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Evaluation of GDx parameters by using information theory

Umut ARSLAN[1], Banu BOZKURT[2], Ahmet Ergun KARAAĞAOĞLU[1], Murat Tanju İRKEÇ[3]

Aim: To evaluate the performance of GDx parameters in the diagnosis of glaucoma by using information theory and compare the results obtained using receiver operating characteristic (ROC) curve analysis, which is a traditional method.

Materials and methods: Retinal nerve fiber layer thickness was measured in 270 eyes with glaucoma and 81 normal eyes with scanning laser polarimeter (NFA GDx version, 1.0.08), and 14 GDx parameters were calculated. Both ROC curve analysis and information theory were used to determine the best GDx parameters. The best cut-off points of these parameters were obtained using information theory for glaucoma prevalence (Pr) of 1%, 2%, and 5%.

Results: The parameters having the maximum information content and discriminatory power are The Number, Ellipse modulation, and Maximum modulation, respectively. The best cut-off points associated with these parameters are 32.08, 1.65, and 1.20 for specified Pr values considered, respectively. The best cut-off value for inferior ratio is 1.95 when Pr is 1% or 2%, whereas the best cut-off point of the parameter is 2.11 when Pr is 5%.

Conclusion: Although ROC curve analysis can be used for evaluating the performance of the diagnostic test, it cannot determine the best cut-off point for certain prevalence. Information theory approach seems to be more superior to the traditional ROC curve analysis for tackling this problem.

Key words: Diagnostic test, glaucoma, information theory, ROC curve

Bilgi kuramı kullanılarak GDx parametrelerinin değerlendirilmesi

Amaç: Bu çalışmanın amacı glokom tanısında kullanılan GDx parametrelerinin performanslarını bilgi kuramı ile değerlendirmek ve geleneksel yöntemlerden biri olan işlem karakteristiği eğrisi (İKE) (ROC: receiver operating characteristic) analizinden elde edilen sonuçlarla karşılaştırmaktır.

Yöntem ve gereç: Tarayıcı lazer polarimetri (NFA GDx versiyon, 1.0.08) ile 270 glokomlu ve 81 normal gözde retina sinir lifi tabakası kalınlığı değerlendirildi ve 14 GDx parametresi hesaplandı. En iyi GDx parametrelerini belirlemek için İKE ve bilgi kuramı kullanıldı. Bu parametrelerin % 1, % 2 ve % 5 glokom prevalans (Pr) değerlerindeki en iyi kesim noktaları bilgi kuramı kullanılarak elde edildi.

Bulgular: En fazla bilgi içeriği ve en fazla ayırıcılık gücüne sahip parametreler, sırasıyla Sayı, Elips modülasyon ve Maksimum modülasyondur. Bu parametrelerin belirtilen Pr değerleri için en iyi kesim noktaları sırayla 32,08, 1,65 ve 1,20 dir. Alt oran için en iyi kesim noktası Pr değeri % 1 ve % 2 olduğunda 1.95, Pr % 5 olduğunda 2.11 dir.

Sonuç: İKE, tanı testlerinin performanslarının değerlendirilmesinde kullanılmasına rağmen, belirli prevalans değeri için testlerin en iyi kesim noktasını belirleyemez. Bilgi kuramı yaklaşımı bu problemin üstesinden gelebilmek için İKE analizinden daha üstün bir yöntemdir.

Anahtar sözcükler: Tanı testi, glokom, bilgi kuramı, ROC eğrisi

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[1] Department of Biostatistics, Faculty of Medicine, Hacettepe University, Ankara - TURKEY
[2] Department of Ophthalmology, Meram Faculty of Medicine, Selçuk University, Akyokuş, Konya - TURKEY
[3] Department of Ophthalmology, Faculty of Medicine, Hacettepe University, Ankara - TURKEY
Correspondence: *Umut ARSLAN, Department of Biostatistics, Faculty of Medicine, Hacettepe University, Ankara-TURKEY*
E-mail: umutars@hacettepe.edu.tr

Introduction

Many diagnostic tests used in medicine produce results that are non-binary (1). The receiver operating characteristic (ROC) curve analysis is one of the most powerful methods for evaluating the performance of such tests. The ROC curve is a graph that plots the true positive (TP) rate of a test as a function of its false positive (FP) rate for different possible test outcomes.

The discriminating power of a diagnostic test is not only affected by sensitivity and specificity, but also by the prevalence (Pr) of the disease (2). By using information theory, it is possible to determine which test has the maximum information for a given disease prevalence, and to choose the best cut-off value, the point that maximize the information, at different prevalence values. The graphical methods introduced by information theory enables us to compare diagnostic tests over a wide range of prevalence values in terms of their information content, and to identify how the best cut-off point may change as the disease prevalence changes (3-5).

Somoza and Mossman used ROC curve analysis and information theory to develop a mathematical and graphical technique that can be used to evaluate, compare, and optimize diagnostic tests for any value of disorder prevalence (4).

Early detection of retinal nerve fiber layer (RNFL) loss and following up the change in RNFL thickness are crucial for the proper treatment of glaucoma patients. Nerve Fiber Analyzer (GDx NFA) provides automated, objective, quantitative, and highly reproducible measurements of the RNFL based upon the birefringence property of RNFL and compares the results with those from age, sex, and race matched healthy subjects (6-12). However, there is no clear-cut point for the GDx parameters separating the glaucoma patients from the healthy subjects, since most of the measurements show overlap between the groups.

Many statistical techniques are used to evaluate the measurements and make a correct diagnosis. In this study, our aim was to evaluate GDx parameters using information theory, and compare the results with our previous study, in which ROC curve analysis was performed (6).

Materials and methods

Glaucoma patients, totalling 270, and 81 control subjects underwent a detailed examination including visual acuity measurement, biomicroscopy, gonioscopy, fundus examination, Goldmann applanation tonometry, and visual field examination. Scanning laser polarimetry was performed by the same experienced operator [BB] using Nerve Fiber Analyzer (NFA GDx version, 1.0.08, Laser Diagnostics Technologies, San Diego, CA, USA), after informed consent was obtained from the patients.

As described in our previous study (6), the glaucoma patients (primary open angle glaucoma, exfoliation, or pigmentary glaucoma) had IOP > 21 mmHg measured on 2 occasions, and/or glaucomatous optic nerve cupping, and/or visual field defects. The eyes of the normal subjects studied had a best corrected visual acuity above 20/25, a refractive error (spherical equivalent) between - 3 and + 3 dioptres, a normal IOP less than 21 mmHg, a normal optic nerve head appearance, and visual field analysis.

By using ROC curve, the indices showing the discriminatory power of the test and the best cut-off point between diseased and non-diseased subjects can be calculated (4,13). The area under the ROC curve is one of these indices. When FP and TP rates for different cut-offs are transformed into normal deviates, the resulting Z_{FP} and Z_{TP} pairs lie along a straight line. This straight line, which is fitted to Z_{FP} and Z_{TP} pairs, is described by the following equation (3):

$$Z_{TP} = sZ_{FP} + s\Delta m \quad (1)$$

This transformation allows us to use 2 curves, one belonging to the diseased and the other to healthy subjects, with different means and variances. With the help of this binormal assumption, the 2 indices, Δm and s, can be calculated, where Δm is the difference between the means of the 2 groups measured in units of the standard deviation of healthy population, and s is the ratio of the standard deviation of healthy population to diseased population (2,3,14). Δm and s are the 2 indices of diagnostic performance, and are used for calculating the normal deviate of the area under the ROC curve (14,15). The equation is shown below:

$$z(A) = \frac{s \, \Delta \, m}{\sqrt{1 + s^2}} \quad (2)$$

Although ROC curves help us to understand many important features of diagnostic tests, they cannot be used to determine whether one test performs better than another at a different cut-off point at a given prevalence, and so new approaches are needed to evaluate test performances. The clinical effectiveness of a test depends on its information content, which is related to the uncertainty remaining after the test. At this point, information theory seems as powerful a tool for handling such problems (4,16).

The uncertainty related to the disease under consideration before the diagnostic test is applied is referred to as "a priori uncertainty", and after the test results the uncertainty is referred to as "a posterior uncertainty". Uncertainty is measured in terms of bits, and as indicated by Shannon and Weaver, for i mutually exclusive events (Z_i), each with probabilities P (Z_i) of occurring (17,18).

$$H(Z) = -\sum_i P(Z_i)\log_2 P(Z_i) \quad (3)$$

The difference between "a posterior uncertainty" and "a priori uncertainty" is regarded as the gain in information obtained by the diagnostic test, and is referred to as the information content of that test. Metz et al. developed an equation that measures the information content, I, in bits, below (4,19).

$$\begin{aligned} I &= [(TP)(Pr)] \times \log_2 (TP/B) \\ &+ [(FP)(1-Pr)] \times \log_2 (FP/B) \\ &+ [(1-TP)(Pr)] \times \log_2 (1-TP)/(1-B)] \\ &+ [(1-FP)(1-Pr)] \times \log_2 [(1-FP]/(1-B)] \end{aligned} \quad (4)$$

where

$$B = (TP)(Pr) + (FP)(1-Pr)$$

Note that, for a given test, the information gain will be a function of the cut-off and the prevalence. For a given prevalence, by using s and Δm values, a curve of information versus the diagnostic variable was drawn. The diagnostic performance of GDx parameters was evaluated by using the technique developed by Somoza et al. (3). The steps of this technique are as follows:

Step 1. For different cut-off values, the TP and corresponding normal deviates Z_{TP} were calculated. The set of cut-off values and Z_{TP} were then fitted to a polynomial, and for each value of Z_{TP} a cut-off was calculated.

Step 2. For a set of values of Z_{FP}, corresponding Z_{TP} values were calculated by using Equation 1.

Step 3. The Z_{TP} and Z_{FP} values were converted to TP and FP.

Step 4. To calculate the information, FP and TP values found in step 3 and the prevalence (1%, 2%, and 5%) were substituted into Equation 4.

Step 5. In order to express the information as a function of the diagnostic variable by using Equation 1, each Z_{FP} and Z_{TP} value was calculated, and this was substituted in the polynomial defined in Step 1 to get the corresponding cut-off.

Results

The ages [mean ± SD] of the healthy subjects and patients with glaucoma were 59.9 ± 10.1 [range 39-79 years], and 63.1 ± 9.1 [range 37-86 years] years, respectively. There were 88 males and 92 females in the glaucoma group, and 44 males and 37 females in the control group. The best cut-off points were determined (for each parameter) for 1%, 2%, and 5% prevalence rates. For such small prevalence values, the cut-off points are almost the same. Although many interpretations change as the frequency of disorder increases, it would be unrealistic to display the results when the prevalence is as high as 50% or 90%. In order to evaluate and compare different GDx parameters at different prevalence rates, maximum information contents and best cut-off points are displayed in Table 1.

The parameter that has the maximum discriminatory power is "the Number" since it has the greatest information content. The poorest one is the "symmetry". Similar results can be obtained also by means of graphical tools, one of which is the graph of maximum information versus prevalence (MIP Curves) (4). In Figure 1, each curve belongs to a parameter and helps us to understand the ability of each parameter to distinguish normal and diseased subjects, within a wide range of prevalence values. The parameter that has the maximum information content and the maximum discriminatory power within this range is "the Number", and "symmetry" is

Table 1. Maximum information contents of GDx parameters and best cut-off points at different prevalence rates (1%, 2%, and 5%).

GDx Parameters	Maximum Information Content at Pr = 1%	Maximum Information Content at Pr = 2%	Maximum Information Content at Pr = 5%	Best Cut-off Point at Pr = 1% and 2%	Best Cut-off Point at Pr = 5%
Symmetry	0.00024	0.00047	0.00112	1.23	1.23
Superior Ratio	0.00843	0.01667	0.04022	2.09	2.09
Inferior Ratio	0.00934	0.01840	0.04404	1.95	2.11
Superior/Nasal	0.00733	0.01449	0.03493	1.86	1.86
Maximum Modulation	0.00888	0.01752	0.04206	1.20	1.20
Superior Maximum	0.00875	0.01718	0.04088	74.28	80.21
Inferior Maximum	0.00808	0.01590	0.03788	77.08	77.08
The Number	0.03340	0.06303	0.13752	32.08	32.08
Ellipse Modulation	0.00999	0.01955	0.04587	1.65	1.65
Average Thickness	0.00345	0.00682	0.01649	63.58	63.58
Ellipse Average	0.00531	0.01048	0.02524	62.98	62.98
Superior Average	0.00852	0.01675	0.03973	62.90	62.90
Inferior Average	0.00696	0.01375	0.03306	72.30	72.30
Superior Integral	0.00687	0.01354	0.03233	0.18	0.18

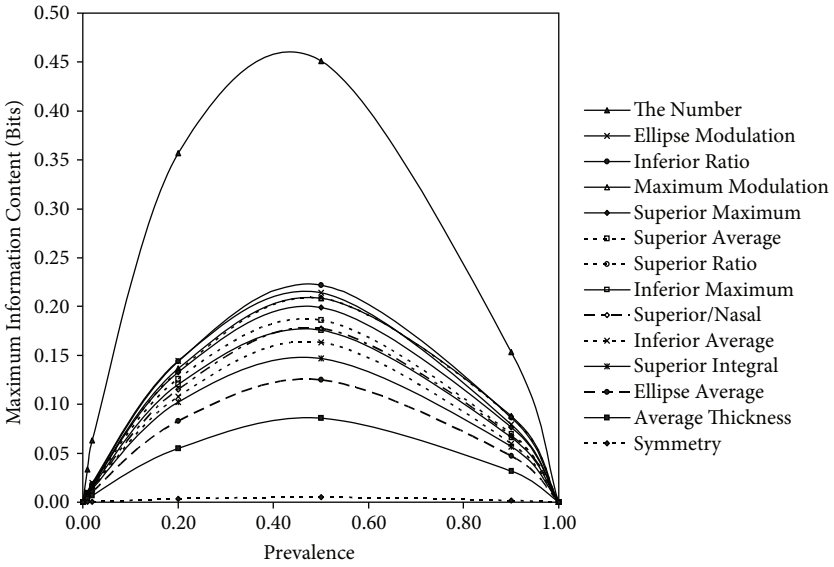

Figure 1. Maximum information contents of parameters versus prevalence (MIP curves).

the parameter which has the smallest information content and minimum discriminatory power. Although Figure 1 is very helpful in showing the performances of different parameters at different prevalence values, it does not give us any idea about the best cut-off point that maximizes the parameter's (test's) performance.

Information theory makes it possible, by plotting the information content of a parameter versus different possible cut-offs, at different prevalence rates to determine the point with the best performance. For different prevalence values, there is one point where the information gain is at a maximum level. This point is referred to as the best cut-off point at that

prevalence rate. When diagnostic tests are evaluated with this approach, the best cut-off point is determined for a given prevalence rate (5).

Figure 2 displays the information content of "the Number" at different cut-offs for the 3 selected prevalence rates. Each curve belongs to a different prevalence rate. "The Number" seems to be the most promising one, and when the prevalence of the underlying disorder is 1%, 2%, or 5%, the best cut-off point is found to be 32.08.

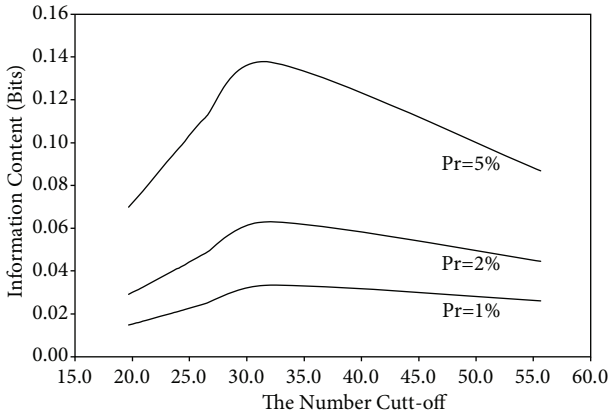

Figure 2. Information content versus cut-off values of "the Number" at 3 different prevalences.

Discussion

Experimental and clinical studies have shown that scanning laser polarimetry provides quantitative and reproducible measurements of the RNFL thickness, and the retardation measurements were significantly lower among glaucomatous and ocular hypertensive eyes when compared with the healthy subjects (6,11,12). The sensitivity and specificity of NFA were found to be 96% and 93% by Tjon-Fo-Sang and Lemij (20), 73% and 75% by Choplin et al. (21), and 87% and 72.8% in our previous study (6). Weinreb et al. (12), using the combination of average thickness, ellipse modulation, and average ellipse thickness, found the sensitivity as 74% and specificity as 92%. Trible et al. (9) used the combination of superior/nasal ratio, maximum modulation, and average thickness to find a sensitivity of 39%, 69%, and 75% for early, moderate, and severe glaucoma at a specificity of 91%. Funaki et al. (22) defined the eye as glaucomatous when at least one of the GDx parameters had a P value < 5%, and found the sensitivity to be 76.7% for normal tension glaucoma, and 85.5 % for POAG at a specificity of 66.7%.

In our previous study, "the Number" (0.898), maximum modulation (0.850), and inferior ratio (0.850) had the highest area under the ROC curve, while the ROC curve area of the "symmetry" was only 0.502, indicating no value in discrimination of the glaucoma group from the healthy subjects. The area under the ROC curve for each GDx parameter is given in Table 2 (6). Lauande-Pimentel et al. (8), found the highest values of the area under the ROC curve for "the Number" (0.87), superior/nasal ratio (0.86), and ellipse modulation (0.85), whereas the lowest value of the area was "symmetry" (0.54). Weinreb et al. (12), found the area under ROC curve for "the Number" as 0.78, when the cut-off point was set at 16.

These results seem to agree with the results of the information theory approach. However, ROC curve analysis lacks some vital parameters, such as the prevalence of the glaucoma. Information theory utilizes the prevalence rate as an input and provides more accurate results, thus enabling us to set different

Table 2. The area under the ROC curve and standard error for each GDx parameter.

GDx Parameters	Area ± SE
Symmetry	0.502 ± 0.035
Superior Ratio	0.846 ± 0.022
Inferior Ratio	0.850 ± 0.024
Superior/Nasal	0.825 ± 0.024
Maximum Modulation	0.850 ± 0.022
Superior Maximum	0.837 ± 0.023
Inferior Maximum	0.825 ± 0.023
The Number	0.898 ± 0.017
Ellipse Modulation	0.846 ± 0.023
Average Thickness	0.735 ± 0.029
Ellipse Average	0.781 ± 0.026
Superior Average	0.828 ± 0.023
Inferior Average	0.810 ± 0.024
Superior Integral	0.800 ± 0.025

cut-offs at different settings with different prevalences. In Table 3 slight differences are observed between the rankings of the areas under the ROC curves of GDx parameters, and their information contents at a prevalence rate of 1%, 2%, and 5%. "The Number" was determined as the best (with a rank of 1) parameter in both analysis, whereas "symmetry" was assigned as the poorest (with a rank of 14).

When the best cut-off points in our study are compared with those suggested by Lauande-Pimentel et al. (8), similar values can be observed. The cut-off values for "the Number" (32.08, 32.00), superior integral (0.18, 0.19), ellipse average (62.98 μm, 60 μm), superior average (62.90 μm, 64 μm), inferior average (72.30 μm, 73 μm), and inferior ratio (1.95, 1.95) were found to be very close to each other when prevalence was set at 1% or 2% in our study, and the study of Lauande-Pimentel et al., respectively (8). However, when prevalence was increased to 5%, the best cut-off point for inferior ratio is increased from 1.95 to 2.11, and for superior maximum, it increased from 74.28 to 80.21. The differences between the rankings of parameters according to maximum information content (at Pr = 1%, 2%, and 5%) and area under the ROC curve can be attributed to the consideration of the prevalence rate in information theory approximation. Since ROC curve is a plot of TP versus FP, which is assumed to be independent of the prevalence of the condition being studied, for specific decision rules they yield the same best cut-off point. However, as the frequency of the condition changes, the best cut-off point, in terms of the maximum information, is supplied by the test changes. The frequency of many diseases differs worldwide. The prevalences cannot be assumed to be constant for different populations. This makes information theory more powerful than other traditional methods for the evaluation of diagnostic tests.

The device used in this study is GDx, which is a third generation of NFA. It has a fixed corneal compensator (GDx FCC) that assumes all individuals to have a corneal birefringence with a slow axis of 15° nasally downward, and a magnitude of 60 nm. However, corneal polarization axis and magnitude

Table 3. Rankings of GDx parameters according to information content when Pr = 1% or Pr = 2% and area under the ROC curve.

GDx Parameters	Ranking According to	
	Information Content When Pr = 1% or 2%	**Area Under the ROC Curve**
The Number	1	1
Ellipse Modulation	2	3
Inferior Ratio	3	2
Maximum Modulation	4	2
Superior Maximum	5	4
Superior Average*	6	5
Superior Ratio*	7	3
Inferior Maximum	8	6
Superior/Nasal	9	6
Inferior Average	10	7
Superior Integral	11	8
Ellipse Average	12	9
Average Thickness	13	10
Symmetry	14	11

*: When prevalence increases to 5%, rankings of Superior Ratio and Superior Average interchange.

vary interindividually. Several studies show that corneal polarization affects the RNFL thickness measurements obtained with SLP, and correction for both of axis and magnitude with GDx variable corneal compensator (GDx VCC) increases the discriminating power of this technology for glaucoma detection when compared with the GDx FCC (23-25).

In this study, our aim was not to show the diagnostic accuracy of GDx FCC, but to compare 2 statistical methods, ROC analysis and the information theory. In medical science, generally ROC analysis is used to evaluate the sensitivity and specificity of the variables for separating the diseased from the healthy, without taking the prevalence into consideration. However, the glaucoma prevalence varies in different populations. Although this variation may be small for glaucoma, considerable changes can be observed in other diseases. Primary open-angle glaucoma (POAG) prevalence is higher in the black population, and exfoliation glaucoma is more common in Scandinavian and Mediterranean countries. The information theory is a more sophisticated analysis, giving more details about the disease. It would be interesting to re-evaluate the parameters of glaucoma diagnostic devices, such as GDx VCC, Optical Coherence Tomography (OCT), and Heidelberg Retina Tomography, using information theory based on the prevalence rates in the studied populations.

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