ความแม่นยำของการแปลผลภาพถ่ายจอประสาทตาโดยใช้ Five Rules ในการคัดกรองโรคต้อหิน

The diagnostic accuracy of the application of Five Rules in fundus-camera-based eye ground examination for glaucoma screening

วรนารี เจริญรุ่งรัตน์[1], วิน เตชะเคหะกิจ[1]

Worranaree Charoenrungrat[1], Win Techakehakij[1]

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บทคัดย่อ

งานวิจัยนี้ศึกษาผู้ป่วยของโรงพยาบาลลำปางที่ได้รับการถ่ายภาพจอประสาทตาบันทึกไว้ในปีพ.ศ. 2560 จักษุแพทย์แปลผล Five rules จากภาพถ่ายจอประสาทตาโดยใช้ใบรายการตรวจสอบถูกผิด ผลถูกเท่ากับ 1 คะแนน ผลการประเมินดังกล่าวได้นำมาเปรียบเทียบกับผลวินิจฉัยโรคต้อหิน คำนวณความไว ความจำเพาะ ความถูกต้องในการวินิจฉัย likelihood ratios และพื้นที่ใต้กราฟ Receiver Operating Characteristic(ROC) จากผู้ป่วยจำนวน 27 ราย(52 ตา) ตาจำนวน 15 ตาได้รับการวินิจฉัยโรคต้อหิน จาก Five rules

ผลการศึกษาพบว่าความจำเพาะสูงสุด(97.3%) พบใน Rule 1 3 และ 5 ขณะที่ความไวต่ำสุดปรากฏใน Rule 3(6.67%) จุดตัดของคะแนนทั้งหมดที่วินิจฉัยถูกต้องสูงสุด(88.46%) คือ ≥2 โดยมีความไวและความจำเพาะที่ยอมรับได้ 73.33% และ 94.59% ตามลำดับ พื้นที่ใต้กราฟ ROC แสดงความสามารถในการจำแนกเท่ากับ 0 .891

คำสำคัญ: ความแม่นยำในการวินิจฉัย, Five Rules, ภาพถ่ายจอประสาทตา, การคัดกรองโรคต้อหิน

ABSTRACT

This study examined the diagnostic accuracy of Five Rules used in glaucoma screening by fundus camera. Patients were recruited at Lampang Hospital in 2017 whose fundus photographs were on record. An ophthalmologist interpreted the fundus photographs using a yes/no checklist of Five Rules. A point was assigned for each rule with a positive answer. These results were compared with the diagnosis of glaucoma. Sensitivity, specificity, diagnostic accuracy, likelihood ratios, and area under the Receiver Operating Characteristic (ROC) curve were calculated.

Results: Twenty-seven patients (52 eyes) were included, of which 15 eyes were diagnosed with glaucoma. The highest specificity (97.3%) was found in Rules 1, 3, and 5 whereas Rule 3 showed the lowest sensitivity (6.67%). The cut-off score giving the highest diagnostic accuracy (88.46%) was ≥2, with acceptable sensitivity and specificity of 73.33% and 94.59%, respectively. The area under the ROC curve gives the power of discrimination of 0.891.

and satisfactory specificity. Applying Five Rules seems practical in the Thai healthcare context as only small additional costs are incurred.

Keywords: Diagnostic accuracy, Five Rules, fundus photographs, glaucoma screening

[1] พบ. โรงพยาบาลเกาะคา จังหวัดลำปาง

Introduction

Glaucoma is a leading cause of irreversible vision loss worldwide[1] .Most people with glaucoma have slowly progressive but irreversible damage .Often there are no obvious symptoms until a relatively late stage, meaning that a diagnosis may be delayed[2, 3].

Glaucoma is found in 3.54% (95% CI: 2.09, 5.82) of the global population aged 40-80. In 2013, it was estimated that 64.3 million middle-aged to elderly people had glaucoma. It has been forecast that by 2020 this number will be 76.0 million and by 2040 it will be 111.8 million, disproportionally affecting Asian and African ethnicities[1] . In Thailand, a population-based survey revealed the prevalence of glaucoma to be 3.8[4].

Although it is irreversible, early detection is very important because prompt treatment could stop the visual loss progression and potentially save incurred costs in comparison with late diagnosis and treatment[5].

Despite its cost to health, the early detection rate is very low. Silent glaucoma remains undetected in the general population. In developed countries, it was estimated that only approximately one-third of glaucoma patients knew of their disease. In the developing world, only about 8% of all people with glaucoma are aware of the fact[6].

In Thailand, there is hardly any evidence documenting the tools used in screening for glaucoma in the general population[7]. One possible explanation for the impracticality of glaucoma screening in the general population could be that, to achieve high sensitivity, the current practise always requires at least one ophthalmologist to perform the diagnosis using specialist equipment. This was echoed in a Thai study indicating a low sensitivity of glaucoma diagnosis among general practitioners (21.7%), compared with ophthalmologists (100%)[7]. While glaucoma screening largely depends on the availability of ophthalmologists, there are currently insufficient ophthalmologists to perform all the screening work in Thailand. Moreover, economic studies have shown that glaucoma screening in the population may only be cost-effective in older age groups[8, 9].

Five Rules[10] is a systematic approach, devised for non-ophthalmologists, to screen for glaucoma by looking at the eye ground. It includes the evaluation of optic disc size, rim shape and area, presence of retinal nerve fibre layer (RNFL) loss, parapapillary atrophy (PPA), and retinal or optic disc haemorrhages. This Five Rules systematic process could improve the availability of glaucoma screening. While using Five Rules as the criteria in screening for glaucoma by fundus camera appears to be simple and economical, no one has ever performed an accuracy test of these criteria in practise. This study aims to examine the diagnostic accuracy of Five Rules in glaucoma screening

Methods

Population and Samples

This study recruited patients who registered at the outpatient Ophthalmology Department of Lampang Hospital in 2017 and whose fundus photographs were taken using a fundus camera. Fundus photographs are not routinely taken and so only some patients who registered had photographs taken and stored in the camera to use in following the progression of the diseases and/or teaching medical students. The exclusion criteria were those patients whose fundus photographs were not within the required interpretable quality for this study.

Study design

The patients' fundus photographs were extracted from the fundus camera and sent to an ophthalmologist to interpret and complete a yes/no checklist of Five Rules.

Five Rules[10] were used as the diagnostic indicants to evaluate the optic disc and retinal nerve fibre layer for glaucoma. These Five Rules are:

Rule 1 evaluates the vertical cup disc ratio (VCDR) which is achieved by observing the scleral ring, and assessing the optic disc size. (Yes = enlarged VCDR, No = No enlarged VCDR)

Rule 2 evaluates the neuroretinal rim by the ISNT Rule which is used to identify the size of the neuroretinal rim. (Yes = Not Respect ISNT Rule, No = Respect ISNT Rule)

Rule 3 evaluates the retinal nerve fibre layer (RNFL) which is examined for the loss of areas (Yes = RNFL loss, No = no RNFL loss seen)

Rule 4 evaluates the region of parapapillary atrophy (PPA) by examining the region adjacent to the optic disc for the presence of parapapillary atrophy. (Yes = PPA seen, No = No PPA seen)

Rule 5 evaluates retinal and optic disc haemorrhage by looking for retinal and optic disc haemorrhages. (Yes = Retinal and/or optic disc haemorrhage seen, No = No Retinal or optic disc haemorrhage seen)

A point was assigned for each rule with a positive answer, giving a maximum total of 5 points.

The gold standard is the diagnosis of glaucoma, defined as patients having the diagnosis of glaucoma by ophthalmologists present in their medical records.

Analysis of diagnostic indicants

The results obtained with each of the Five Rules were compared with the diagnosis of glaucoma for each patient. Sensitivity, specificity, diagnostic accuracy, and likelihood ratios were calculated for each rule.

The sensitivity, specificity, and diagnostic accuracy of each total score as a possible cut-off point for detecting glaucoma were calculated. A receiver operator characteristic (ROC) curve was plotted using STATA version 13[11], with the area under the ROC curve representing the discriminatory power of the index test.

Results

A total of 36 patients who matched the inclusion criteria were identified. Nine of these patients were excluded by an ophthalmologist because the quality of their pictures did not match the requirements. Two of the patients have only one eye. Therefore, there were 52 eyes (N=52) in the study and 15 eyes (28.85% of all) were diagnosed as glaucomatous. All samples were more than 40 years of age; the majority were between the ages of 51-60. Demographic characteristics of the samples are as shown in Table I.

Table II shows the sensitivities, specificities, diagnostic accuracies, and likelihood ratios of each rule. Among the Five Rules, the highest specificity (97.3%) was found in Rule 1 (Vertical cup disc ratio), Rule 3 (Retinal nerve fibre layer), and Rule 5 (Retinal and optic disc haemorrhage. In contrast, Rule 3 (Retinal nerve fibre layer) has extremely low sensitivity.

The diagnostic accuracy between the total points of positive signs and glaucoma was plotted, as seen in Table III. The cut-off for total scores which gives the highest sensitivity (93.33%) is $\geq$1 but it also gives the lowest specificity (56.76%). The cut-off for total scores that gives 100% specificity is $\geq$4 but this gives an extremely low sensitivity (6.67%). The ROC curve was plotted, with the area under the curve of 0.8910, as illustrated in Fig1.

Discussion

To the author's knowledge, this is the first attempt to use Five Rules as the criteria in screening for glaucoma by fundus camera. Results of this study showed that Five Rules appears to be an effective tool, with a strong power of discrimination of 0.891. A relatively high diagnostic accuracy of this equipment indicates that it may be possible to use the tool in real clinical practise.

Considering a cut-off for the tool to be used in general screening, there was a trade-off between minimising false negatives and an excessive workload due to false positives. When the cut-off of $\geq$1 point is applied, the sensitivity is as high as 93.33%, with a relatively low specificity of 56.76%. Despite advantages of high sensitivity to minimise false negatives, however, the cut-off of $\geq$1 causes a rate of false positives as high as 43% or more. This implies, if a mass screening is undertaken, almost half of the glaucoma-free participants would yield a positive result and require further investigation. This in turn, incurs unnecessary workload and subsequent medical costs. Considering applying a 1 point cut-off is recommended only for ophthalmology healthcare providers which can manage a large number of referrals and have enough ophthalmologists.

Despite having lower sensitivity than the cut-off of 1, cut-offs of $\geq$2 and $\geq$3 points yield a relatively higher diagnostic accuracy, with high specificities of 94.59% and 97.3%, respectively. Application of the cut-offs of 2 or 3 points thus seems to be realistic in terms of preventing excessive workload and extra costs from the false positive results. However, with a relatively higher sensitivity of 73.33% when applying the $\geq$2 point cut-off, compared with a sensitivity of 60% for the $\geq$3 point cut-off, using $\geq$2 points as a cut-off will result in a lower rate of undetected glaucomatous patients, which may be suitable for mass screening in the general population.

False positive results of the test may occur with patients who had not only glaucomatous eye but also other eye conditions such as diabetic retinopathy and retinal diseases; that is, a positive test in each rule may be associated with other medical conditions, apart from glaucoma. For example, a positive result from Rule 5 (Retinal and optic disc haemorrhage) may imply the existence of diabetic retinopathy, a history of typical migraine headache and increasing systolic blood pressure[12]. Interpretation of the positive results should be done with caution, accounting for other possible health conditions that might affect the test.

The highest sensitivity when using Five Rules as a tool in glaucoma screening is 93.33%. It indicated that about 6.67% of all samples with glaucomatous eye had negative test results. In practice, there are other controversial clinical criteria to diagnose glaucoma, such as detection of progressive damage of the optic nerve head with ambiguous appearance[13] or specific pattern of visual function deficit[13, 14], especially when compounded with high intraocular pressure. These were not included in the Five Rules and lead to false negative results.

Some of the Five Rules, such as measuring the vertical cup to disc ratio, are based on visual inspection, which may be influenced by the personal experience and clinical judgement of each ophthalmologist. This can possibly leads to false negative results.

One of the limitations of this study is the measurement validity as there was only one general ophthalmologist who interpreted the Five Rules scores. However, the practical recommendation suggests that diagnosis of glaucoma should be based on the opinions

from at least three ophthalmologists[15]. Future study may improve the accuracy of the outcome measurement by employing three glaucoma specialists in the diagnosis.

Another source of false negatives could be from the equipment used in this study. The fundus camera itself is not generally used as a standard tool to inspect eye ground for diagnosing glaucoma, possibly owing to the limited quality of fundus photographs produced. This concern was raised in a previous study[16] which compared the evaluation of vertical cup to disc ratio in glaucoma patients between the standard indirect ophthalmoscope with a 78 D lens and the non-mydriatic fundus camera. The estimated VCDR values were similar)p<0.001 (but the non-mydriatic fundus camera yielded only 68.4% sensitivity. To improve sensitivity of the screening, incorporating other screening tools, such as measuring intraocular pressure, may be recommended.

An issue worth mentioning is the possible selection bias which could affect the sensitivity in this study. This could result from some clinical criteria which appear in the screening tests presenting only in the late phase of glaucoma. Five rules are thus inclined to give a positive result when screening in late stage glaucoma[17, 18], whereas these signs may be missing in the early phase of glaucoma. Samples of this study were recruited from out-patients at the Ophthalmology Department, which contains a high proportion of patients in late stage of glaucoma, presenting with progressively and severely glaucomatous eyes. These samples might not be representative of the silent glaucomatous patients in the population of which the majority might still be in the early stages. Future research, using samples from the general population, is suggested.

The other limitation of this study is the result uncertainty as a consequence of the small sample size used. The power would have increased if there had been more samples in this study. To reduce this result uncertainty, conducting a prospective study may be required to collect a larger sample size.

The feasibility of utilising the Five Rules in glaucoma screening by non-ophthalmologists requires nurses to be trained to use Five Rules to screen for glaucoma using a fundus camera. This possibility works particularly well in the context of the Thai public health, where at least one fundus camera is currently available in all hospitals for diabetic retinopathy screening, and primary care nurses are assigned to perform the fundus screening in this regard. Using the Five Rules could be an effective method to screen for glaucoma with low costs and small additional workload in the current setting. Nonetheless, a diagnostic test would be required to demonstrate the accuracy of screening by nurses, compared with ophthalmologists, before implementing the screening in real practise.

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TABLES / FIGURES

Table I: Patients' demographic characteristics

Characteristics	N (%)
Samples	
Total	27 (100)
Gender	
Male	12 (44.44)
Female	15 (55.55)
Age group	
41-50	3 (11.11)
51-60	10 (37.04)
61-70	8 (29.63)
>70	6 (22.67)
Diabetes mellitus	15 (55.56)
Family history of glaucoma	2 (7.41)
History of ocular trauma	4 (14.81)
Eyes (from 27 samples)	
Blind	2
Intact	52
Glaucoma	15

Table II: The sensitivities, specificities, diagnostic accuracies, and likelihood ratios of each rule

Five Rules	Sensitivity	Specificity	Diagnostic Accuracy	LR+	LR-
Rule 1 VCDR	73.33%	97.30%	90.38%	27.1334	0.2741
Rule 2 ISNT RULE	66.67%	89.20%	82.69%	6.1667	0.3737
Rule 3 RNFL	6.67%	97.30%	71.15%	2.4667	0.9593
Rule 4 PPA	66.67%	67.57%	67.31%	2.0556	0.4933
Rules 5 Haemorrhage	20.00%	97.30%	75%	7.4000	0.8222

Table III: The diagnostic accuracy between the total numbers of positive points and glaucoma

Number of positive points	Sensitivity (%)	Specificity (%)	Diagnostic Accuracy	LR+	LR-
0	100.00%	0.00%	28.85%	1.00	
≥1	93.33%	56.76%	67.31%	2.16	0.12
≥2	73.33%	94.59%	88.46%	13.55	0.28
≥3	60.00%	97.30%	86.54%	22.22	0.41
≥4	6.67%	100.00%	73.08%		0.93
5	0.00%	100.00%	71.15%		1.00

Figure (1) The area under the ROC curve represents the power of discrimination between glaucoma and normal