A hybrid unsupervised approach improved the representation of central visual field loss

Seungtae Yoo  
Pusan National University

Sang Wook Jin  
Dong-A University College of Medicine

Jung Lim Kim  
Inje University College of Medicine

Jonghoon Shin  
Pusan National University Yangsan Hospital, Pusan National University School of Medicine

Seung Uk Lee  
Kosin University College of Medicine

Jiwoong Lee  
Pusan National University Hospital

Giltae Song (✉ gsong@pusan.ac.kr)  
Pusan National University

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Abstract

Background

Quantitative recognition of visual field loss is important for glaucoma patients and has implications for follow-up management. This study aimed to identify the characteristic patterns of 10 − 2 visual field (VF) test results and effectively express central VF loss using a machine learning approach.

Methods

We obtained 7,927 10 − 2 VF test data from 3,328 patients in five hospitals. We propose a hybrid approach that combines archetypal analysis (AA) and fuzzy c-means (FCM) to identify characteristic patterns and decompose VF without loss. To demonstrate the clinical usefulness of our approach, mean deviation (MD) change prediction was performed through supervised learning using decomposition coefficients change and a linear mixed model was performed to examine the relationship between the MD slope and baseline decomposition coefficients.

Results

We identified ten characteristic and representative archetypes (AT) for the central VF test results. FCM decomposition results outperformed the AA-only approach in MD change prediction based on mean squared error (MSE) and Pearson correlation coefficient (PCC) prediction evaluation metrics (all $P \leq 0.039$). In the linear mixed model, the FCM is more suitable in the prediction of MD slope compared with the AA model for both Akaike (AIC) and Bayes information criteria (BIC) (AIC decrease: 20.31, BIC decrease: 13.33). The FCM baseline coefficients of AT 3, and AT 4 were significantly associated with a faster MD slope (both $P \leq 0.026$).

Conclusions

In this study, we used a hybrid approach of unsupervised learning to identify hidden aspects of central VF loss via a characteristic archetype and lossless decomposition. We believe that our approach can help discover hidden clinical features of glaucoma.

Background

Glaucoma is an optic neuropathy characterized by loss of retinal ganglion cells (RGC) and axons. Given that approximately 50% of RGCs are located within 4.5 mm of the foveal center, determining the central visual field (VF) pattern and change is critical to the long-term goal of vision preservation in patients with glaucoma. Previous studies have reported that central VF loss may be present in the eyes of many more
patients with glaucoma than expected. Traynis et al. found that 16% of the eyes with normal 24 – 2 VF are classified abnormal on 10 – 2 VF. Grillo et al. reported that 24 – 2 VF missed 52.5% of eyes with abnormal macula. De Moraes et al. also found that central VF damage identified on 10 – 2 VF is often missed on 24 – 2 VF. Therefore, a better understanding of the central VF pattern and change would assist clinicians in better tailoring strategies to preserve central visual function in patients with glaucoma.

However, a few studies have reported the pattern of central 10 – 2 VF loss. Hood et al. found that macular damage was typically arcuate and associated with an inferior region of macula located in the inferior quadrant of the disc, which is the macular vulnerable zone. De Moraes et al. proposed that the progression regions of 10 – 2 VF were clustered into seven sectors. Lee et al. discovered that 21 of the 68 10 – 2 VF test points have the majority of the information on sectoral ganglion cell/inner plexiform layer thickness as measured with optical coherence tomography.

Artificial intelligence (AI) has recently been used in the treatment of glaucoma. However, only one study has investigated the central VF pattern with artificial intelligence and its clinical relevance in patients with glaucoma. Seventeen central VF archetypes were determined using archetypal analysis (AA) and the inclusion of these central VF patterns improved the prediction of central VF worsening. However, representing all data as a convex combination in AA decomposition in a high-dimensional space may result in projection loss.

In this study, we propose a hybrid unsupervised learning approach that combines the strengths of fuzzy c-means (FCM) and AA to represent the central VF loss more accurately than the AA-only approach. We validate that our hybrid approach characterizes the central VF loss patterns in patients with glaucoma more systematically and with better clinical relevance than AA. We quantified central VF loss using the total deviation values and demonstrated the clinical usefulness of our approach.

**Materials And Methods**

**1. Data preparation and preprocessing**

This retrospective study was conducted in accordance with the tenets of the Declaration of Helsinki. This study was approved by the institutional review boards of all institutions. The requirement for patient consent was waived by the institutional review boards because of the retrospective and de-identified nature of the study. All VF data were obtained from subjects who had visited the glaucoma clinic at the Pusan National University Hospital, Donga University Hospital, Inje University Hospital, Kosin University Gospel Hospital, and Pusan National University Yangsan Hospital.

The training data were not labeled according to the diagnosis. As a result, data from subjects with normal visual fields, as well as those with glaucoma and other optic neuropathies, were included. Eyes with...
retinal disease or ocular media opacity (cataract, corneal opacity, etc.) were excluded from the analysis. Automated perimetry was performed using a Humphrey Visual Field Analyzer 750i instrument (Carl Zeiss Meditec) with the Swedish interactive threshold algorithm (SITA) central 10 – 2. The reliability criteria for VF selection were a fixation loss rate ≤ 33%, a false-negative rate ≤ 20%, and a false-positive rate ≤ 20%.7,14,15 For longitudinal analyses, eyes with at least 2 reliable 10 – 2 VF results were selected to predict MD change from decomposition coefficient change and eyes with at least 5 reliable 10 – 2 VF results were selected to predict the slope of the 10 – 2 VF MD from baseline central VF patterns. Descriptive statistics of the data for the cross-sectional and longitudinal analyses are presented in Tables 1, 2, and 3, respectively, and a flow chart of the analyzed data is shown in Fig. 1.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic characteristics of the entire subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td></td>
</tr>
<tr>
<td>Total number of 10 – 2 visual field tests</td>
<td>7927</td>
</tr>
<tr>
<td>Number of eyes (patients)</td>
<td>5426 (3328)</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>1644 (49.4%)</td>
</tr>
<tr>
<td>Age, mean ± SD (years)</td>
<td>59.8 ± 15.1</td>
</tr>
<tr>
<td>10 – 2 MD, mean ± SD (dB)</td>
<td>−10.5 ± 9.2</td>
</tr>
<tr>
<td>10 – 2 PSD, mean ± SD (dB)</td>
<td>6.3 ± 4.8</td>
</tr>
</tbody>
</table>

MD = mean deviation; PSD = pattern standard deviation; SD = standard deviation
<table>
<thead>
<tr>
<th>Demographic characteristics of the subjects selected for longitudinal analysis with 5 or more reliable 10 - 2 visual field tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
</tr>
<tr>
<td>Number of eyes (patients)</td>
</tr>
<tr>
<td>Sex (male)</td>
</tr>
<tr>
<td>Age, mean ± SD (years)</td>
</tr>
<tr>
<td>Total number of 10 - 2 visual field test</td>
</tr>
<tr>
<td>Number of 10 - 2 visual field tests per eye, mean ± SD</td>
</tr>
<tr>
<td>MD slope, mean ± SD (dB/year)</td>
</tr>
<tr>
<td>Initial 10 - 2 MD, mean ± SD (dB)</td>
</tr>
<tr>
<td>Initial 10 - 2 PSD, mean ± SD (dB)</td>
</tr>
<tr>
<td>Follow-up times, mean ± SD (years)</td>
</tr>
<tr>
<td>Diagnosis</td>
</tr>
<tr>
<td>Glaucoma suspect</td>
</tr>
<tr>
<td>Primary open angle glaucoma</td>
</tr>
<tr>
<td>Primary angle closure glaucoma</td>
</tr>
<tr>
<td>Pseudoexfoliation glaucoma</td>
</tr>
<tr>
<td>Other secondary glaucoma</td>
</tr>
<tr>
<td><strong>MD = mean deviation; PSD = pattern standard deviation; SD = standard deviation</strong></td>
</tr>
</tbody>
</table>
Table 3
Demographic characteristics of the subjects selected for longitudinal analysis with 2 or more reliable 10–2 visual field tests

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of visual field tests</td>
<td>3866</td>
</tr>
<tr>
<td>Number of 10–2 visual field tests per eye, mean ± SD</td>
<td>2.8 ± 1.6</td>
</tr>
<tr>
<td>Number of eyes (patients)</td>
<td>1365 (911)</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>484 (53.1%)</td>
</tr>
<tr>
<td>Age, mean ± SD (years)</td>
<td>60.8 ± 14.1</td>
</tr>
<tr>
<td>Initial 10–2 MD, mean ± SD (dB)</td>
<td>−13.7 ± 9.6</td>
</tr>
<tr>
<td>Initial 10–2 PSD, mean ± SD (dB)</td>
<td>7.8 ± 4.7</td>
</tr>
</tbody>
</table>

MD = mean deviation; PSD = pattern standard deviation; SD = standard deviation

2. Machine learning for VF loss representation

A. Archetypal analysis for identifying characteristic patterns of VF loss

Since each 10–2 VF test result includes values for 68 test points, it is too high-dimensional to cluster these VF test results using general unsupervised machine learning due to the curse of dimensionality. Several unsupervised learning methods have been applied to characterize VF loss patterns to deal with this issue. Among these approaches, archetypal analysis (AA) has shown the most similar results to patterns identified by clinical experts in clinical interpretable form. An archetype represents a factor in a collection of data sets, each of which is represented as a convex combination of archetypes. As shown in Eq. (1), archetype $Z_k(k = 1, \ldots, p)$ is a mixture of data $X_1, X_2, \ldots, X_n$. Each data point can be approximated as a mixture of archetypes. A constraint is formulated in Eq. (2), implying that this representation needs to be in a convex combination.

$$Z_k = \sum_{i=1}^{n} \beta_{ki} X_i, X_i \equiv \sum_{k=1}^{p} \alpha_{ik} Z_k \quad (1)$$

where $\alpha_{ik} \geq 0, \sum_i \alpha_{ik} = 1 \quad (2)$

$$\beta_{kj} \geq 0, \sum_j \beta_{kj} = 1$$

$$\sum_{i=1}^{n} \|X_i - \sum_{k=1}^{p} \alpha_{ik} Z_k\|^2$$
\[ \sum_{i=1}^{n} \| X_i - \sum_{j=1}^{n} \sum_{k=1}^{p} \alpha_{ik} \beta_{kj} X_j \|^2 \] (4) \text{ by (1) and (3)}

The archetypes were determined to minimize the error in Eq. (3) when expressing individual data as a combination of archetypes. We derived Eq. (4) by substituting \( \sum_{i=1}^{n} \beta_{ki} X_i \) for \( Z_k \) in Eq. (3). Ultimately, the key to the AA algorithm is determining \( \alpha \) and \( \beta \) that minimize the reconstruction error while satisfying the convex combination constraint. Once \( \alpha \) and \( \beta \) have been determined, each data point can be expressed as a combination of archetypes. From a geometric perspective, archetypes constitute convex hulls. Figure 2 shows a two-dimensional illustration of the AA. In Fig. 2, a vertex represents an archetype, and the position of each vertex is determined by minimizing the reconstruction errors when all data are projected onto the archetype convex hull, as indicated by a red line. The original data is represented by black dots, while the projected data is represented by green dots on the red line. All green dots can be expressed as convex archetype combinations (red dots). As shown in the figure, AA is often referred to as corner learning, which is useful for detecting characteristic patterns in high-dimensional space.23

B. Fuzzy c-means for lossless decomposition

To decompose all data points in terms of archetypes, each data point is projected onto each archetype and represented as a convex combination of archetypes using AA coefficients computed in this projection. Unfortunately, there was some projection loss during this AA decomposition step. To prevent this projection loss, we applied FCM to the decomposition process.

\[ w_{ij} = \frac{1}{\sum_{k=1}^{c} \left( \frac{\| x_i - c_j \|}{\| x_i - c_k \|} \right)^2} \] (5)

where \( x_i \) : i-th instance, \( c_j \) : j-th archetype

FCM is designed based on the membership grade, which indicates the clusters to which each data point belongs. It also quantifies the relevance of a data point to each cluster to which it belongs. The membership grade \( w_{ij} \) between data point \( x_i \) and archetype \( c_j \) is formulated in Eq. (5).

Figure 3 depicts the differences in decomposition between AA and FCM for an instance circled in red (see Fig. 2). A data point is projected onto the archetype convex hull in Fig. 3(A) to express the data point as a convex combination of archetypes. The convex combination coefficients of the archetypes calculated in this process are the decomposition coefficients in the AA. In FCM, the archetype membership grade for the data point is determined as the ratio of the distance from the original data point to each archetype without projection. Figure 3(B) shows the difference in the decomposition coefficients of AA (values in red) and FCM (values in blue). Because AA decomposition coefficients do not reflect the original distance, they result in a projection loss. We attempted to resolve this projection loss using FCM during decomposition.

3. Statistical analyse
A. Machine learning for evaluation of AA and FCM decomposition results

We developed a supervised learning model to predict MD changes using decomposition coefficient differences for eyes with at least two reliable 10–2 VF results. We used this machine learning prediction to compare the performance of AA and FCM decomposition results, that is, determining which decomposition coefficient results include more clinically relevant information on MD change.

According to GIGO (garbage in, garbage out), we expect that a model with input data that includes more relevant information will make a more accurate prediction of MD change, provided that the same machine learning approach with two different input data is applied. In this prediction model, the decomposition coefficient difference from the baseline examination (i.e., the first VF test of an individual patient) is an independent variable, and the change in MD (MD at each visit – baseline MD) is a dependent variable. We computed decomposition coefficient differences and MD changes from the baseline examination of each patient, that is, we obtained \((N - 1)\) pairs of both coefficient difference values and MD changes if the patient performed the VF test \(N\) times. We used 1,750 of the 2,501 instances as the training dataset and the remaining as the test dataset in a 7:3 ratio.

To build the MD change prediction models, we applied a support vector machine (SVM), random forest (RF), gradient boosting machine (GBM), and light gradient boosting machine (LGBM). For each method, we trained two models: one using AA decomposition coefficient differences and the other using FCM decomposition coefficient differences as input. We implemented the prediction models using Python scikit-learn library 0.24.2.

We used the mean squared error (MSE) and Pearson correlation coefficient (PCC) (in Eq. (6)) as the predictive evaluation metrics.

\[
MSE = \frac{1}{N} \sum_{i=1}^{N} (y_i - x_i)^2 \quad \text{and} \quad PCC = \frac{\sum_{i=1}^{N} (x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_{i=1}^{N} (x_i - \bar{x})^2} \sqrt{\sum_{i=1}^{N} (y_i - \bar{y})^2}} , \quad (6)
\]

where \(x_i = \text{predictedMDchange (byAAandFCM)}\) and \(y_i = \text{actualMDchange}\)

We trained the model 30 times using different partitions of the training and test datasets to determine the statistical significance of the prediction results. A paired t-test was performed on these 30 results to evaluate whether there were any statistically significant differences compared with the previous method.

B. Linear regression models for MD slope prediction

For eyes with at least 5 reliable 10–2 VF results, the decomposition coefficients of the baseline examination were used to predict the MD slope to compare the clinical relevance of decomposition coefficients obtained by each decomposition method (AA and FCM) at baseline. Some archetypes may
be irrelevant to the regression analysis. To eliminate these irrelevant variables, we used a stepwise variable selection method, which selects an optimal combination of variables via iterative additions and removals, as well as evaluation of each selection.\textsuperscript{27}

We built linear regression models to predict the MD slope using the selection of optimal variables for AA and FCM. Mixed-effects linear models were used to account for the non-independence of the two eyes from the same subject.\textsuperscript{28} We determined which regression model fits better using three evaluation criteria. The first is the adjusted $R^2$, which indicates the usefulness of the regression model. This was calculated as the ratio of how much of the response variable's variance can be explained by the regression model. The other criteria are the Akaike information criterion (AIC) and a Bayes information criterion (BIC). Both estimate the relative amount of information loss in AA and FCM. All $P$ values were 2-sided and differences were considered statistically significant at $P < 0.05$.

Results

1. Representation of central visual field loss patterns using 10 archetypes

We determined the number of archetypes (denoted as $k$) using AA to find representative central VF patterns in our high-dimensional VF data, each of which included 68 test points. The larger the number of archetypes used, the more the reconstruction errors can be reduced in AA; however, the use of many archetypes makes understanding the characteristics of the central VF pattern difficult. To find the optimal $k$ considering this trade-off relationship, we observed changes in the reconstruction errors in the test dataset while adjusting the number of archetypes in the training dataset using 5-fold cross-validation. Figure 4 shows the reconstruction errors according to the change in $k$ values (from 1 to 20); the reconstruction error for $k = 11$ increases, whereas the reconstruction errors decrease until $k = 10$. Hence, we set the number of archetypes to 10.

Figure 5 shows the ten central VF patterns determined by AA from the 7,927 10−2 VF results from 5,426 eyes of 3,328 patients, with the average decomposition weight for each archetype for AA and FCM. The mean ± standard deviation of age and 10−2 MD was 59.8 ± 15.1 years, and −10.5 ± 9.2 dB, respectively.

The most central VF pattern was an intact field, accounting for 38.6% (archetype 8), and two central VF patterns were associated with isolated superior hemifield loss, accounting for 7.6% and 8.2%, respectively (archetypes 1 and 2). One pattern was associated with isolated inferior hemifield loss, accounting for 5.2% (archetype 3), and four patterns were associated with both hemifield losses accounting for 6.9%, 6.5%, 7.8%, and 5.4%, respectively (archetypes 4, 5, 6, and 7).

An arcuate pattern of central VF defect was found in two isolated superior hemifield loss patterns (archetypes 1 and 2) and one isolated hemifield loss pattern (archetype 3), accounting for 21.0% of the central VF pattern. Five of the ten central VF patterns (archetypes 1, 2, 4, 5, and 6), accounting for 37% of
the central VF loss, preserved the less vulnerable zone, while they lost the more vulnerable zone proposed by Hood et al. Notably, archetype 6 showed temporal-sparing loss with preservation of the central isle.\(^8\)

2. Central visual field decomposition using archetypal analysis and fuzzy c-means

We decomposed the 10 − 2 VF test results as a combination of the characteristic archetypes using AA and FCM and compared the decomposition results of AA and FCM. Figure 6 depicts a quantitative decomposition of the two patients’ central VF by AA and FCM. The decomposition results were sorted in the order of the decomposition coefficients. The decomposition coefficients of AA and FCM were equal to 1, but their values were calculated differently.

Figure 6(A) shows a case in which the top three archetypes were identical in both AA and FCM, but their ratios were different. The area with the greatest VF loss was located at the superior hemifield, while some VF loss was also found in the inferonasal area. Both AA and FCM showed the same three top archetypes: 1, 2, and 4, although their decomposition coefficients were different (63.5%, 15.0%, and 14.7% for AA, and 45.1%, 16.0%, and 9.7% for FCM, respectively). Figure 6(B) shows a case in which the top three archetypes differed between AA and FCM. The majority of VF loss in the original VF is located in the superonasal area, with some loss in the other area. Interestingly, superior hemifield loss (archetype 1) was assigned as the primary archetype with the largest decomposition coefficient of 32.9% in AA, while both hemifield losses (archetype 4) were assigned as the primary archetype with the largest decomposition coefficient of 20.3% in FCM.

3. Performance evaluation of two central visual field decomposition results using supervised learning

The performance of the MD change prediction between the AA and FCM decomposition results was compared using 3866 10 − 2 VF results from 1365 eyes of 911 patients, and the prediction results using the four machine learning models are shown in Table 4. The mean ± SD of age, initial 10 − 2 VF MD, number of 10 − 2 VF tests, and follow-up time were 60.8 ± 14.1 years, −13.7 ± 9.6 dB, 6.6 ± 2.0, and 1.7 years, respectively.

There were statistically significant differences in both the MSE and PCC of the four prediction models between the AA and FCM decomposition results. The MSE from the FCM decomposition results was significantly smaller than that from the AA decomposition results (all \(Ps \leq 0.034\)). The Pearson correlation coefficient of the FCM decomposition results was significantly greater than that of the AA decomposition results (all \(Ps \leq 0.039\)). These results show that MD change prediction using FCM decomposition results outperforms prediction using AA decomposition results. According to GIGO, FCM decomposition provides more information for MD change prediction, that is, FCM generates more lossless decomposition clinically.
Table 4
Results from the machine learning models for 10−2 visual field mean deviation change prediction with the decomposition ratio change

<table>
<thead>
<tr>
<th></th>
<th>Archetypal analysis</th>
<th>Fuzzy c-means</th>
<th>P-value</th>
<th>Archetypal analysis</th>
<th>Fuzzy c-means</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean squared error</strong></td>
<td>1.42 ± 0.19</td>
<td>1.30 ± 0.21</td>
<td>0.034*</td>
<td>0.91 ± 0.01</td>
<td>0.92 ± 0.01</td>
<td>0.039*</td>
</tr>
<tr>
<td><strong>K-Nearest Neighbor</strong></td>
<td>Support Vector Machine</td>
<td>2.86 ± 0.71</td>
<td>2.47 ± 0.73</td>
<td>&lt;0.001**</td>
<td>0.82 ± 0.03</td>
<td>0.85 ± 0.03</td>
</tr>
<tr>
<td><strong>Random Forest</strong></td>
<td>Light Gradient Boosting</td>
<td>1.02 ± 0.20</td>
<td>0.81 ± 0.12</td>
<td>&lt;0.001**</td>
<td>0.93 ± 0.01</td>
<td>0.95 ± 0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.84 ± 0.19</td>
<td>0.69 ± 0.13</td>
<td>&lt;0.001**</td>
<td>0.94 ± 0.01</td>
<td>0.95 ± 0.01</td>
</tr>
</tbody>
</table>

*, ** Significant at 5 and 0.1% level, respectively

4. Linear regression of mean deviation slope on baseline coefficients

One hundred thirty-nine eyes from 108 patients with at least 5 reliable 10−2 VF results were selected for longitudinal analyses to compare the clinical usefulness of AA and FCM decomposition results. The mean ± SD of age, initial 10−2 VF MD, number of 10−2 VF tests, and follow-up time were 63.4 ± 11.7 years, −19.0 ± 8.0 dB, 6.6 ± 2.0, and 3.6 years, respectively.

We fitted mixed-effects regression models between archetype decomposition coefficients at baseline and 10−2 VF MD slope, and the optimal combination of variables in the regression models was determined using stepwise selection, as presented in Table 5.

In the regression model based on the AA decomposition results, higher coefficients of archetype 3 (isolated inferior loss) were significantly associated with a more negative 10−2 VF MD slope (P = 0.041). However, the coefficient of determination was very small (adjusted $R^2 = 0.087$). In the regression model based on FCM decomposition results, higher coefficients of archetype 4 (both hemifield loss sparing less vulnerable zone of the macula), archetype 3 (isolated inferior loss), and lower coefficients of archetype 7 (nearly total loss) and archetype 8 (intact field) were significantly associated with a more negative 10−2 VF MD slope. In addition, the coefficient of determination improved compared with the model based on the AA decomposition results (adjusted $R^2 = 0.330$ vs. 0.087). The FCM is found to be more suitable than the AA model for explaining the 10−2 VF MD slope. Notably, FCM decomposition results strongly improved the prediction of the 10−2 VF MD slope compared to the AA decomposition results (AIC and BIC decrease by 17.62 and 12.96, respectively).29
Table 5
Results from stepwise variable selection of regression analysis for association between baseline archetypal analysis and fuzzy c-means decomposition as predictors and 10 − 2 visual field mean deviation slope as outcome in separate regression models

| Variable       | Coefficients (β) | P (β>|t|) | Adjusted $R^2$ | AIC     | BIC     |
|----------------|------------------|---------|----------------|---------|---------|
| Archetypal analysis |                 |         |                |         |         |
| AT 3           | −0.940           | 0.041*  | 0.087          | 122.50  | 136.48  |
| AT 9           | −1.877           | 0.051   |                |         |         |
| Fuzzy c-means |                  |         |                |         |         |
| AT 3           | −4.788           | <0.001**| 0.330          | 104.88  | 123.52  |
| AT 4           | −1.267           | 0.026*  |                |         |         |
| AT 7           | 1.063            | 0.025*  |                |         |         |
| AT 8           | 1.395            | <0.001**|                |         |         |

AIC = Akaike information criterion; AT = archetype; BIC = Bayes information criterion
* , ** Significant at 5 and 0.1% level, respectively.

Discussion
Quantitative recognition of central VF defects is crucial for improving the quality of life of patients with glaucoma. For this purpose, in this study, we determined the characteristic patterns from 7,927 10 − 2 VFs and expressed the central VF loss using more efficient decomposition.

While previous studies applied AA for determining the patterns of VF loss and decomposing the original VF into specific patterns, we designed a hybrid approach of AA and FCM that can produce more favorable results compared to a single expert system. To avoid projection loss caused by representing all data as a convex combination in AA decomposition in a high-dimensional space such as a 10 − 2 VF with 68 test points, We used FCM decomposition with the original distance in Euclidean space rather than forcing the projection to convert the data into a geometric convex combination of archetypes.

To express central VF loss with better clinical relevance, we combined AA, which is advantageous for finding distinctive patterns in high-dimensional space, and FCM, thus enabling lossless expression via summation of the patterns obtained by the AA. We demonstrated that our approach produces a clinically informative decomposition using supervised learning to predict MD changes. We also assessed the clinical usefulness of our approach by using regression analysis to fit the relationship between the archetype ratio at baseline and the rate of MD change. Our VF decomposition results are more clinically meaningful than those of AA. These findings indicate that the outcome extracted using our approach could become a new indicator of the progression of glaucoma and help manage glaucoma better.

We found arcuate patterns of 10 − 2 VF loss, including two superior arcuate defects (archetypes 1 and 2) and one inferior arcuate defect (archetype 3), accounting for 18.1% of the 10 − 2 VF results. Three of the
four patterns of hemifield loss, accounting for 21.2% of 10–2 VF loss, preserved the less vulnerable zone of the macula or central isle, as proposed by Hood et al. These findings agree with the results of previous studies which reported that macular optical coherence tomography, and 10–2 VF relationships have localized arcuate characteristics in the central region of the macula and 68% of the abnormal 10–2 VF were arcuate. The hybrid approach for quantifying 10–2 VF loss confirmed the preservation of the less vulnerable zone in the cecocentral region of the inferior macula and the majority of the superior macula projected to the temporal quadrant.

We demonstrated that the inclusion of baseline 10–2 VF features decomposed with FCM improved the prediction of the 10–2 VF MD slope compared with AA. Higher coefficients of archetypes 3 (inferonasal loss) and 4 (both hemifield loss preserving the main less vulnerable zone) were inversely associated with the 10–2 VF MD slope. Intact VF was directly associated with the 10–2 VF MD slope. The direct association between archetype 7 (nearly total loss) and 10–2 VF MD slope may be due to a floor effect. Predicting the rate of central VF change from baseline VF features can help clinicians to individualize the frequency of the 10–2 VF test to individual patients to prevent central VF progression.

However, our approach may not be preferable from other perspectives. In the case of AA decomposition, when a projection is performed, the weights of archetypes that do not constitute the convex hull become 0% (see Fig. 2), and the weights of the other archetypes increase by that amount. In other words, AA decomposition can take more weights of interested archetypes, and like LASSO, can function as a feature selection by making the weights for certain variables 0%. On the other hand, FCM decomposition has a very small value rather than making the archetype's weight 0%. In some cases, AA decomposition may be advantageous if the goal is to extract only the characteristic archetypes.

Our study has some limitations. First, there are insufficient longitudinal data to generalize the findings. Although the regression analysis produced more meaningful results than the previous approach, the regression coefficients could change if more data were collected. Second, other clinical variables such as optic disc features, intraocular pressure, and history of glaucoma surgery were not taken into account in this study. Hence, it is recommended that future studies include these variables to improve the performance of MD change prediction.

In general, MD is considered a global index of VF loss and identifying VF loss using this global index is straightforward. However, MD is relatively less sensitive to progressive glaucomatous VF loss and spatial information can be lost. We believe that our approach could enable the discovery of hidden features of glaucoma and contribute to the study of early detection of VF loss and its progression.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the guidelines of the World Medical Association Declaration of Helsinki and approved by the Institutional Review Boards of Pusan National University Hospital (approval number: 2203-018-113), Kosin University Gospel Hospital (approval number 2018-12-028), Dong-A University Hospital (approval number, 22-074), Busan Paik Hospital (approval number 2021-03-014-002), and Pusan National University Yangsan Hospital (approval number 05-2018-172). The requirement for patient consent was waived by each institutional review board because of the retrospective nature of the study.

Consent for publication

Not applicable.

Availability of data and materials

The data generated or analyzed during this study are available from the corresponding author [J. L.] upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

Seungtae Yoo developed methodology and was a major contributor in writing the manuscript. Sang Wook Jin, Jung Lim Kim, Jonghoon Shin, and Seung Uk Lee conducted data collection and clinical chart review. Jiwoong Lee contributed to the study design, interpretation of the study results, and the revision of the manuscript. Giltae Song supervised the study and reviewed the manuscript. All authors read and approved the final manuscript.

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References


Figures

Flow chart of the analyzed data: Reliable VFs were secured based on reliability criteria, and it was divided into subgroup according to the purpose of analysis; Supervised learning for MD change prediction (presented Table 4) vs. Linear regression analysis for MD slope prediction (presented Table 5).
prediction (presented Table 4), Linear regression analysis for MD slope prediction (presented Table 5)

**Figure 2**

Archetypal analysis projection illustration: The black dots are the original data, the green dots are projection data, and the red line is a convex hull composed of archetypes. The black line represents the projection line of original data onto the convex hull. The red dotted circle highlights the projection

**Figure 3**
(A) Scope on projection data: project the original data onto a convex hull composed of archetypes. (B) Discrepancy between original and projection distance: the relative ratio of the coefficients is 4:3 (blue) based on original distance to the archetypes, but the relative ratio of coefficients after projection is 3.2:1.8 (red).

Figure 4

Scree plot in archetypal analysis: The number of archetypes (x-axis), the reconstruction error of test set (y-axis). As the capacity to represent data increases, the reconstruction error naturally tends to decrease, but the trend is broken at the 11th.
Figure 5

Ten representative central visual field (VF) patterns determined by archetypal analysis based on total deviation value (TDV). Red color means low TDV (deterioration) and white or blue color indicates high TDV (normal). Relative mean decomposition ratio in two methods are shown on the right side of each archetype for comparison. Note that All VFs are plotted in right eye format.

AA = archetypal analysis; FCM = fuzzy c-means
Figure 6

Two representative cases with visual field decomposition by archetypal analysis (left) and fuzzy c-means (right): (A) Case 1: The decomposition coefficients of each archetype changed while the order of decomposition remain unchanged after fuzzy c-means decomposition. (B) Case 2: The primary archetype with the greatest loss pattern changes after fuzzy c-means decomposition. Note that all VFs were plotted in the right-eye format.

AA = archetypal analysis; AT = archetype; FCM = fuzzy c-means; VF = visual field