PLR in each region were compared.

All statistical analyses were performed using R software (version 4.1.1; R Foundation for Statistical Computing, Vienna, Austria). The RMSE were compared using repeated-measures analysis of variance (ANOVA). A paired pairwise t-test using the Bonferroni correction method was used for post-hoc testing.

RESULTS

Baseline age (mean±SD) was 54.20±14.38y and 54.88±15.22y in training and testing group, respectively (P=0.719). The number of VF was 13.30±2.87 and 13.60±3.11 in training and testing group, respectively (P=0.502). Initial VF MD was -7.43±6.68 dB and -8.35±7.57 dB in training and testing group, respectively (P=0.304; Table 1).

Fifty-two test points were clustered into 9 regions using the K-means algorithm and 11 regions using HOPACH (Figure 1). From n=1:3 to n=1:5, K-means clustering had the lowest prediction error compared to HOPACH and PLR (all P<0.006; Table 2). In post-hoc test, K mean method outperformed PLR and HOPACH (all P≤0.022) except n=1:3 when there was no statistically significant difference in prediction error between K-means and HOPACH (P=0.680).

When n=1:6, K-means clustering had the lowest RMSE of 5.56±2.55 dB compared to those of HOPACH (RMSE=5.99±2.93 dB) and PLR (RMSE=5.70±2.69 dB) although the difference among three methods was marginally significant (P=0.059). However, in the post-hoc test, K-means clustering had significantly lower prediction error than HOPACH (P<0.001).

Table 1 Demographic and ophthalmological characteristics of the subjects mean±SD

Parameters	Training group	Testing group	P
Number of eyes/patients, n	228/228	81/81	
Age (y)	54.20±14.38	54.88±15.22	0.719[a]
Sex			
Male/female	123/105	43/38	0.894[b]
Right eye/left eye	130/98	42/39	0.421[b]
Baseline IOP (mm Hg)	15.39±4.12	15.01±2.80	0.362[a]
Visual acuity (logMAR)	0.12±0.16	0.13±0.16	0.943[a]
Axial length (mm)	24.54±1.71	24.70±1.75	0.539[a]
Central corneal thickness (μm)	546.79±37.24	544.92±39.89	0.706[a]
Number of visual fields	13.30±2.87	13.60±3.11	0.502[c]
Initial mean deviation (dB)	-7.43±6.68	-8.35±7.57	0.304[a]
Final mean deviation (dB)	-8.23±7.34	-8.95±8.19	0.462[a]
Follow-up (y)	7.29±2.39	6.95±2.48	0.273[a]

SD: Standard deviation; IOP: Intraocular pressure; logMAR: Logarithm of the minimum angle of resolution. [a]Student t-test; [b]Chi-squared test; [c]Mann-Whitney U test.

As more VF data (n) were used for prediction, the prediction error of the PLR method decreased substantially compared with those of the others. Among the three methods, PLR had the lowest prediction error from n=1:7 to n=1:9 (all P<0.001). PLR had lower prediction error than HOPACH in post-hoc test from n=1:7 to n=1:9 (all P≤0.002). However, there was no statistically significant difference in the prediction error between K-means clustering and PLR at n=1:7 (P=0.287), and PLR outperformed the K-means clustering only at n=1:8 and n=1:9 (P=0.020 and P<0.001, respectively).

Overall, K-means clustering outperformed HOPACH from n=1:4 to n=1:9 (all P≤0.011), except for n=1:3 (P=0.680). Figure 2 shows the prediction errors of the regression using the K-means, HOPACH, and PLR methods for predicting the 10th VF. The "n" which is variable of Figure 2 means the number of VFs used to predict the 10th VF.

Table 2 Multiple comparison of average RMSE (post-hoc test) among HOPACH clustering, K-means clustering and PLR analysis for predicting the 10th visual field

Items	HOPACH	K-means	PLR	*P*	P^a	P^b	P^c
n=1:3	8.94±5.32	8.57±4.89	12.30±7.01	<0.001	0.680	<0.001	<0.001
n=1:4	7.06±3.74	6.69±3.51	8.06±4.32	<0.001	0.011	<0.001	0.003
n=1:5	6.24±3.01	5.78±2.58	6.40±3.30	0.006	<0.001	0.022	1.000
n=1:6	5.99±2.93	5.56±2.55	5.70±2.69	0.059	<0.001	1.000	0.580
n=1:7	5.76±2.95	5.28±2.53	4.97±2.20	<0.001	<0.001	0.287	0.002
n=1:8	5.74±3.04	5.22±2.59	4.69±2.14	<0.001	<0.001	0.020	<0.001
n=1:9	5.72±4.89	5.19±2.65	4.43±2.18	<0.001	<0.001	<0.001	<0.001

P: Repeated-measures analysis of variance; P^a: Paired pairwise *t*-test using Bonferroni correction method HOPACH *vs* K-means; P^b: Paired pairwise *t*-test using Bonferroni correction method K-means *vs* PLR; P^c: Paired pairwise *t*-test using Bonferroni correction method PLR *vs* HOPACH. RMSE: Root mean squared error; HOPACH: Hierarchical ordered partitioning and collapsing hybrid; PLR: Pointwise linear regression.

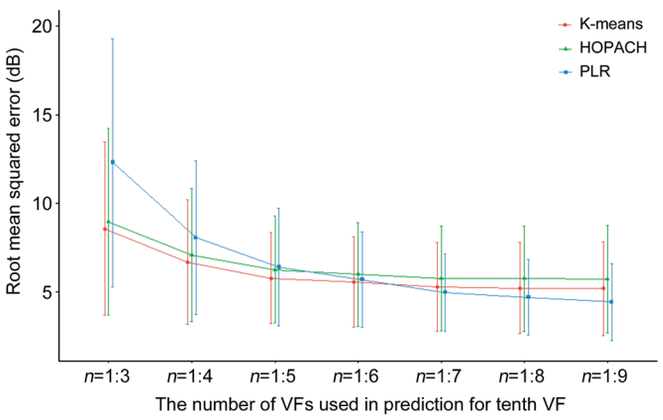

Figure 2 Comparing RMSE for regression based on HOPACH algorithm, K-means algorithm and PLR analysis for predicting the 10th visual field RMSE: Root mean squared error; HOPACH: Hierarchical ordered partitioning and collapsing hybrid; PLR: Pointwise linear regression; VF: Visual field.

DISCUSSION

In this study, 52 VF test points were clustered into nine regions using K-means clustering based on their progression rates in the training group. We found that K-means clustering outperformed the prediction of the 10th VF compared to that of the 11 progression regions based on HOPACH-PAM. In addition, with a smaller number of VFs (*n*=1:3 to *n*=1:5), the prediction error of K-means clustering was significantly lower than that of the PLR. PLR outperformed K-means clustering only when eight and nine VFs were used to predict the 10th VF. The finding of our study are in agreement with the results of previous study which indicated that PLR exhibits low reliability when based on a small amount of VF data[20]. In another study, at least seven to eight, or even more VF tests were required for PLR to obtain precise results[22]. In our study, with 3-5 VF data (*n*=1:3 to *n*=1:5), the RMSE of PLR was greater than that of K-means clustering. However, with a larger number of VFs (*n*=1:8 to *n*=1:9), the prediction accuracy of PLR improved compared with that of K-means clustering. Therefore, it can be inferred that K-means clustering may be more capable of predicting future VF with small VFs than the PLR.

Hierarchical clustering is a commonly used and powerful clustering method. However, the pattern of cluster can vary depending on the linkage criterion, which specifies the pairwise distances between observations in the clusters[23]. Hierarchical clustering requires computationally high demanding calculation process and has a high time complexity for large dataset[23-24]. In contrast, K-means clustering, one of the partitioning-based clustering, figures out the centroid to minimize the sum of the distances between each observations and the centroid to which it belongs[24]. It has low time complexity and can be easily implemented to large dataset[24]. However, the number of clusters (K) must be specified before the process, and clustering result could be significantly influenced by K[23]. With too many clusters, test-retest variability could be considerably high[25]. Conversely, with too small number of clusters, the focal progression may not be detected because of the masking effect.

In this study, we utilized several clustering indices along with the elbow technique to obtain a candidate for the optimal value of K[26]. We then determined the optimal K objectively by comparing the RMSE of the clustering results derived from the candidates. As a result, compared to HOPACH, K-means had a lower prediction error in almost all sections (*n*=1:4 to *n*=1:9) with even fewer clusters, which indicating that the performance of K-means is superior to that of the hierarchical algorithm with an appropriate number of clusters[27].

Previous studies have suggested various VF clusters based on either cross-sectional correlation of VF test locations or longitudinal rates of VF change and projection of RNFL bundles[20,28-29]. The longitudinal approach provides information on how these VF clusters evolve over time and can be used to predict future changes in VF. In addition, Gardiner and Mansberger[30] reported that cluster trend analysis can detect VF deterioration earlier than global metrics such as MD. Hirasawa

et al[20] clustered 52 VF points into 23 progression regions by using the HOPACH clustering algorithm. In their study, some of the central regions comprised a single test point. Similarly, in this study, using HOAPCH clustering, some progression regions, such as regions 8 and 9 (Figure 1B), included a single test point within the central region. In contrast, all progression regions derived using K-means clustering included at least two test points. In terms of structure-function relationship, the progression regions clustered with K-means algorithm seems to have more correspondence to the distribution of the arcuate RNFL bundle and typical glaucomatous VF damage, such as the nasal step, Bjerrum scotoma and cecocentral scotoma, than the previous study[20,29]. Garway-Heath *et al*[29] suggested structure-function map relating VF test points to positions at the optic nerve head derived from RNFL images and the VF clusters determined with K-means algorithm in this study followed this structure-function map. The issue with regard to the relationship between structure and function changes in glaucoma is whether or not structural changes are clinically relevant to functional outcomes[31]. When glaucomatous structural change is suspicious in a region, the clinical evidence of progression might be better corroborated with corresponding changes in the VF clusters. Additionally, VF clusters can be integrated with structural information to improve the detection of glaucoma progression in future studies. A previous study has reported that a combination of structural and functional measurements performed better than structural or functional measurements alone in detecting and monitoring glaucoma[32].

In this study, PLR showed a lower prediction error than K-mean clustering only when using a larger number of VFs (n=1:8 to n=1:9). This finding is consistent with the results of previous studies which reported that the differences in prediction error between PLR and regional analysis became nonsignificant when predicting the 10th 24-2 VF using the first eight or nine VF data. In addition, Omoto *et al*[33] reported that the prediction error was greater in the sectorwise regression than in the PLR when predicting the 10th 10-2 VF using the first nine VF data and no significant difference was observed when the first seven or eight VFs were used for predicting the 10th 10-2 VF. While K-means clustering showed superior performance with fewer VFs, PLR demonstrated lower prediction errors with eight or more VFs. This is likely because PLR utilizes the full granularity of individual pointwise trajectories, gaining statistical precision as more longitudinal data accumulates. In contrast, clustering-based averaging may dilute focal progression signals as data points are aggregated into regions.

The findings of this study have certain limitations. One limitation of this study is the relatively smaller sample size in the testing group, which could increase the variability of the prediction performance. Although baseline demographics were comparable between the groups, a larger testing sample would enhance the generalizability and robustness of the findings. All patients in this study were of Asian ethnicity and diagnosed with POAG. The performance of K-mean clustering may differ among other ethnic and diagnostic populations. In clinical practice, the simplicity and low computational cost of K-means clustering could be advantageous for real-time integration in electronic health record systems or VF monitoring software. However, further studies are needed to validate clustering-based models across different populations and platforms before clinical deployment.

In conclusion, the clustering of VF points with the K-means algorithm can predict long-term VF test results more accurately with less VF data in patients with POAG than with existing algorithms. In terms of model simplicity, K-means clustering is better than HOPACH clustering and could be helpful for the early detection of glaucomatous VF progression and the prevention of vision loss in patients with POAG.

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Data Availability: The data that support the findings of this study are not openly available for reasons of sensitivity but are available from the corresponding author upon reasonable request.

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Conflicts of Interest: Lee J, None; **Kim J,** None; **Kim H,** None; **Moon S,** None; **Kim EA,** None; **Jeong S,** None; **Yang H,** None; **Lee J,** None.

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