Comparison of Non-mydriatic Fundus Photography and Optical Coherence Tomography with Dilated Fundus Examination for Detecting Diabetic Retinopathy Including Diabetic Macular Edema

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ABSTRAK

Memandangkan kadar diabetes di seluruh dunia meningkat, alat saringan yang lebih baik untuk diabetes retinopati (DR) dan edema makula (DME) adalah diperlukan. Tujuan kajian adalah untuk membandingkan nilai kebolehpercayaan dan ramalan antara fotografi fundus 'non-mydriatic' (NMFP) dan tomografi koheren optik-domain spektrum (OCT) untuk mengesan DR dan DME dengan pemeriksaan fundus dilatasi (DFE). Ini adalah kajian perbandingan tanpa intervensi. Pesakit kencing manis menjalani NMFP dan macula OCT, diikuti oleh DFE. Gambar ditafsirkan oleh dua pakar oftalmologi dwi-buta Hasil DFE dianggap garis piawaian emas. Seratus lima puluh empat mata dari 83 pesakit direkrut. Sensitiviti NMFP untuk DR adalah 77.3% dan 80.3% untuk OCT. Kekhususan bagi NMFP adalah 81.8% dan OCT 55.7%. "Area under Receiver Operating Characteristics Curve" (AROC) untuk DR adalah 0.80 untuk NMFP dan 0.68 untuk OCT. Sensitiviti NMFP untuk DME adalah 63.2% dan oleh OCT 82.5%. Kekhususan untuk DME adalah 90.1% oleh NMFP dan 61.5% untuk OCT. Nilai ramalan positif (PPV) NMFP dan OCT untuk DR masing-masing adalah 76.1% (95% CI: 63.9-85.3%) dan 57.6% (46.8-67.7%). Nilai ramalan negatif (NPV) NMFP dan OCT masing-masing adalah 82.7% (95% CI: 72.8-89.7%) dan 79.0% (66.4-87.9%). Nilai ramalan positif NMFP dan OCT untuk DME masing-masing adalah 80.0% (95% CI: 67.6-88.5%) dan

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57.3% (45.9-68.0%). Nilai ramalan negatif NMFP dan OCT masing-masing adalah 79.6% (95% CI: 70.3 - 86.7%) dan 84.8% (95% CI: 73.4 - 92.1%). Mata dengan OCT normal kehilangan 21% DR. Kesimpulannya, NMFP lebih baik daripada OCT untuk penyaringan DR, manakala OCT lebih baik daripada NMFP dan DFE untuk pengesanan DME. Untuk pemeriksaan DR yang lebih baik; kedua-dua kaedah itu harus digunakan.

Kata kunci: edema makula diabetes, fotografi fundus, makulopati diabetes, retinopati diabetes, tomografi koheren optik

ABSTRACT

Given increasing diabetes rates worldwide, better screening tools for diabetic retinopathy (DR) and macular edema (DME) are needed. The study aim was to compare reliability and predictive values between non-mydriatic fundus photography (NMFP) and spectral-domain optical coherence tomography (OCT) for detection of DR and DME with dilated fundus examination (DFE). This was a non-interventional, comparative study. Diabetics underwent both NMFP and macula OCT, followed by DFE. Images were interpreted by two masked ophthalmologists. The DFE result was considered gold standard. One hundred and fifty-four eyes of 83 patients were recruited. Sensitivity of NMFP for DR was 77.3% and 80.3% for OCT. Specificity for NMFP was 81.8% and 55.7% for OCT. Area under Receiver Operating Characteristics Curve (AROC) for DR was 0.80 for NMFP and 0.68 for OCT. The sensitivity of NMFP for DME was 63.2% and 82.5% for OCT. Specificity for DME was 90.1% by NMFP and 61.5% for OCT. Positive predictive value (PPV) of NMFP and OCT for DR was 76.1% (95% CI: 63.9-85.3%) and 57.6% (46.8-67.7%), respectively. Negative predictive value (NPV) of NMFP and OCT was 82.7% (95% CI: 72.8-89.7%) and 79.0% (66.4-87.9%) respectively. Positive predictive value of NMFP and OCT for DME was 80.0% (95% CI: 67.6-88.5%) and 57.3% (45.9-68.0%), respectively. Negative predictive value of NMFP and OCT was 79.6% (95% CI:70.3 - 86.7%) and 84.8% (95% CI:73.4 - 92.1%), respectively. Eyes with normal OCT miss 21% of DR. In conclusion, NMFP is better than OCT for DR screening, while OCT is better than NMFP and DFE for detection of DME. Both modalities should be for better DR screening.

Keywords: diabetic maculopathy, diabetic retinopathy, diabetic macular edema, fundus photography, optical coherence tomography

INTRODUCTION

The incidence and prevalence of diabetes are increasing throughout the world. According to the International Diabetes Federation, there were 285 million adults diagnosed with diabetes in 2010 which is expected to increase to 439 million adults by 2030 (Wan Nazaimoon et al. 2013). In Southeast Asia alone, the total number of people with diabetes expected to reach more than 140 million by 2040. In Malaysians, the prevalence of DM in 2006 compared to 2013 more than doubled among those aged 30 years or more. The prevalence was 22.6% in 2013, with Type 2 diabetics at a prevalence of 20.8% involving 2.8 million persons (Wan Nazaimoon et al. 2013; Hussein et al. 2016). Diabetic retinopathy (DR) is the single largest cause of new cases of blindness in adults (Hussein et al. 2016).

In Malaysia, the prevalence of DR detected on a patient's first visit to the eye clinic was 29.2% among those with Type 2 diabetes at a tertiary referral centre (Keenan et al. 2013). At a teaching hospital located in the north of Malaysia, the prevalence was 39.3% (Abougalambou & Abougalambou 2015). Treatment of DR has been shown to reduce the risk of vision loss, including blindness, increasing the chance of vision gain (Wilkinson 2003; Wu et al. 2013; Stewart 2016). As a result, there is a national movement in Malaysia to implement screening for retinopathy which aims at detecting retinopathy earlier (Guidelines Development Group 2011)

The similarities between Non-mydriatic Fundus Photography (NMFP) and Optical Coherence Tomography (OCT) include the advantages of the non-contact acquisition of retinal images through an undilated pupil. Both techniques utilise safe forms of light energy. In the presence of clear ocular media, both techniques allow images to be stored and interpreted later. The digital storage mode for both these modalities also provides the potential for automated evaluation, staging and risk predictions in the future. While NMFP has been established as a screening tool for DR and diabetic macular oedema (DME), its limitations for DME detection are well known. Spectral-domain OCT (SD-OCT) is an established gold standard and provides irrefutable evidence for DME. However, many rural centres in Malaysia and other countries have limited resources to implement OCT screening usage. Some OCT instruments come with an infrared photograph which gives information on DR changes involving the posterior pole and DR changes which are seen in the OCT thickness scans. The cross-sectional images of the retina and thickness measurements on OCT detects DR. The American Academy of Ophthalmology recommends that SD-OCT be performed in patients with diabetes mellitus (DM) as part of complete ocular examination (American Academy of Ophthalmology 2019). Given that cases of centre-involving DME may have normal vision, there should be more urgency for OCT to be performed as a screening test, at least together with NMFP.

Despite these observations and recommendations, no study to date has compared the detection of DR, including DME, between NMFP and SD-OCT in diabetes mellitus within a cohort undergoing screening for this pathology in Malaysia or similarly structured countries. A study by D'Aloisio et al. in 2019 reported the low predictive value of digital retinal fundus image (DRFI) analysis in detecting DME using three manual grading systems (MGS) as compared with OCT findings. Nevertheless DRFI had good specificity and sensitivity in detecting DME. This made DRFI a useful tool in routine clinical settings, although its potential in diabetic eye screening was still unknown (D'Aloisio et al. 2019). However, neither NMFP nor OCT can definitively stage DR as defined by the clinical DR scale in virtue of their limited view through undilated pupils.

Hence, this study aimed to compare the reliability in terms of sensitivity and specificity as well as predictive values between OCT and NMFP as screening tools for detecting DR and DME among patients with known diabetes mellitus undergoing screening for DR.

MATERIALS AND METHODS

This study was a non-interventional, comparative, cross-sectional study. Ethics approval was obtained from the Hospital Human Research Ethics Committee before the commencement of the study. The project code was FF-2014-119.

Recruitment of Patients

Recruitment of patients for this research involved medical student investigators in their fourth year of study approaching patients registered for appointments in the waiting area of Universiti Kebangsaan Malaysia (UKM) Medical Centre eye clinic, a busy tertiary referral centre in Kuala Lumpur, Malaysia, during a 6-week study period beginning on 1th April 2014 in a random fashion (convenient sampling). The project was part of their Special Study Module. Investigators asked patients if they had diabetes mellitus. If they answered yes, they were offered to participate in the study. Investigators recruited both Type 1 and Type 2 diabetics. Details of the research and tests to be performed as well as the risk was provided to each patient by two investigators. Patients were required to sign an informed consent form. The two investigators recorded the demographical data for each patient and sent the patient for NMFP and OCT.

Inclusion Criteria

Inclusion criteria included people with diabetes mellitus who had been diagnosed by a physician under regular follow-up, who were well, who consented to participate in the study, and were able to cooperate in obtaining NMFP and OCT, with sufficient media clarity for these tests in an undilated state. Patients who were less than three months post-operative for any ocular surgery, had received an intravitreal injection of any kind (for example, intravitreal anti-vascular endothelial agents) within the

preceding month, uncooperative or did not undergo a subsequent dilated ophthalmoscopic examination for DR and DME staging were excluded from the study.

The Workflow of the Study

Subjects meeting the criteria and consenting to the imaging underwent either NMFP or OCT first by a technician with a minimum of 2 years' experience in a sequential alternate fashion before the other screening procedure. Subsequently, an ophthalmologist in training performed pupillary dilation with topical phenylephrine 2.5% (Mydfrin™, Alcon, USA) and tropicamide 1% (Mydriacyl ™, Alcon, USA). This was followed by a dilated fundus examination (DFE) by an ophthalmologist at the patient's regular clinic appointment. The ophthalmologist recorded the retinopathy status of each patient in their respective medical records. Two other investigators were masked to the retinopathy status of the patient. They coordinated the screening with the two instruments, but were not involved with the grading of NMFP, OCT or DFE. They recorded the time taken for each screening test using a stop-clock. Scans from both eyes of recruited subjects were used. Non-validated assessment of the patient's subjective report of comfort and the occurrence of side effects were also recorded.

The Procedure of the NMFP

The NMFP was obtained with the Canon CR-2 Plus Digital Retinal camera (Canon, USA). Two fields were taken in a dim room. The first 45 field was centred on the fovea, and included the optic disc, the main temporal vascular arcades, and the entire macula. By convention, the right eye is always photographed first. The second 45% field centred on the optic disc with the subject given a dim red target to fixate on with the fellow eye to obtain a second disc centred photograph. These fields were insufficient to stage DR.

The findings by (Aptel et al. 2008) showed that at least one field photo assessment was sufficient to detect DR, and this is practised in some centres (Roser et al. 2016). However, the training module for DR screening in Malaysia, which cites Grade C evidence, recommends two-field fundus photography for NMFP (Guidelines Development Group 2011). Hence, investigators adopted this guideline for the NMFP technique used in this study. A study in Indian eyes using NMFP for DR screening used three views (Gupta et al. 2014).

The Procedure of the OCT

The OCT was performed in a dim room to allow some degree of physiological pupil dilatation, without using mydriatic eyedrops with the Spectralis SD-OCT scanner (Heidelberg Engineering, USA). The scan setting was the "fast macula scan", which produced "thickness single exam reports" containing the infrared photograph of the posterior pole centred on the macula, a macula thickness map and a macula cross-

section scan.

Methods to Minimise Error

To minimise interobserver error, two masked examiners, ophthalmologists of at least five years' experience, analysed the OCT and NMFP images separately to provide the DR and DME status. Both consultants were the supervisors for the students on the project. Both were familiar with DR analysis and usage of OCT. The values for each specialist were calculated separately to see whether there was any significant difference in the detection rate between the screening modalities. This also quantified interobserver variability. If the detection rate were similar, it would make the screening modalities more acceptable to general ophthalmologists and users.

Screening Algorithm for NMFP Interpretation

Analysis of the NMFP involved noting any DR changes such as microaneurysms, haemorrhages, lipid, nerve fibre layer infarcts, blood vessel changes, new vessels, and laser photocoagulation marks from the digital photographs. The changes were noted based on the international clinical DR severity scale (Wilkinson 2003). However, in this study, the DR was not staged; only the presence or absence of DR. Table 1 shows the screening algorithm of NMFP for DR and DME. The presence of DR would then result in the patient referred to in the standard screening process for DFE. The presence of DME in NMFP is determined from hard exudates within one disc diameter from the centre of the fovea with loss of a foveal reflex. The presence of these signs from the photograph was considered positive for detecting DME but did not diagnose DME definitively. In typical situations, this authorised referral and further evaluation usually by an ophthalmologist. Hence, if correct, this would have prompted the appropriate

Table 1: Grading algorithm for DR and DME on NMFP

Fundus changes outside the fovea area on the photograph	Present	Absent
Microaneurysm Dot haemorrhage Blot haemorrhage Hard exudate Cotton wool spots Intraretinal microvascular abnormalities Venous beading Neovascularisation at the disc or elsewhere Vitreous haemorrhage	Positive for DR	Negative for DR
Laser photocoagulation scars	Positive for DR	Negative for DR
Fovea area on the photograph	**Present**	**Absent**
Loss of foveal reflex Hard exudates at the macula Microaneurysms at macula Dot/ blot haemorrhage at the macula	Positive for DME	Negative for DME

Figure 1: Figure shows a typical OCT scan of a patient with DR and non- centre involving DME
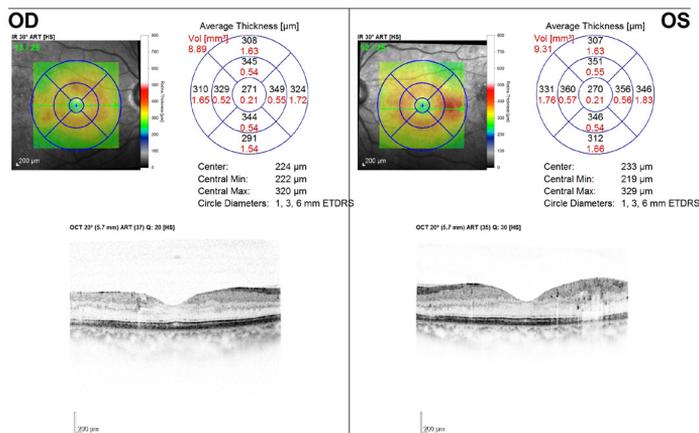
thorough eye assessment, and fulfilled the purpose of screening.

Screening Algorithm for OCT Interpretation

OCT provides information on DR and DME through its infrared photograph, macula thickness map, and macula cross-section image. Analysis of the OCT for DR involved examining the infrared photograph and noting the presence of "dark spots" corresponding to microaneurysms and haemorrhages or "light spots" corresponding to nerve fibre layer infarcts or hard exudates (Gupta et al. 2014). The OCT used does not provide colour photography. Vascular changes such as intraretinal microvascular abnormalities, or venous beading or neovascularisation could also be seen in the infrared photograph. Table 2 shows the screening algorithm for DR and DME using OCT. Figure 1 shows a typical infra-red OCT photograph. Figure 2 shows a typical OCT scan showing DR in both eyes from a subject in

Figure 2: Figure shows a typical OCT scan showing DR in both eyes from a subject in the study. It also exemplifies centre involving DME in the right eye.
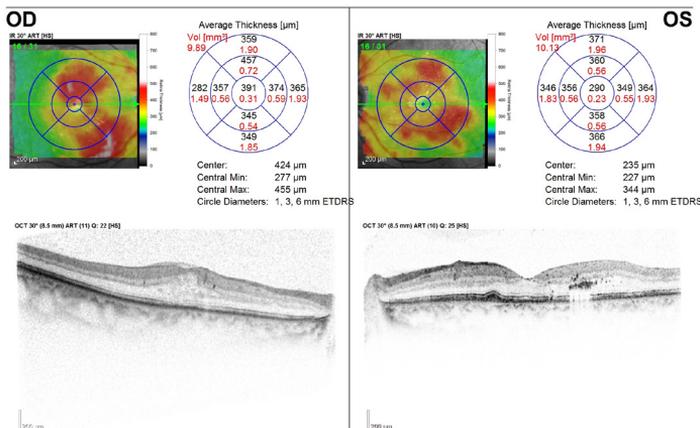
Table 2: Grading algorithm for DR and DME on OCT

Infrared images	Present	Absent
Hyporeflective/ Dark spots (indicative of Microaneurysm, Dot/ blot haemorrhage) Hyperreflective/ Light spots (Hard exudates) Intraretinal microvascular abnormalities Venous beading Neovascularisation at the disc or elsewhere Vitreous haemorrhage	Positive for DR	Negative for DR
Laser photocoagulation scars	Positive for DR	Negative for DR
Macula thickness map – outside circle	Present	Absent
Red or white (area of retinal thickening)	Positive for DR	Negative for DR
Macula thickness map – inside the circle	Present	Absent
Red or white (area of retinal thickening)	Positive for DME	Negative for DME
Macula cross-sectional scan	Present	Absent
Foveal dip	Negative for DME	Positive for DME
Hyporeflective cystoid cavities (indicative of intraretinal or subretinal fluid) Highly reflective spots in deeper areas (hard exudates) Nodular/ elongated nodular highly reflective areas in the superficial nerve fibre layer with posterior shadowing (cotton wool spots) Hyper-reflective areas located preretinally or intraretinally (haemorrhages)	Positive for DME	Negative for DME

the study. It also exemplifies centere involving DME in the right eye.

Superimposed on this photograph was a macula thickness map centred on the fovea with a radius of 3 mm. Any thickening in the healthy population was visible with a colour coding of red or white. When thickening was present outside the central subfield circle, this indicated that referral for DFE was needed. The presence of any of these abnormalities would result in the grader marking the scan as positive for DR.

DME on OCT was detected using the macula thickness map and macula cross-sectional scans. In the macula thickness map, the presence of any thickened subfield was considered positive for DME. The cross-section macula scan then evaluated for loss of normal foveal contour or dip indicating centre involving DME. The presence of intraretinal or subretinal fluid, which disrupted the typical arrangement of the retinal layers, would result in hyporeflective cystoid cavities (Gella et al. 2014). Hard exudates appeared as highly reflective areas in the deeper layers. Cotton wool spots appeared as nodular or elongated highly reflective areas in the superficial nerve fibre layer and cast a shadow posteriorly. Shadowing also was seen posterior to haemorrhages and retinal vessels. Haemorrhages on OCT appeared as hyperreflective areas located preretinally or intraretinally. When preretinal, they cast a cone-shaped shadow (Lang 2007). The presence of any of the above on cross-sectional macula scan was considered positive

Table 3: Demographic studies

Variables	Number of Samples (n=83)
Age	
32-88 years old	
Mean (s.d)	62.9 ± 10.3
Gender	
Men	48 (57.8%)
Women	35 (42.2%)
Ethnicity	
Malay	39 (47.0%)
Chinese	29 (35.0%)
Indian	15 (18.0%)
Co-morbidities (hypertension, hyperlipidemia)	
Yes	76 (91.6%)
No	7 (8.4%)
Duration of diabetes mellitus	1-36 years
Mean (s.d)	13.8 ± 8.3 years

in routine general ophthalmology practice are made with the results of DFE in Malaysia. Grading of the DFE was performed according to the international clinical DR and DME disease severity scales (Wilkinson 2003). However, to test the reliability, predictive values, sensitivity, and specificity of NMFP and OCT, only the presence or absence of DR and DME on the DFE was used in the analysis, rather than stanging of DR. This would, therefore, test the screening abilities of NMFP and OCT in the study group. Following DFE and staging of the DR and DME, patients were managed by the ophthalmology team according to the latest treatment and follow-up recommendations.

Statistical Analysis

Interpretation and analysis of the data computed by the latest version of the Statistical Package for Social Sciences (SPSS) version 20 (IBM Corp., Armonk, NY, USA). All data collection forms were identified using serial numbers. Descriptive statistics (mean, standard deviation, and percentages) were used for summarising the demographic

for detecting DME. Most OCT images did not include a complete view of the optic disc as they were macula OCT obtained with the patient focusing on the fixation light. OCT is capable of imaging the fundus centred on the optic disc. The imaging of the optic nerve was not done in this study in the interest of time.

The DR and DME status from DFE was used as the basis for comparison of the NMFP and OCT results. Investigators used DFE as the standard because management decisions

Table 4: Staging of diabetic retinopathy status according to dilated fundus examination

Stage of DR	Number of eyes	% of the total
Any stage	37	24.0
None	117	76.0
Mild	4	2.6
Moderate	2	1.3
Severe	1	0.6
Proliferative	22	14.3
Could not be traced for staging	8	5.2
Previous pan-retinal photocoagulation	22	14.3

Table 5: kappa (κ) values for both the specialists in the assessment of DR and DME using the NMFP and OCT

DFE	NMFP		OCT	
	κ for specialist 1 ±SE (95%CI)	κ for specialist 2 ±SE (95% CI)	κ for specialist 1 ±SE (95% CI)	κ for specialist 2 ±SE (95% CI)
DR	0.59 ± 0.08 (0.49 - 0.75)	0.64 ± 0.09 (0.45 - 0.82)	0.36 ± 0.08 (0.2 to 0.52)	0.31 ± 0.07 (0.17 to 0.45)
DME	0.52 ± 0.08 (0.36 to 0.68)	0.45 ± 0.09 (0.27 to 0.63)	0.36 ± 0.08 (0.2 to 0.52)	0.39 ± 0.08 (0.23 to 0.55)

κ = kappa values ± standard error; DFE = dilated fundus examination; NMFP = nonmydriatic fundus photography; OCT = optical coherence tomography; DR = diabetic retinopathy; DME = diabetic macula edema

* Kappa value < 0: less than chance agreement; 0.01-0.20: slight agreement; 0.21-0.40: fair agreement; 0.41-0.60: moderate agreement; 0.61-0.80: substantial agreement; 0.81-0.99: almost perfect agreement

data. Two by two tables were used to statistically compare between the OCT and NMFP with DFE, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and kappa values.

RESULTS

Eighty-three patients with diabetes were selected randomly for a total of 154 eyes. In 12 patients, only one eye was able to meet the set criteria. The mean age was 62.9 ± 10.3 years (range, 32-88 years). There were 35 women (42.2%). Regarding self-reported ethnicity, 39 (47.0%) were Malay, 29 (35.0%) were Chinese and 15 (18.0%) were Indian. The ethnicity were checked against the patient record. Seventy-six patients (91.6%) had comorbidities, including hypertension and hyperlipidaemia. The mean duration of diabetes was 13.8 ± 8.3 years (range, 1-36 years) (Table 3). The number of eyes with DR on DFE was 37 and the number with DME was 38. Files were retraced through the medical record office to document their DR staging (Table 4).

In this study, DFE was used as the standard of comparison for DR and DME. There was moderate to substantial agreement with DFE for DR assessment using NMFP for specialist 1 and 2, respectively (κ=0.59 and 0.64), whereas when using the OCT, there was an only fair agreement by the two specialists (κ=0.36 and

Table 6: Percentages of eyes testing positive for DR and DME from NMFP and OCT compared to DFE

	NMFP		OCT	
	Yes	No	Yes	No
Clinical DR on DFE				
Yes, n (%)	51 (76.12)	15 (17.24)	53 (57.61)	13 (20.97)
No	16 (23.88)	72 (82.76)	39 (42.39)	49 (79.03)
Clinical DME on DFE				
Yes, n (%)	36 (80.0)	21 (20.39)	47 (82.46)	10 (17.54)
No	9 (9.89)	82 (90.11)	35 (38.46)	56 (61.54)

Table 7: Sensitivity and specificity of NMFP and OCT compared among the two tools and compared with DFE as the gold standard

	Sensitivity (95% CI)	Specificity (95% CI)	AROC	95% CI
Clinical DR vs NMFP DR	77.27% (65.3 - 86.7%)	81.82% (72.2 - 89.2%)	0.7955	0.73036 0.86055
Clinical DR vs OCT DR	80.30% (68.7 - 89.1 %)	55.68% (44.7 - 66.3%)	0.6799	0.60878 0.75107
Clinical DME vs NMFP DME	63.16% (49.3 - 75.6%)	90.11% (82.1- 95.4%)	0.7663	0.69604 0.83663
Clinical DME vs OCT DME	82.46% (70.1 - 91.3%)	61.54% (50.8 -71.6%)	0.7200	0.64922 0.79073
NMFP DR vs OCT DR	88.06%	63.64%	0.7585	0.69686 0.82011
NMFP DME vs OCT DME	93.62%	60.50%	0.7706	0.71410 0.82711
AROC = area under the receiver operating curve				

0.31, respectively). Likewise, there was moderate agreement for DME assessment using NMFP for the two specialists (κ=0.52 and 0.45, respectively) whereas when using the OCT, both the specialists showed only fair agreements (κ=0.36 and 0.39, respectively) (Table 5). This result shows that diagnosing DR with NMFP is relatively accurate and reproducible between specialists when DFE is considered the gold standard, whereas there is less agreement with OCT screening for DR. As for DME, the fair agreement with DFE for both specialists highlights the higher rate of missed DME with DFE and NMFP.

The analysis hereafter involves reporting the presence of DR or DME by at least one of the specialists. Among those who had DR on OCT and NMFP, 57.6% and 76.1% had DR on DFE, respectively. Whereas among those with DME detected on both OCT and NMFP, 82.5 % and 80% of them had DME on DFE, respectively (Table 6).

Using DFE as standard, OCT yielded a higher sensitivity (80.3%) than NMFP (77.3%) in detecting DR. Similarly, OCT had a higher sensitivity (82.5%) in detecting DME compared to NMFP (63.2%). However, OCT has lower specificity in diagnosing both

Table 8: Comparison between disease status on DFE for DR and DME among those who tested positive on NMFP and OCT

	Variables	PPV (%) (95% CI)	NPV (%) (95% CI)
DR	NMFP	76.1 (64.9 - 85.3)	82.7 (72.8 - 89.7)
	OCT	57.6 (46.8 - 67.7)	79.0 (66.4 - 87.9)
DME	NMFP	80.0 (67.6 - 88.5)	79.6 (70.3 - 86.7)
	OCT	57.3 (45.9 - 68.0)	84.8 (73.4 - 92.1)
*PPV = positive predictive value; NPV = negative predictive value; 95% CI = 95% confidence interval			

conditions compared to NMFP (Table 7).

Positive predictive value (PPV) of NMFP in detecting DR and DME was 76.1% and 80.0%, respectively; both of which was significantly higher than OCT while both modalities had comparable NPV in detecting DR and DME (Table 8).

The mean time taken to complete an NMFP test was 1.4 $\pm$ 1.1 minutes, while OCT took a mean time of 1.7 $\pm$ 1.1 minutes.

DISCUSSION

This study showed that OCT, as graded in this study, was more sensitive in detecting DR and DME than NMFP, while the correlation between DME on OCT with NMFP and DFE was fair. In our study, the proportion of eyes with any form of retinopathy was at least 24% (Table 4). This value was lower than the study by Lopez-Bastida et al. in 2007, but higher than the value in South Israel (Lopez-Bastida et al. 2007; Mizrachi et al. 2014). The proportion of proliferative retinopathy in our study was high at 14.3% compared to the study by Lopez-Bastida et al. (2007). This may be a reflection of the sampling pool of our tertiary referral centre.

The substantial correlation of NMFP and DFE for DR by both consultant ophthalmologists was observed in previous studies (Neubauer et al. 2008; Rani et al. 2018). Both specialists had a close correlation rate for NMFP. In contrast, OCT showed only a fair agreement with DFE for DR for both specialists with similar correlation

rates. Nonetheless, this finding seems encouraging as the infrared photograph and thickness map found to correctly identify 57.6% of DR cases found positive for DR. Sensitivity of OCT for DR was 80.3%. Non-mydriatic Fundus Photography in this study picked up 76.1% of proven DR on DFE. Of note, our study results are similar to the 86% agreement of NMFP with DFE in the study by Ahmed et al. (2006), but higher than Gupta et al. (2014). Non-mydriatic Fundus Photography already has a significant advantage in detecting proliferative diabetic retinopathy (PDR) and DR changes outside the macula under its slightly wider field of view and colour photography. Modern hand-held NMFP devices capable of obtaining two views also have a high level of accuracy for detecting higher grades of DR from moderate non-proliferative disease onwards with the sensitivity of at least 88.7% and specificity of 94.9% when ungradable images were considered positive (Piyasena et al. 2019).

Low sensitivity of the infrared image of the OCT detection was due to the small field of the infrared image and limitations associated with the usage of near-infrared reflectance images. Near-infrared reflectance images were standard with the SD-OCT machine we used. Fundus photographs taken by the SD-OCT were centred on the fovea. Depending on the refractive error of the patient, OCT infrared pictures will generally image from the temporal edge of the optic disc to just beyond the temporal vascular arcades, and the watershed area temporally. The present research is the first to

document the actual sensitivity and specificity of SD-OCT for DR.

Near-infrared images have the ability to detect and image choroidal and retinal pigment epithelial abnormalities under its deeper wavelength and penetration. This aids in the diagnosis and detection of dry and wet AMD changes. The images also depict vitreoretinal interface abnormalities quite well, such as epiretinal membranes. However, there is very little literature on the ability of the pictures to illustrate DR changes. These abnormalities are visible in the infrared OCT images and when noted, prompted a diagnosis of DR. The detection rate can be further improved by incorporating a wider field of view in colour photography or a wider area of the infrared photograph of the OCT for DR screening with the Optomap™ (Neubauer et al. 2008; Goh et al. 2016). Our study may be the first to quantify the ability of OCT in detecting DR among the Malaysian population.

Of those that had a negative DR finding on OCT, 21.0% were found to have DR on subsequent DFE. This rate was only slightly higher than the 17.2 % DR cases missed by NMFP, that were subsequently detected by DFE. The OCT did tend to overdiagnose DR, with up to 42.4% of DR positive cases on OCT, actually not having any DR. The positive predictive value of OCT for DR was lower than NMFP which suggests OCT was limited in its application as a screening tool for DR. However, the NPV was comparable to NMFP for DR suggesting that normal findings on both likely exclude DR (Table 8). In comparison with the study conducted in South Israel, the sensitivity for DR by NMFP was lower but similar to that conducted elsewhere (Lin et al. 2002; Mizrachi et al. 2014; Goh et al. 2016).

The results from the present study is useful for providing a percentage of cases that may be missed by OCT infrared photograph and thickness map. Surprisingly, this is not as high as one would think. With this in mind, the potential for wide-field imaging by OCT and the incorporation of colour fundus photography into OCT machines provided the added advantage of picking up DR.

The moderate correlation of NMFP for DME with DFE by both specialists reiterates the difficulties of diagnosing early or subtle macula edema on NMFP alone. The good correlation seen with using OCT to diagnose DME when correlated with DFE by both specialists further confirms that up to 38.5% of DME seen in OCT was missed by DFE when we assume that OCT represents the irrefutable structural "truth" of DME (Virgili et al. 2015; Azrak et al. 2015; Goh et al 2016). These are most likely cases of early and subtle DME and occurs despite DFE offering a binocular view of the macula during binocular biomicroscopy.

This percentage of missed DME on fundus examination was higher than the DR missed by OCT. The present study showed that DFE colluded 80% of the DME cases detected on NMFP. This finding emphasises the importance of OCT for accurate diagnosis of macular edema and that both NMFP and DFE were somewhat unreliable for confirming macular

edema, especially early-stage macula edema. The clinical relevance of missing early cases of DME, even before visual symptoms, include a loss of the potential for early reversibility of macular edema with treatment. We should not miss the opportunity to prevent permanent structural changes.

As for sensitivity and specificity in detecting DME and DR, NMFP showed a higher specificity while OCT showed a higher sensitivity. Interestingly the area under the receiver operating curve (AROC) values all lie in the fair range making both modalities susceptible to missing cases of DR and DME. Therefore, correlation with vision is essential. Referral for complete ocular examination should also be sooner rather than later should there be any image abnormality.

The higher sensitivity of OCT for DME reflects the accuracy of this tehcnique for picking up early and often subtle DME changes. These DME changes were missed on DFE and NMFP. Some reviews have also supported this and suggested the role of OCT to screen for DME (Virgili et al. 2015; Azrak et al. 2015; Goh et al 2016).

It is possible to image the optic disc on OCT. While optic nerve OCT images were not obtained in this study, optic disc OCT with its infrared photograph can potentially detect disc neovascularisation of the disc. This view on the OCT may be comparable to the disc centred view of the NMFP. This is another potential use of OCT images and technology.

Recent advances in NMFP technology include ultra-widefield scanning laser ophthalmoscopy (Optomap™), which has an excellent detection rate for PDR and automated analysis using Bosch DR Algorithm (Neubauer et al. 2008; Goh et al. 2016; Bawankar et al. 2017). The sensitivity of Optomap™ is 94% for moderate non-proliferative DR and worse. The range of sensitivity for DME was 89-93% (Neubauer et al. 2008). However, this equipment is more expensive and not readily available in most centres and is undergoing rapid hardware and software revisions, precluding an analysis of such imaging in this study. As for automated analysis, high rates of sensitivity and specificity of 90% or more were achieved (Goh et al. 2016). However, the number of DME missed by this screening system was not stated and will be a limitation of any screening test that cannot offer a three-dimensional thickness analysis of the retina such as that provided by OCT.

Although we have not conducted a cost analysis in this study, we note the higher cost for OCT machines in general. However, the price is likely to come down as time goes by and with more devices being available in the market. Optical coherence tomography also has a potential advantage of detecting macula edema before the patient becomes symptomatic or changes become irreversible while also providing more information and the ability to generate an automated risk score for each patient.

This study was limited by several factors. Firstly, we conducted the research in a university ophthalmology clinic, with principal investigators

being medical students. The patients attending the clinic included people with diabetes who were already under treatment. The visual complaints and visual acuity of the subjects included in the study was also not formally a part of the analysis or decision making. This omission makes the patient pool slightly different from those encountered on the broader community who are usually asymptomatic, never seen an ophthalmologist previously, or people that come for a quick screening. Only those with reduced vision and abnormalities on NMFP are referred. The aim of DR screening is to reduce patient load at tertiary centres, which can deal with more severe forms of retinopathy or sight-threatening retinopathy. However, all patients who attended the Ophthalmology clinic during the study period had a chance to be recruited for the study, provided they fulfilled the inclusion criteria.

Another limitation was that DR was not staged during the initial data collection. In this study, we were not able to trace all the medical records for the staging of DR during the stipulated time. However, the aim of this study was not to determine whether OCT could stage DR as its limited view clearly would make this unreliable, if not impossible. Instead, the study aimed to determine how often an OCT scan with its fundus image could correctly detect abnormality and refer a patient for DFE by an ophthalmologist, confirming the diagnosis. Another limitation was the small sample size compared to some other studies (Roser et al. 2016; D'Aloisio et al. 2019).

The strengths of this study were the comparison of fundus and OCT images of a diverse group of diabetic patients for their value in predicting DR and DME as compared to the gold standard of DFE. There were two evaluators for every photograph and image. The evaluators of the fundus photographs were also masked to the DFE findings. For the first time in a Malaysian cohort of diabetics, we have found that OCT was more sensitive than NMFP in detecting DR and DME but less specific. Optical coherence tomography agreement for DR was only fair. This finding suggests that within a cohort in Malaysia and likely similar cohorts throughout the world, the images on OCT cannot replace NMFP as a standard screening tool for DR.

The fair agreement of DFE with OCT suggests that we are missing DME during NMFP and DFE. Non-mydriatic Fundus Photography had higher PPV for DR than OCT, while both modalities had high NPV. Positive predictive value of NMFP for DME was much higher than OCT, but NPV of both was high for DME. These findings indicated that NMFP detects DR better. However, DFE and NMFP are not picking up cases of DME. Thus, this study would suggest the need, ideally, to obtain both NMFP and OCT to supplement DFE in the screening and monitoring of DR, including DME. We therefore recommend that future devices incorporate the features of both OCT and NMFP to better screen for DR and DME.

CONCLUSION

NMFP was better than OCT for preliminary DR screening, but OCT was better than NMFP for the detection of DME. For better DR screening, screening with both modalities is advantageous.

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