Doc Ophthalmol
https://doi.org/10.1007/s10633-019-09734-2

ORIGINAL RESEARCH ARTICLE

Screening for diabetic retinopathy in diabetic patients with a mydriasis-free, full-field flicker electroretinogram recording device

Yunkao Zeng · Dan Cao · Dawei Yang · Xuenan Zhuang · Honghua Yu · Yunyan Hu · Yan Zhang · Cheng Yang · Miao He · Liang Zhang

Received: 14 June 2019 / Accepted: 5 November 2019

Abstract

Purpose To investigate the accuracy of the RETeval full-field flicker ERG in the screening of diabetic retinopathy (DR) and vision-threatening diabetic retinopathy (VTDR) and to determine a suitable range of DR diagnostic reference for patients with type 2 diabetes mellitus (T2DM).

Methods This was a cross-sectional study involving 172 subjects with T2DM, including 71 subjects without clinically detectable DR (NDR), 25 subjects with mild non-proliferative diabetic retinopathy (NPDR), 24 subjects with moderate NPDR, 27 subjects with severe NPDR and 25 subjects with proliferative diabetic retinopathy (PDR). All the subjects underwent a full-field flicker ERG using the RETeval device (DR assessment protocol), which is a mydriasis-free, full-field electroretinogram (ERG) recording system. The performance of the DR assessment protocol in detecting the DR (including mild NPDR, moderate NPDR, severe NPDR and PDR) and VTDR was analyzed with the receiver operating characteristic (ROC) curve.

Results For the detection of DR (mild NPDR, moderate NPDR, severe NPDR, PDR), the area under the ROC curve was 0.867 ($p < 0.001$, 95% CI 0.814–0.920), and the best cutoff value for DR was determined to be 20.75, with a sensitivity of 80.2% and specificity of 81.7%. Meanwhile, for the detection of VTDR, the area under the ROC curve was 0.965 ($p < 0.001$, 95% CI 0.941–0.989), and the best cutoff value was set to 23.05, with a sensitivity of 94.6% and a specificity of 88.8%.

Conclusion The DR assessment protocol in RETeval device was effective in screening for DR (mild NPDR, moderate NPDR, severe NPDR, PDR) and VTDR in patients with diabetes. It could be helpful in referring and managing patients with T2DM in primary healthcare setting. However, caution should be taken that optimal cutoff value of DR assessment protocol may vary in different ethnic populations.

Keywords Diabetic retinopathy · Screening · Electroretinogram · Retinal diagnostic test

Yunkao Zeng and Dan Cao have contributed equally to the work.

Y. Zeng · D. Cao · D. Yang · X. Zhuang · H. Yu · Y. Hu · Y. Zhang · C. Yang · M. He · L. Zhang (✉)
Department of Ophthalmology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, No. 106, Zhongshan Er Road, Yuexiu District, Guangzhou, Guangdong, China
e-mail: zhangliang5413@163.com

Y. Zeng · D. Yang · X. Zhuang · Y. Zhang
Shantou University Medical College, Shantou, China

Published online: 12 November 2019

Introduction

Diabetic retinopathy (DR) is a common complication of diabetes mellitus (DM) and remains the leading cause of blindness among the working age population worldwide [1]. It was estimated that the total number of the diabetic population would double from 171 million in 2000 to 366 million by 2030, and the greatest increases were expected in Asia (China and India) [2]. The estimate prevalence of DR and vision-threatening DR (VTDR) in the adult diabetic population worldwide was 34.6% (93 million) and 10.2% (28 million), respectively [3]. Such huge amount of patient with DR may cause high socioeconomic burden and lead to a great challenge to the healthcare system. The present treatments for DR mainly target the late stages when vision may be affected, and once DR progresses to the late stage, loss of vision can be irreversible. Therefore, early diagnosis of DR is essential in providing timely intervention to prevent the visual impairment in patients with DR.

DR screening programs are challenged by issues related to implementation, availability of human resources and long-term financial sustainability [4, 5]. Conventional methods for screening and diagnosing DR include ophthalmoscopy, color fundus photography and stereoscopic color fundus photography in 7-standard fields [6]. However, the obtainment of the stereoscopic color fundus photography in 7-standard fields is time-consuming and requires experienced photographers and trained physicians to analyze the results [7]. The above-mentioned issues hindered accurate and efficient screening of DR in community healthcare settings.

RETeval (LKC Tech. Inc., Gaithersburg, MD, USA) is a novel handheld, mydriasis-free, full-field ERG recording system, which is simple to use and time saving. The system has a DR assessment protocol to screen VTDR, and it was effective in screening VTDR in Caucasians, African-Americans and Turkish [8, 9]. After the examination, the device will display a numerical value according to the age, implicit time, amplitude and pupil response. Although the recommended cutoff value of the DR assessment was determined to be 19.9 for the detection of VTDR, it might not be an universal standard for the different ethnic population [8, 9]. Given the high prevalence of DR in China, a study to evaluate the usefulness of the DR assessment protocol of RETeval system in Chinese is of great importance. Therefore, the purposes of the current study are to investigate the performance of RETeval system in the screening of DR (mild NPDR, moderate NPDR, severe NPDR and PDR) and VTDR and to determine a suitable cutoff value for the DR assessment protocol in patients with type 2 diabetes mellitus (T2DM).

Methods

This was a cross-sectional study approved by the Medical Research Ethics Committee of the Guangdong Provincial People's Hospital (No. 2016232A), and it was performed in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all the subjects.

Subjects

One-hundred and seventy-two subjects with T2DM were enrolled in the current study, including 71 subjects without clinically detectable DR (NDR), 25 subjects with mild non-proliferative diabetic retinopathy (NPDR), 24 subjects with moderate NPDR, 27 subjects with severe NPDR and 25 subjects with proliferative diabetic retinopathy (PDR). The diagnosis of T2DM was determined by endocrinologists according to the diagnostic criteria of American Diabetes Association [10]. The diagnosis and classification of DR were established according to the International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity Scales [11]. Clinically significant macular edema (CSME) was diagnosed on slit-lamp examination, fundus photograph and further confirmed by optical coherence tomography (RTVue XR Avanti; Optovue, Fremont, CA, USA). CSME was defined as retinal thickening at or within 500 microns of center of macula, hard exudates at or within 500 microns of the center of the macula with adjacent retinal thickening and retinal thickening greater than one disk diameter in size which is within 1 disk diameter from the center of the macula [12].

Vision-threatening DR was defined as severe NPDR, PDR and CSME at any stage. All the subjects were firstly classified as: NDR, mild NPDR, moderate NPDR, severe NPDR and PDR. In addition, subjects were further divided as NDR, mild NPDR without

CSME, moderate NPDR without CSME, mild and moderate NPDR with CSME, severe NPDR and PDR, and the last three groups were grouped together as VTDR. The eye with higher stage was selected and determined to be the stage of DR of patient if both eyes of the subject were eligible. Since Maa's study used the best eye's amplitude of 16Td-s and implicit time of the 32Td-s flicker ERG and the worst's eye's pupil area ratio to formulate the equation correlating with the presence of VTDR, the data were collected as the same as the first published study [8]. Subjects with the following condition were excluded: (1) patients with other ocular conditions other than DR (glaucoma, uveitis, spherical equivalents > 3 diopters [D], etc.); (2) subjects with the history of photosensitive epilepsy; (3) history of retinal laser photocoagulation; (4) history of anti-VEGF therapy; (5) history of ocular surgery; (6) subjects with ocular conditions that affect imaging of fundus; (7) ungradable photographs.

Clinical parameters

All the participants underwent comprehensive ocular examinations, including best-corrected visual acuity (BCVA), intraocular pressure, refractive error (autorefractometry) and mydriatic slit-lamp fundus examination. The stage of DR was determined independently by 2 experienced ophthalmologists based on the result of slit-lamp fundus examination and ETDRS 35 degree 7-standard field color retinal photographs (Topcon TRC; Topcon, Tokyo, Japan) and according to the International Clinical Diabetic Retinopathy Disease Severity Scale [11]. Age, sex and duration of T2DM of each patient were recorded, as well as data on the levels of glycated hemoglobin (HbA1c), serum creatinine, blood urea nitrogen (BUN), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglyceride.

Mydriasis-free, full-field flicker ERG examination

The details of the RETeval device have been described in previous studies [6, 8, 13]. The device was used according to the guidance for DR assessment protocol provided by the manufacturer. The DR assessment protocol defaults the flash retinal illuminance as 16 and 32 photopic Td-s, aiming to assess the cone pathway in the inner retina. The frequency of the flicker stimuli was set to 28.3 Hz, and the pulse duration was less than 1 ms. The system uses a special skin electrode array to pick up electrical signals from the retina. The implicit times and amplitudes were recorded simultaneously. The DR assessment protocol generates a DR score with default reference range of 7.0–19.9. The cutoff value was set for the purpose of screening VTDR and detailed data could be found in previous study [8].

Statistical methods

We performed the data analyses with SPSS software version 19.0 (SPSS Inc, Chicago, IL). One-way ANOVA was performed to analyze the differences if the numerical variables were normally distributed, and non-normally distributed data were analyzed with Kruskal–Wallis H test. Chi-square test was used to compare categorical variables. The area under the receiver operating characteristic (ROC) curve was used to analyze the detection performance, sensitivity and specificity of the DR score to discriminate DR and VTDR. The cutoff values were determined by using the Youden index (sensitivity + specificity − 1) for the purpose of balancing sensitivity and specificity. p value less than 0.05 was considered as statistically significant.

Results

The demographic and clinical characteristics of the NDR group, mild NPDR group, moderate NPDR group, severe NPDR group and PDR group are demonstrated in Table 1. There were no statistically significant differences in age ($p = 0.177$), gender ($p = 0.778$) and duration of DM ($p = 0.445$) among the 5 groups. The levels of HbA1c, cholesterol, HDL, LDL and TRIG were comparable among the 5 groups ($p = 0.770$, $p = 0.344$, $p = 0.736$, $p = 0.223$, $p = 0.675$, respectively). There were significant differences in the levels of serum creatinine ($p = 0.019$) and BUN ($p = 0.001$) among the 5 groups. Post hoc analysis with Bonferroni correction showed that the levels of serum creatinine in severe NPDR group, PDR group were significantly higher than NDR group ($p = 0.050$, $p = 0.015$), but they were significantly different from mild NPDR group ($p = 0.420$, $p = 0.631$) and moderate NPDR group ($p = 0.837$, $p = 1.000$). The levels of BUN in severe NPDR group,

Table 1 Demographic and clinical characteristics of the subjects

	NDR (n = 71)	Mild NPDR (n = 25)	Moderate NPDR (n = 24)	Severe NPDR (n = 27)	PDR (n = 25)	p value
Age (years)	59.35 ± 12.54	59.16 ± 9.06	59.83 ± 9.40	60.15 ± 9.47	53.76 ± 8.36	0.177[a]
Gender (M/F)	42/29	13/12	16/8	16/11	13/12	0.778[b]
Duration of DM	9.87 ± 5.09	11.64 ± 4.64	11.45 ± 6.55	10.67 ± 6.63	11.72 ± 4.35	0.445[a]
HbA1c (%)	8.98 ± 2.45	9.61 ± 2.06	9.24 ± 2.12	9.22 ± 2.34	8.72 ± 1.83	0.770[a]
SCr (μmol/L)	69.58 (29.72)	70.77 (84.98)	69.80 (90.16)	96.89 (137.96)	105.92 (104.58)	**0.019**[c]
BUN (mmol/L)	5.70 (2.23)	5.68 (2.11)	6.40 (5.38)	8.25 (7.49)	7.74 (9.90)	**0.001**[c]
Chol (mmol/L)	4.90 (1.83)	6.01 (1.31)	5.17 (1.63)	5.27 (1.97)	4.88 (1.83)	0.344[c]
HDL (mmol/L)	0.98 (0.29)	1.02 (0.46)	0.94 (0.27)	0.94 (0.20)	0.89 (0.32)	0.736[c]
LDL (mmol/L)	3.10 (1.21)	3.85 (1.28)	3.40 (1.50)	3.44 (1.43)	3.27 (1.54)	0.223[c]
TRIG (mmol/L)	1.50 (1.13)	1.36 (1.31)	2.19 (1.55)	1.72 (1.73)	1.94 (1.57)	0.675[c]
Spherical equivalent (D)	0.23 ± 1.78	0.16 ± 1.35	0.51 ± 1.57	0.10 ± 1.39	0.22 ± 1.56	0.899[a]
Phakia/pseudophakia	60/11	21/4	18/6	22/5	24/1	0.321[b]

[a]Data were described as (mean ± standard deviation) and analyzed with one-way ANOVA

[b]Data were analyzed with Chi-squared test

[c]Data were described as median (interquantile range) and analyzed with Kruskal–Wallis H test with Bonferroni correction

NDR: diabetic patients without retinopathy, NPDR: non-proliferative diabetic retinopathy, PDR: proliferative diabetic retinopathy, DM: diabetes mellitus, M: male, F: female, HbA1c: glycated hemoglobin, SCr: serum creatinine, BUN: blood urea nitrogen, Chol: total cholesterol, HDL: high-density lipoprotein, LDL: low-density lipoprotein, TRIG: triglyceride

Significant values are shown in bold type

PDR group were significantly higher than NDR group (p = 0.008, p = 0.017), but they were significantly different from mild NPDR group (p = 0.154, p = 0.170) and moderate NPDR group (p = 1.000, p = 1.000). However, the levels of serum creatinine, BUN were comparable between severe NPDR group and PDR group (all $p > 0.05$) and also comparable among NDR group, mild NPDR group and moderate NPDR group (all $p > 0.05$). Besides, the spherical equivalents were comparable among the 5 groups (p = 0.899). Part of the subjects were pseudophakia, and no significant differences were found on the proportion of phakia/pseudophakia among the 5 groups (p = 0.321).

Table 2 shows the details and comparison of the parameter in the DR assessment protocol. There were statistically significant differences in the DR scores among the 5 groups (all $p < 0.001$), and the score tends to increase with the progression of DR (all $p < 0.05$). There were also significant differences in the implicit time, amplitude (both 16Td-s and 32Td-s) and pupil area ratio among the 5 groups ($p < 0.001$). The representative results of fundus photograph and the waveform of ERG in the 5 groups are displayed in Fig. 1.

In order to divide the subjects into groups with or without VTDR, we further classified the patients into NDR (n = 71), mild NPDR without CSME (n = 24), moderate NPDR without CSME (n = 19), mild and moderate NPDR with CSME (n = 6), severe NPDR (n = 27) and PDR (n = 25). The data are demonstrated in Table 3, and there were also significant differences in the implicit time and amplitude of both 16Td-s and 32Td-s, DR scores and pupil area ratio among the 6 groups (all $p < 0.001$). The box plots of the DR score, best eye's amplitude of 16Td-s and implicit time of the 32Td-s flicker ERG and the worst's eye's pupil area ratio are shown in Fig. 2. The ROC curves for the detection of DR (mild NPDR, moderate NPDR, severe NPDR, PDR) and VTDR are demonstrated in Fig. 3. For the detection of DR (both NPDR and PDR), the area under the ROC curve was 0.867 ($p < 0.001$, 95%

Table 2 The parameters of DR assessment protocol in different groups

	NDR (n = 71)	Mild NPDR (n = 25)	Moderate NPDR (n = 24)	Severe NPDR (n = 27)	PDR (n = 25)	p value
16Td-s						
Implicit time (ms)	30.08 ± 2.19	30.22 ± 2.34	31.52 ± 3.73	35.89 ± 3.79	37.70 ± 3.72	**< 0.001**[a]
Amplitude (μV)	18.98 ± 5.78	15.65 ± 34.41	13.55 ± 4.40	9.31 ± 3.60	8.20 ± 3.23	**< 0.001**[a]
32Td-s						
Implicit time (ms)	28.78 ± 1.63	29.54 ± 1.96	30.50 ± 2.77	34.69 ± 3.33	36.73 ± 3.44	**< 0.001**[a]
Amplitude (μV)	22.10 ± 6.89	19.31 ± 5.55	16.74 ± 5.15	10.88 ± 4.31	9.87 ± 3.64	**< 0.001**[a]
Pupil area ratio	1.92 ± 0.31	1.72 ± 0.25	1.68 ± 0.28	1.49 ± 0.24	1.37 ± 0.24	**< 0.001**[a]
DR score	19.00 ± 2.27	20.62 ± 2.85	22.73 ± 4.04	27.60 ± 3.61	31.54 ± 3.82	**< 0.001**[a]

NDR: diabetic patients without retinopathy, DR: diabetic retinopathy, NPDR: non-proliferative diabetic retinopathy

[a]Data were described as (mean ± standard deviation) and analyzed with one-way ANOVA

Significant values are shown in bold type

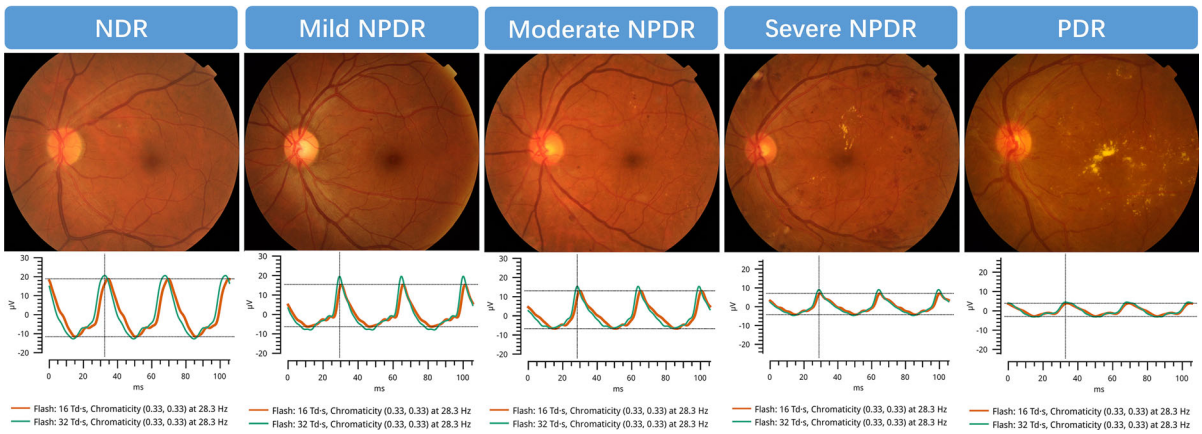

Fig. 1 The representative fundus photographs and ERG waveforms of NDR, mild NPDR, moderate NPDR, severe NPDR and PDR were showed from left to right, respectively

CI 0.814–0.920), and the best cutoff value for DR was determined to be 20.75, with a sensitivity of 80.2% and specificity of 81.7%. Meanwhile, for the detection of VTDR, the area under the ROC curve was 0.965 ($p < 0.001$, 95% CI 0.941–0.989), and the best cutoff value was set to 23.05, with a sensitivity of 94.6% and a specificity of 88.8%.

Discussion

In the current study, we found that the DR assessment protocol was able to differentiate DR from NDR and differentiate VTDR from those without VTDR. The AUC for detecting VTDR was higher than that of DR. With good sensitivity and specificity, the DR assessment protocol was effective in screening DR with a cutoff value of 20.75 and screening VTDR with a cutoff value of 23.05.

Researchers had tried to use single-field fundus photography for the screening of DR. By reviewing 32 articles on screening VTDR, Williams and colleagues found that single-field fundus photography interpreted by trained readers had sensitivity ranging from 61 to 90% and specificity ranging from 85 to 97% when compared with the gold standard reference of

Table 3 The parameters of DR assessment protocol in different groups

	NDR (n = 71)	Mild NPDR CSME(−) (n = 24)	Mo NPDR CSME(−) (n = 19)	Mi/Mo NPDR CSME(+) (n = 6)	Severe NPDR (n = 27)	PDR (n = 25)	p value
16Td-s							
Implicit time (ms)	30.08 ± 2.19	30.00 ± 2.10	31.04 ± 3.27	33.72 ± 4.72	35.89 ± 3.79	37.70 ± 3.72	**< 0.001**[a]
Amplitude (μV)	18.98 ± 5.78	16.01 ± 4.12	12.84 ± 4.00	14.73 ± 6.01	9.31 ± 3.60	8.20 ± 3.23	**< 0.001**[a]
32Td-s							
Implicit time (ms)	28.78 ± 1.63	29.35 ± 1.76	30.16 ± 2.46	31.65 ± 2.89	34.69 ± 3.33	36.73 ± 3.44	**< 0.001**[a]
Amplitude (μV)	22.10 ± 6.89	19.79 ± 5.11	15.98 ± 4.80	17.65 ± 7.23	10.88 ± 4.31	9.87 ± 3.64	**< 0.001**[a]
Pupil area ratio	1.92 ± 0.31	1.70 ± 0.22	1.66 ± 0.26	1.78 ± 0.31	1.49 ± 0.24	1.37 ± 0.24	**< 0.001**[a]
DR score	19.00 ± 2.27	20.36 ± 2.61	22.35 ± 3.71	24.28 ± 4.48	27.60 ± 3.61	31.54 ± 3.82	**< 0.001**[a]

[a]Data were described as (mean ± standard deviation) and analyzed with one-way ANOVA

NDR: diabetic patients without retinopathy, Mi: mild, Mo: moderate, CSME: clinically significant macular edema, DR: diabetic retinopathy, NPDR: non-proliferative diabetic retinopathy

Significant values are shown in bold type

7-standard field stereophotographs [14]. Another conventional screening method for DR was 3-field stereoscopic non-mydriatic photograph of the fundus, and Bursell et al. reported a sensitivity of 85% and specificity of 100% for the detection of severe NPDR or PDR in the subject's with diabetes [15]. The RETeval DR assessment protocol had better sensitivity (94.6%) but a worse specificity (88.8%) than the screening using 3-field stereoscopic non-mydriatic photograph in the same scenario. In terms of ultrawide field scanning laser ophthalmoscopy, the study found that the sensitivity of detecting DR and VTDR in Chinese patients was 67.7% and 72.6%, respectively, and the specificity was 97.8% and 97.8%, respectively [16]. The results of the ultrawide field scanning laser ophthalmoscopy had a poorer sensitivity and a higher specificity. Different screening programs have their strength and weakness. All the conventional DR screening program mentioned above needs skilled photographers and trained physician to obtain and interpret the results. The RETeval system was small, easy to use and takes a short time to obtain a numerical result [8]. Our results showed that the DR assessment protocol was useful in detecting both DR and VTDR.

ERG is an effective tool in measuring the functional changes of retina in patients with DR. Decreased amplitude and prolonged implicit time of flicker ERG has started even in the absence of any clinically detectable DR lesion in patient with T2DM [17]. Multifocal ERG studies also revealed that local retinal dysfunction in diabetic eyes occurs before the onset of retinopathy and it was in direct proportion to the degree of clinical abnormality [18]. Once DR occurs, the functional impairment becomes more obvious. With regard to pupil response in diabetic patients, studies found that the velocity of pupillary constriction decreased progressively with increasing severity of retinopathy [19]. ERG has been used to evaluate the changes of retinal function in DR, and it could also be used to monitor the onset and progression of DR [20, 21]. However, it is not practical for conventional ERG recordings to serve as a method for the mass screening of DR because the recording device occupies a large space and it is also time-consuming for data collection.

The DR assessment protocol was developed by Maa et al. [8]. Although we staged and classified DR with the same criteria, our results were quite different. There was an increasing trend for the DR scores as the

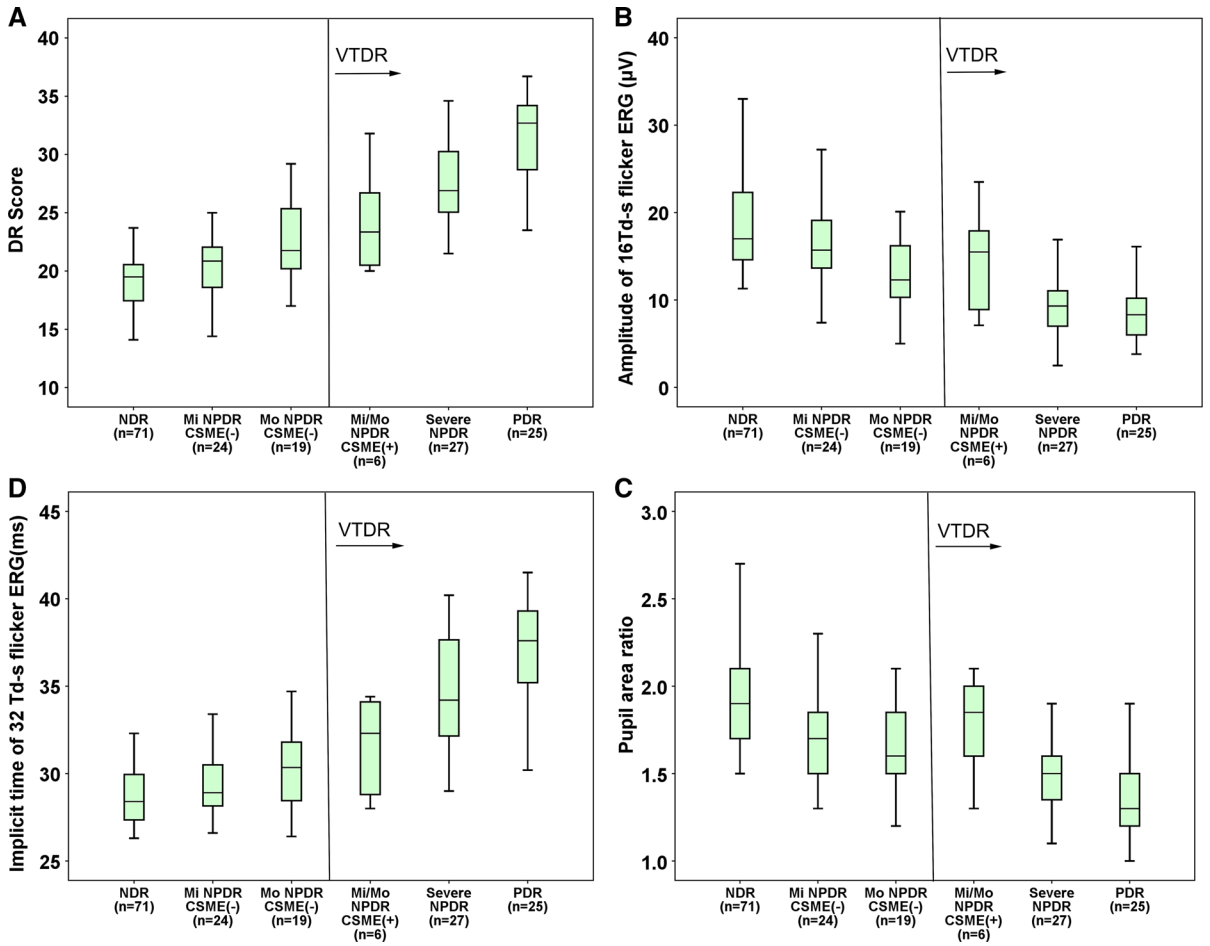

Fig. 2 Box plots of the DR score (**a**), best eye's amplitude of 16Td-s (**b**) and implicit time of the 32Td-s flicker ERG (**c**) and the worst's eye's pupil area ratio (**d**)

disease advanced, which was consistent with the previous study. However, the mean DR scores in each DR stage seemed to be higher in our study. Our patients tended to have longer implicit time, lower amplitude and smaller pupil area ratio. Different situation and ethnic population might have influence on the results. In the current study, the subjects had high levels of HbA1c (around 9%), which indicated a poor control of blood glucose in the past few months. Poorer control of blood glucose might relate to the lower amplitude, pupil area ratio and longer implicit in our subjects, which contributed to higher DR scores. Our published study showed that poor control of blood glucose was associated with delayed implicit time of flicker ERG in preclinical diabetic retinopathy [17]. Multifocal ERG study showed that poor long-term glycemic control was related to an increase in areas of localized neuroretinal dysfunction in adolescents with type 1 diabetes mellitus without clinically visible DR [22]. Using short wavelength-sensitive cone ERG, Yamamoto and colleagues found that the amplitudes were significantly lower in diabetic patients treated with insulin than those did not, suggesting that poor glucose control might lead to severe neuroretinal impairment [23]. Besides, the subjects in the Maa's study were mainly male Caucasian and African-American, with only two Asian subjects. Previous ERG study reported that the implicit time in people with blue iris was shorter than those with dark pigmentation and the amplitude differences were substantially larger from eyes with light pigmentation [24]. The study also found that the higher amplitude in eyes with blue iris was found to be associated with the OFF retinal pathways [25]. In our study, the damage of

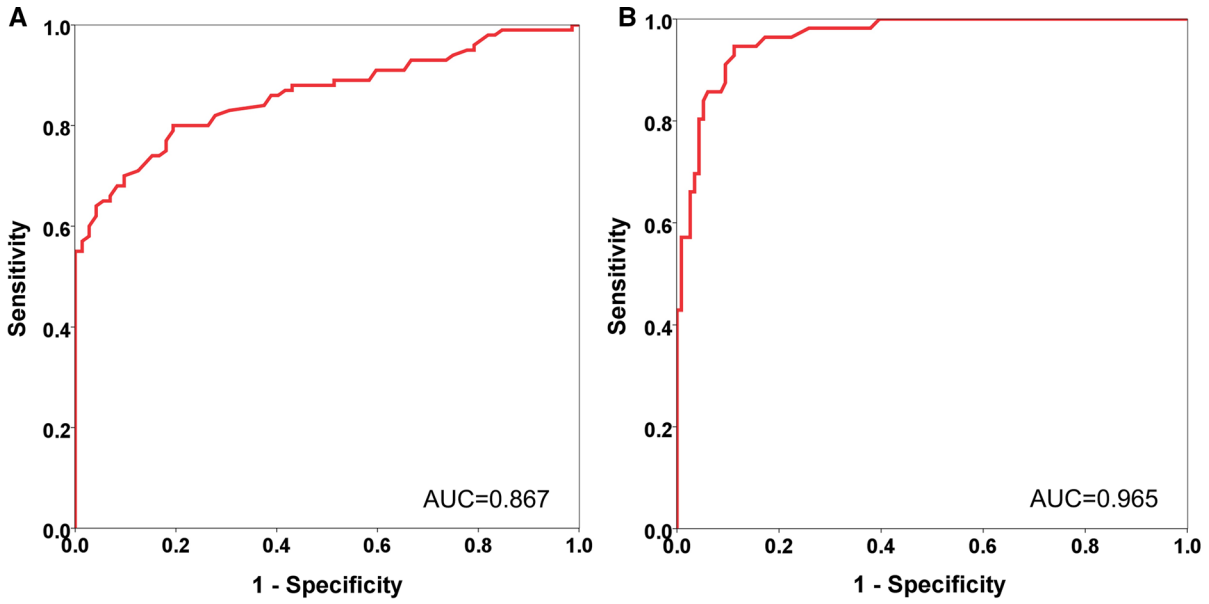

Fig. 3 **a** ROC curve for the detection of DR (mild NPDR, moderate NPDR, severe NPDR and PDR); **b** ROC curve for the detection of VTDR (mild NPDR with CSME, moderate NPDR with CSME, severe NPDR and PDR)

the ERG pathway might be more severe because of the poor control of blood glucose. Moreover, the fundus pigmentation is denser in eyes with darker pigmentation and thus greater light absorption by the denser choroidal pigment should reduce the effective retinal illumination and hence the ERG amplitude [24, 25]. Different ethnic group might response differently to the testing of the DR assessment protocol. Up to date, there has been only one study evaluating the performance of the DR assessment protocol [9]. Forty-two diabetic patients from Turkey were involved in the study, and the cutoff value for detecting vision-threatening moderate–severe NPDR and PDR was determined to be 22.0, with a sensitivity of 92% and a specificity of 92% [4]. In our cohort, the optimal cutoff value for detecting VTDR was 23.05, with the sensitivity slightly higher (94.6%) and the specificity slightly lower (88.8%) than the above study. And at the cutoff value of 19.9, the sensitivity and specificity were 100% and 52.6% in our study. Therefore, the reference range of DR score of the RETeval system may vary in different ethnic populations, and more investigations are needed to determine the most suitable cutoff value in each ethnic population.

The current study has several limitations. The sample size of the NDR group, NPDR groups and PDR group was small, and the distribution of groups was uneven. China has a great number of patients with T2DM, multi-centered study with a larger sample size needed to investigate the best suitable cutoff value.

In conclusion, early screening of DR allows a better management of patients with diabetes, and the DR assessment protocol in the RETeval device is effective in discerning DR and VTDR. Our study found that the best cutoff DR score value for detecting DR and VTDR in our patients using the RETeval system was 20.75 and 23.05, respectively. It should be taken into consideration that reference range may vary depending on each ethnic population when using DR assessment protocol.

Funding This work was supported by Medical Scientific Research Foundation of Guangdong Province, China (Grant Number B2018096), and National Natural Science Foundation of China (Grant Number 81800829). The sponsors or funding organizations had no role in the design or conduct of this research.

Compliance with ethical standards

Statement of human rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Statement on the welfare of animals This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Lee R, Wong TY, Sabanayagam C (2015) Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. Eye Vis 2(1):17. https://doi.org/10.1186/s40662-015-0026-2
2. Wild SH, Roglic G, Green A, Sicree R, King H (2004) Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 27(5):1047–1053
3. Yau JWY, Rogers S, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, Chen S, Dekker JM, Fletcher AE, Grauslund J (2012) Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care 35(3):556–564
4. Ting DSW, Cheung G, Wong TY (2016) Diabetic retinopathy: global prevalence, major risk factors, screening practices and public health challenges: a review. Clin Exp Ophthalmol 44(4):260–277
5. Ting DSW, Pasquale LR, Peng L, Campbell JP, Lee AY, Raman R, Tan G, Schmetterer L, Keane PA, Wong TY (2019) Artificial intelligence and deep learning in ophthalmology. Br J Ophthalmol 103(2):167–175
6. Fukuo M, Kondo M, Hirose A, Fukushima H, Ikesugi K, Sugimoto M, Kato K, Uchigata Y, Kitano S (2016) Screening for diabetic retinopathy using new mydriasis-free, full-field flicker ERG recording device. Sci Rep 6(1):36591
7. Lawrence MG (2004) The accuracy of digital-video retinal imaging to screen for diabetic retinopathy: an analysis of two digital-video retinal imaging systems using standard stereoscopic seven-field photography and dilated clinical examination as reference standards. Trans Am Ophthalmol Soc 102:321–340
8. Maa AY, Feuer WJ, Davis CQ, Pillow EK, Brown TD, Caywood RM, Chasan JE, Fransen SR (2016) A novel device for accurate and efficient testing for vision-threatening diabetic retinopathy. J Diabetes Complicat 30(3):524–532
9. Degirmenci MFK, Demirel S, Batioglu F, Ozmert E (2018) Role of a mydriasis-free, full-field flicker ERG device in the detection of diabetic retinopathy. Doc Ophthalmol 137(3):131–141
10. Basevi V (2011) Diagnosis and classification of diabetes mellitus. Diabetes Care 36:S67–S74
11. Wilkinson CP, Ferris FL, Klein R, Lee PP, Agardh C, Davis MD, Dills DG, Kampik A, Pararajasegaram R, Verdaguer J (2003) Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 110(9):1677–1682
12. Grading Diabetic Retinopathy from Stereoscopic Color Fundus Photographs; An Extension of the Modified Airlie House Classification: ETDRS Report Number 10 (1991). Ophthalmology 98(5):786–806. https://doi.org/10.1016/s0161-6420(13)38012-9
13. Kato K, Kondo M, Sugimoto M, Ikesugi K, Matsubara H (2015) Effect of pupil size on flicker ERGs recorded with RETeval system: new mydriasis-free full-field ERG system. Invest Ophthalmol Vis Sci 56(6):3684–3690. https://doi.org/10.1167/iovs.14-16349
14. Williams GA, Scott IU, Haller JA, Maguire AM, Marcus DM, Mcdonald HR (2004) Single-field fundus photography for diabetic retinopathy screening: a report by the American Academy of Ophthalmology. Ophthalmology 111(5):1055–1062
15. Bursell S, Cavallerano JD, Cavallerano AA, Clermont AC, Birkmirepeters DP, Aiello LP, Aiello LM (2001) Stereo nonmydriatic digital-video color retinal imaging compared with Early Treatment Diabetic Retinopathy Study seven standard field 35-mm stereo color photos for determining level of diabetic retinopathy. Ophthalmology 108(3):572–585
16. Szeto SKH, Wong R, Lok J, Tang F, Sun Z, Tso T, Lam TCH, Tham CC, Ng DS, Cheung CY (2018) Non-mydriatic ultrawide field scanning laser ophthalmoscopy compared with dilated fundal examination for assessment of diabetic retinopathy and diabetic macular oedema in Chinese individuals with diabetes mellitus. Br J Ophthalmol. https://doi.org/10.1136/bjophthalmol-2018-311924
17. Zeng Y, Cao D, Yu H, Yang D, Zhuang X, Hu Y, Li J, Yang J, Wu Q, Liu B, Zhang L (2019) Early retinal neurovascular impairment in patients with diabetes without clinically detectable retinopathy. Br J Ophthalmol. https://doi.org/10.1136/bjophthalmol-2018-313582
18. Pescosolido N, Barbato A, Stefanucci A, Buomprisco G (2015) Role of electrophysiology in the early diagnosis and follow-up of diabetic retinopathy. Exp Diabetes Res 2015:319692
19. Jain MK, Devan S, Jaisankar D, Swaminathan G, Pardhan S, Raman R (2018) Pupillary abnormalities with varying severity of diabetic retinopathy. Sci Rep 8(1):5636
20. Ng JS, Bearse MA, Schneck ME, Barez S, Adams AJ (2008) Local diabetic retinopathy prediction by multifocal ERG delays over 3 years. Invest Ophthalmol Vis Sci 49(4):1622–1628
21. Harrison WW, Bearse MA, Ng JS, Jewell NP, Barez S, Burger D, Schneck ME, Adams AJ (2011) Multifocal electroretinograms predict onset of diabetic retinopathy in adult patients with diabetes. Invest Ophthalmol Vis Sci 52(2):772–777
22. Lakhani E, Wright TC, Abdolell M, Westall CA (2010) Multifocal ERG defects associated with insufficient long-term glycemic control in adolescents with type 1 diabetes. Invest Ophthalmol Vis Sci 51(10):5297–5303
23. Yamamoto S, Takeuchi S, Kamiyama M (1997) The short wavelength-sensitive cone electroretinogram in diabetes: relationship to systemic factors. Doc Ophthalmol 94(3):193–200
24. Abdlseaed AA, Mctaggart Y, Ramage T, Hamilton R, Mcculloch DL (2010) Light- and dark-adapted electroretinograms (ERGs) and ocular pigmentation:

comparison of brown- and blue-eyed cohorts. Doc Ophthalmol 121(2):135–146
25. Wali N, Leguire LE (1993) Fundus pigmentation and the electroretinographic luminance-response function. Doc Ophthalmol 84(1):61–69