Asian J Ophthalmol. 2019;16:268-283



# Prevalence of dengue-related fundus and macular optical coherence tomography findings among inpatients in a regional referral hospital

**Mee Ai Loh[1], Mei Fong Chong[1], Umi Kalthum MN[2], Hong Bee Ker[3]**
*[1]Department of Ophthalmology, Hospital Raja Permaisuri Bainun, Ipoh, Malaysia; [2]Department of Ophthalmology, Universiti Kebangsaan Malaysia, Cheras, Malaysia; [3]Department of Internal Medicine, Hospital Raja Permaisuri Bainun, Ipoh, Malaysia*

***Abstract***

***Purpose:*** *To investigate the prevalence of fundus and macular optical coherence tomography (OCT) findings, and the spectrum of dengue-related fundus presentation in a Malaysian tertiary hospital. The associations between platelet count and haematocrit level with fundus and macular OCT findings were also investigated.*

***Design:*** *Cross-sectional study.*

***Methods:*** *The study was conducted at Hospital Raja Permaisuri Bainun, Ipoh, from June to August 2015. Patients who consented to participate underwent a comprehensive ocular examination. Examination included a best-corrected distance (6 m) and near visual acuities, standard black-on-white Amsler chart testing, pupillary light reflex, fundus examination, followed by dilated fundus photographs and OCT of the macula.*

***Results:*** *A total of 134 patients were included in the study. The prevalence of positive fundus finding and macular OCT finding was 35% (95% confidence interval [CI]: 27%, 43%) and 13% (95% CI: 8%, 19%), respectively; 62 eyes of 47 patients had positive fundus findings, whereas 30 eyes of 18 patients had positive macular OCT findings. Scotoma ($p < 0.001$), near vision disturbance ($p = 0.04$), and abnormal Amsler findings ($p < 0.001$) were significantly associated with presence of macular OCT findings compared to absence of macular OCT findings. In the total of 268 eyes, the two most common fundus findings were vessel tortuosity (53 [20%]) and yellow subretinal dot (28 [10%]). Out of 30 eyes, diffuse retinal thickening was the most frequent OCT finding (22 [73%]), followed by 4 (13%) with foveolitis, 3 (10%) with cystoid macular oedema and 1 (3%) with submacular fluid. Platelet count and haematocrit were not associated with abnormal fundus or macular OCT manifestation in patients suffering from dengue fever.*

**Correspondence:** Mee Ai Loh, , Department of Ophthalmology, Hospital Raja Permaisuri Bainun, 30990 Ipoh, Malaysia.
E-mail: meeailoh@yahoo.com

***Conclusion:*** *Our study revealed that the prevalence of clinical fundus and macular OCT findings among dengue inpatients was higher when compared to other countries, especially during dengue outbreaks. Furthermore, the spectrum of fundus and macular OCT findings in our population can be varied.*

***Keywords:*** *dengue, fundus, optical coherence tomography*

## Introduction

Dengue virus (DEN) is a common *Aedes*-borne flavivirus of humans in Malaysia. There are four antigenically related serotypes present in Malaysia, which include DEN-1, 2, 3, and 4.[1] The World Health Organization (WHO) estimates 50 to 100 million dengue infections occurring annually across 100 countries including Asia, Pacific regions, Americas, Africa, and Caribbean.[1]

Dengue is endemic in Malaysia, and the incidence has more than doubled from 2013 to 2014, with an increment over 150%.[2] The cumulative number of reported dengue cases in 2015 alone had reached almost 120,000.[2] Perak is the fourth largest state in Malaysia, and the cumulative incidence of dengue was 8,157 cases from January to October 2015. In comparison to 2014, it was half of the numbers reported within the same period.[3] Our study hospital, Hospital Raja Permaisuri Bainun, is the referral hospital in Perak.

For the past few decades, there have been numerous reports describing ocular manifestations associated with dengue fever. These findings ranged from mild subconjunctival haemorrhage to significant visual morbidities.[4-11] However, the prevalence of dengue-related ocular findings is not well studied and there are no local data available. A study by Teoh *et al*.[12] has shown that optical coherence tomography (OCT) is a useful tool in assessing dengue maculopathy. Three patterns of maculopathy are identified—diffuse retinal thickening, cystoid macular oedema and foveolitis. Approximately 18% of patients with diffuse retinal thickening are asymptomatic. To the best of our knowledge, there is no reported study on the prevalence of macular OCT findings among dengue patients.

The interval between presentation with ocular symptoms and the onset of dengue fever is a mean of 7 days (range of 1-28 days).[8] However, a study by Gupta *et al*. has reported a delayed onset of post-dengue uveitis 3 to 5 months after dengue infection.[9] The precise pathophysiology of dengue ophthalmic complications is not known. Studies have suggested the possibility of immune-mediated process.[10] The management of dengue-related ocular complications is variable, ranging from observation to immunosuppression as there is no consensus for treatment or guideline-based therapy.

This study aims to investigate the prevalence of fundus and macular OCT findings, and the spectrum of dengue-related fundus presentation in a referral

hospital in Malaysia. As dengue infection is associated with derangement in platelet count and haematocrit, the association between the platelet counts (and haematocrit) and the fundus findings (and macular OCT findings) is investigated.

## Methods

This was a cross-sectional study conducted at Hospital Raja Permaisuri Bainun, Ipoh, from June to August 2015. A total of 134 patients were included in the study based on dengue prevalence of 7.5%,[13] with 95% CI of 5% precision.[14] The primary investigator was responsible for the recruitment process and ocular examination. Daily screening of all newly admitted dengue patients (within 24 hours of admission) was carried out at bedside.

All dengue patients who were admitted with a clinical diagnosis of dengue fever[15,16] (confirmation via NS1/dengue serology), age ≥ 12 years, able to sit for ocular examination and investigation, and a presence of clear media allowing fundus examination were included in the study. Patients who were clinically unstable, unwilling to give consent, with other febrile illnesses, with pre-existing ocular diseases or with a history of intraocular surgery within the last 3 months were excluded.

The criteria for admission based on Malaysian Dengue Clinical Practice Guidelines[16] include the presence of alarming symptoms and signs, namely abdominal pain, persistent vomiting, clinical fluid accumulation, restlessness, tender enlarged liver or laboratory results showing increment in haematocrit level with concurrent decrease in platelet count, bleeding manifestations, inability to tolerate oral fluid, urine output reduction or seizures. Other admission criteria are patients with signs of dehydration, shock, bleeding or any organ failure. Patients were also being admitted under special circumstances such as elderly or for social factors that limit follow-up. Informed consent was obtained from all the participants. The study received ethical approval from the Ministry of Health Malaysia (NMRR-15-117-23895), and adhered to the tenets of the Declaration of Helsinki.

All enrolled patients were first subjected to a comprehensive ocular examination of best-corrected distance (6 m) and near visual acuities, standard black-on-white Amsler chart testing, pupillary light reflex, fundus examination using slit-lamp biomicroscope (Topcon SL D7), followed by dilated fundus photographs and OCT of the macula (Cirrus HD-OCT; Zeiss). The fundus and OCT findings were re-checked by another ophthalmologist for agreement on the findings.

Patients were further categorized into either normal or abnormal based on the presence or absence of dengue-related fundus or macular OCT findings. Patients with normal fundus or macular OCT findings were taught self-monitoring with a

near visual acuity chart and Amsler chart, and were advised to report should there be any ocular symptoms within 1 month of dengue infection. Platelet count and haematocrit level were recorded. Subjects with abnormal fundus or macular OCT findings were observed or managed according to our standard clinical practice.

This study used the classification and phases of dengue as proposed by the WHO.[15] According to the suggested WHO classification 2009, dengue is classified based on the level of severity as dengue with or without warning signs and severe dengue. The criteria of severe dengue included severe plasma leakage, severe haemorrhage and severe organ impairment. The clinical course of dengue infection consists of three phases which are febrile, critical and recovery phase.

The degree of thrombocytopenia was divided into $<50 \times 10^9$/l (severe) and $\geq 50 \times 10^9$/l (moderate and mild) for data interpretation.[17] All data were entered into Statistical Package for the Social Sciences version 20.0 for univariate and multivariate analysis; $p < 0.05$ was the cut-off point for statistical significance. Distance visual acuity was recorded in logarithm of the minimum angle of resolution (logMAR) for data analysis.

## Results

During the study period between June and August 2015, a total of 245 (record taken from ward census) dengue patients were admitted. However, 103 patients were excluded based on exclusion criteria. Another eight patients were admitted at odd hours and discharged before screening could be done (admitted <24 hours).

Out of 245 patients, a total of 134 (55%) patients participated in this study, and fundus and OCT findings were recorded from both eyes. There were 75 (56%) male and 59 (44%) female patients. Their ages ranged from 12 to 82 years (median age of 27.5 years). Sixty-three per cent of participants were <35 years old. Malays and Chinese comprised three quarters of the participants, which mirrors the local population. The mean interval between onset of illness and admission was 6.86 days. Seventy-two per cent were admitted as dengue infection with warning signs, while 9.7% had severe dengue infection. More than half were in recovery phase. One quarter of the participants were found with at least one comorbidity. Table 1 illustrates the demographics of the subjects.

Among 134 patients, the prevalence of positive fundus findings was 35% (95% CI: 27%, 43%) and positive OCT findings was 13% (95% CI: 8%, 19%). In other words, out of 134 patients, 47 subjects had positive fundus findings, whereas 18 subjects were found to have positive macular OCT findings. Only one of the patients with positive OCT findings had comorbidity in the form of bronchial asthma.

Table 2 compares the eyes with and without OCT finding. Total 30 eyes were found to have OCT findings. Among the eyes with positive macular OCT findings, the main symptom was blurring of vision (40%), followed by scotoma (30%), near

**Table 1. Characteristics of the study population (n = 134)**

| Characteristic | |
|---|---|
| Age (years), median (min, max) | 27.50 (12, 82) |
| *Gender, n (%)* | |
| Male | 75 (56.0) |
| Female | 59 (44.0) |
| *Ethnicity, n (%)* | |
| Malays | 57 (42.5) |
| Chinese | 45 (33.6) |
| Indians | 26 (19.4) |
| Others | 6 (4.5) |
| Day of illness, mean (SD) | 6.86 (1.76) |
| *Classification of dengue, n (%)* | |
| Without warning sign | 24 (17.9) |
| With warning signs | 97 (72.4) |
| Severe dengue | 13 (9.7) |
| *Phase of dengue fever, n (%)* | |
| Febrile | 8 (6.0) |
| Critical | 52 (38.8) |
| Recovery | 74 (55.2) |
| *Comorbidity, n (%)* | |
| Diabetes | 6 (4.5) |
| Hypertension | 10 (7.5) |
| Diabetes and hypertension | 9 (6.7) |
| Bronchial asthma | 6 (4.5) |
| None | 103 (76.9) |
| Platelet count ($\times 10^9$/l), median (min, max) | 60.00 (7,355) |
| Haematocrit (%), mean (±SD) | 42.86 (4.69) |

SD: standard deviation

**Table 2. The characteristic of eyes with OCT findings (n = 30)**

| Characteristic | Eyes with OCT findings (n = 30) | Eyes without OCT finding (n = 238) | p value |
|---|---|---|---|
| *Visual symptoms, per eye, n (%)*[a] | | | |
| Blurring of vision | 12 (40) | 81 (34.0) | 0.52[b] |
| Scotoma | 9 (30) | 0 (0.0) | <0.001[c] |
| Near vision disturbance | 8 (26.7) | 28 (11.8) | 0.04[c] |
| Metamorphopsia | 2 (6.7) | 1 (0.4) | – |
| Asymptomatic | 14 (46.7) | 151 (63.4) | 0.08[b] |
| Macular findings[a] | 17 (57) | 0 (0.0) | – |
| Dull foveal reflex | 13 (43.3) | | |
| Macular haemorrhage | 8 (26.7) | | |
| Macular oedema | 4 (13.3) | | |
| Normal (subclinical) | 13 (43.3) | | |
| *Distance VA* | | | |
| Worse than logMAR 0.15, n (%) | 17 (56.7) | 93 (39.1) | 0.07[b] |
| *Near VA* | | | |
| N6 or worse, n (%) | 6 (20) | 44 (18.5) | 0.84[b] |
| *Amsler findings, n (%)* | | | |
| Presence | 10 (33) | 0 (0.0) | <0.001[c] |
| Central | 5 (16.7) | | |
| Paracentral | 5 (16.7) | | |

VA: visual acuity
[a]One eye can have more than one type of visual symptoms/macular findings
[b]Pearson Chi-square
[c]Fisher's exact test

vision disturbance (27%) and metamorphopsia (6.7%). Eyes with dengue macular OCT findings were more likely to have scotoma ($p < 0.001$) and near vision disturbance ($p = 0.04$). However, 14 (47%) of affected eyes were asymptomatic or unnoticed symptoms because of mild visual disturbance. Amsler findings had further detailed the types of scotoma, of which paracentral and central scotoma

were equally common. Our study revealed that none of the patients with negative macular OCT findings had scotoma ($p < 0.001$) and abnormal Amsler findings ($p < 0.001$). Moreover, near and distance visual acuities were compared between the two groups based on the study done by Su *et al*.[18] Our study found there was no statistical difference in visual acuities between the two groups. Meanwhile, as high as 13 (43%) eyes with macular OCT findings had been labelled clinically as normal. However, dull foveal reflex (43%) had been shown to be the most frequent macular abnormality, followed by macular haemorrhage (27%) and macular oedema (13%). In our study, none of these subclinical macular OCT finding patients developed clinically significant maculopathy.

In the total of 268 eyes, 62 eyes were found to have one or more fundus findings. Vessel tortuosity and yellow subretinal dot were the two most common clinical fundus findings occurring in 20% and 10% of eyes, respectively. Vessel tortuosity commonly happened bilaterally compared to yellow subretinal dot which tends to occur unilaterally. Other fundus findings were <5% of eyes, and the spectrum of fundus findings are shown in Table 3.

Diffuse retinal thickening was the commonest OCT abnormality in the study (Table 4). Out of these 30 eyes, 73% of macular OCT findings were diffuse retinal thickening. Other findings included foveolitis (13%), cystoid macular oedema (10%) and submacular fluid (3%). Twelve patients were found to have bilateral macular OCT findings and 6 participants with unilateral findings. Out of these

**Table 3. Types of fundus findings**

| Types | Number of eyes | % (n = 268) | Unilateral | Bilateral |
|---|---|---|---|---|
| Vessel tortuosity | 53 | 19.8 | 3 | 25 |
| Yellow subretinal dot | 28 | 10.4 | 12 | 8 |
| Dull foveal reflex | 12 | 4.5 | 4 | 4 |
| Macular haemorrhage | 8 | 3.0 | 2 | 3 |
| Macular oedema | 7 | 2.6 | 1 | 3 |
| Retinal vasculitis | 7 | 2.6 | 1 | 3 |
| Disc swelling and hyperaemia | 4 | 1.5 | 0 | 2 |
| Retinal haemorrhage | 1 | 0.4 | 1 | 0 |
| Cotton wool spot | 1 | 0.4 | 1 | 0 |

One eye can have more than one type of fundus findings

12 patients with bilateral positive macular OCT findings, 9 had similar types of macular OCT findings in each eye.

In terms of univariate analysis, there was no significant association between the presence of fundus abnormalities with patients' demographic (age, gender, ethnicity, day of illness, classification or phase of dengue and comorbidity), platelet count and haematocrit level (Table 5). With regard to

**Table 4. Types of OCT findings**

| Types | Number of eyes, n = 30 (%) | % (n = 268) | Unilateral | Bilateral |
|---|---|---|---|---|
| Diffuse retinal thickening | 22 (73.3) | 8.2 | 6 | 8 |
| Foveolitis | 4 (13.3) | 1.5 | 2 | 1 |
| Cystoid macular oedema | 3 (10.0) | 1.1 | 3 | 0 |
| Submacular fluid | 1 (3.3) | 0.4 | 1 | 0 |

**Table 5. Summary of demographics and laboratory test results of fundus and OCT macula with abnormal features**

| No | Characteristic | Fundus features present (n = 47) | p value | OCT features present (n = 18) | p value |
|---|---|---|---|---|---|
| 1 | *Age (years)* | | | | |
| | Median (min, max) | 25.00 (12, 64) | 0.06[a] | 21.50 (12, 36) | 0.001[a] |
| 2 | *Gender, n (%)* | | | | |
| | Male | 29 (61.7) | 0.33[b] | 12 (66.7) | 0.33[b] |
| | Female | 18 (38.3) | | 6 (33.3) | |
| 3 | *Ethnicity, n (%)* | | | | |
| | Malays | 22 (46.8) | 0.56[b] | 5 (27.8) | 0.04[c] |
| | Chinese | 13 (27.7) | | 11 (61.1) | |
| | Indians and others | 12 (25.5) | | 2 (11.1) | |
| 4 | *Day of illness* | | | | |
| | Median (min, max) | 7 (2, 12) | 0.80[a] | 7 (4, 9) | 0.04[a] |

| No | Characteristic | Fundus features present (n = 47) | p value | OCT features present (n = 18) | p value |
|---|---|---|---|---|---|
| 5 | *Classification of dengue, n (%)* | | | | |
| | Without warning sign | 11 (23.4) | 0.22[b] | 6 (33.3) | 0.09[c] |
| | With warning signs and severe dengue | 36 (76.6) | | 12 (66.7) | |
| 6 | *Phase of dengue fever, n (%)* | | | | |
| | Febrile and critical | 26 (55.3) | 0.07[b] | 7 (38.9) | 0.59[b] |
| | Recovery | 21 (44.7) | | 11 (61.1) | |
| 7 | *Comorbidity, n (%)* | | | | |
| | Present | 9 (19.1) | 0.42[b] | 1 (5.6) | 0.07[c] |
| | Absent | 38 (80.9) | | 17 (94.4) | |
| 8 | *Platelet count ($\times 10^9$/l), n (%)* | | | | |
| | <50 | 22 (46.8) | 0.32[b] | 8 (44.4) | 0.75[b] |
| | 50 and above | 25 (53.2) | | 10 (55.6) | |
| 9 | *Haematocrit, n (%)* | | | | |
| | <40 | 14 (29.8) | 0.58[b] | 6 (33.3) | 0.57[c] |
| | 40 and above | 33 (70.2) | | 12 (66.7) | |

[a]Mann-Whitney U test
[b]Pearson Chi-square
[c]Fisher's exact test

the commonest presentations of fundus findings, both vessel tortuosity and yellow subretinal dot denied association with platelet count or haematocrit. The same parameters were evaluated for OCT macula in univariate analysis (Table 5). Our study showed that patients with abnormal macular OCT findings were significant younger (p = 0.001), Chinese ethnicity predominant (p = 0.04) and day of illness ranged from day 4 to day 9 (p = 0.04). Platelet

count and haematocrit level had no role in the presence of dengue-related macular OCT features.

Similarly, there was no significant association seen between the presence of fundus findings with patients' demographics, platelet count and haematocrit level in both single and multiple logistic regressions (Tables 6 and 7). However, multivariate logistic regression showed Chinese ethnicity (odds ratio [OR] 3.48; 95% CI: 1.05, 11.54; p = 0.04), dengue without warning sign (OR 5.08; 95% CI: 1.35, 19.11; p = 0.02) and absence of comorbidity (OR 8.54; 95% CI: 0.98, 74.30; p = 0.05)

**Table 6. Single logistic regression (SLR) of fundus findings**

| Factors | Fundus findings (n = 47) | No fundus finding (n = 87) | SLR OR (95% CI) | p value |
|---|---|---|---|---|
| *Platelet count ($\times 10^9$/l)* | | | | |
| <50 | 22 (46.8) | 33 (37.9) | 1.44 (0.70, 2.95) | 0.32 |
| 50 and above | 25 (53.2) | 54 (62.1) | 1.00 | |
| *Haematocrit (%)* | | | | |
| <40 | 14 (29.8) | 22 (25.3) | 1.25 (0.57, 2.76) | 0.58 |
| 40 and above | 33 (70.2) | 65 (74.7) | 1.00 | |

**Table 7. Multiple logistic regression (MLR) of fundus findings**

| Factors | Fundus findings (n = 47) | No fundus finding (n = 87) | MLR OR (95% CI) | p value |
|---|---|---|---|---|
| *Platelet count ($\times 10^9$/l)* | | | | |
| <50 | 22 (46.8) | 33 (37.9) | 0.67 (0.32, 1.39) | 0.28 |
| 50 and above | 25 (53.2) | 54 (62.1) | 1.00 | |
| *Haematocrit (%)* | | | | |
| <40 | 14 (29.8) | 22 (25.3) | 1.33 (0.60, 2.97) | 0.48 |
| 40 and above | 33 (70.2) | 65 (74.7) | 1.00 | |

(Tables 8 and 9) were significant confounders in the presence of abnormal macular OCT findings. In our study, 28 of our patients had cataract but none of them had undergone any intraocular surgery. None of the patient with normal fundus or macular OCT finding (or subclinical macular OCT finding) was reassessed due to new eye complaint.

**Table 8. Single logistic regression (SLR) of macular OCT findings**

| Factors | OCT findings (n = 18) | No OCT finding (n = 116) | SLR OR (95% CI) | p value |
|---|---|---|---|---|
| *Platelet count ($\times 10^9$/l)* | | | | |
| <50 | 8 (44.4) | 47 (40.5) | 1.17 (0.43, 3.20) | 0.75 |
| 50 and above | 10 (55.6) | 69 (59.5) | 1.00 | |
| *Haematocrit (%)* | | | | |
| <40 | 6 (33.3) | 30 (25.9) | 1.43 (0.49, 4.16) | 0.51 |
| 40 and above | 12 (66.7) | 86 (74.1) | 1.00 | |
| *Ethnicity, n (%)* | | | | |
| Malays | 5 (27.8) | 52 (44.8) | 1.00 | 0.04 |
| Chinese | 11 (61.1) | 34 (29.3) | 3.37 (1.07, 10.54) | 0.04 |
| Indians and others | 2 (11.1) | 30 (25.9) | 0.69 (0.13, 3.80) | 0.67 |
| *Classification of dengue, n (%)* | | | | |
| Without warning sign | 6 (33.3) | 18 (15.5) | 2.72 (0.91, 8.19) | 0.08 |
| With warning signs and severe dengue | 12 (66.7) | 98 (84.5) | 1.00 | |
| *Comorbidity* | | | | |
| Present | 1 (5.6) | 30 (25.9) | 1.00 | 0.09 |
| Absent | 17 (94.4) | 86 (74.1) | 5.93 (0.76, 46.49) | |

**Table 9 Multiple logistic regression (MLR) of macular OCT findings after adjusting for other confounders.**

| Factors | OCT findings (n = 18) | No OCT finding (n = 116) | MLR OR (95% CI) | p value |
|---|---|---|---|---|
| *Platelet count ($\times 10^9$/l)* | | | | |
| <50 | 8 (44.4) | 47 (40.5) | 1.94 (0.61, 6.19) | 0.27 |
| 50 and above | 10 (55.6) | 69 (59.5) | 1.00 | |
| *Haematocrit (%)* | | | | |
| <40 | 6 (33.3) | 30 (25.9) | 2.43 (0.71, 8.37) | 0.16 |
| 40 and above | 12 (66.7) | 86 (74.1) | 1.00 | |
| *Ethnicity, n (%)* | | | | |
| Malays | 5 (27.8) | 52 (44.8) | 1.00 | 0.04 |
| Chinese | 11 (61.1) | 34 (29.3) | 3.48 (1.05, 11.54) | 0.04 |
| Indians and others | 2 (11.1) | 30 (25.9) | 0.61 (0.10, 3.79) | 0.60 |
| *Classification of dengue, n (%)* | | | | |
| Without warning sign | 6 (33.3) | 18 (15.5) | 5.08 (1.35, 19.11) | 0.02 |
| With warning signs and severe dengue | 12 (66.7) | 98 (84.5) | 1.00 | |
| *Comorbidity* | | | | |
| Present | 1 (5.6) | 30 (25.9) | 1.00 | 0.05 |
| Absent | 17 (94.4) | 86 (74.1) | 8.54 (0.98, 74.30) | |

## Discussion

Out of 134 patients, the prevalence of positive fundus findings is 35% (62 eyes of 47 patients) and of OCT findings is 13% (30 eyes of 18 patients). Vessel tortuosity (53 eyes, 28 patients) and yellow subretinal dot (28 eyes, 20 patients) are the two most common fundus findings. Diffuse retinal thickening is the most

frequent OCT finding. It was found in 73% out of 30 eyes with OCT findings. There is no association between platelet count and haematocrit level, with presence of abnormal fundus or macular OCT findings.

To date, this is the first study to assess the prevalence of macular OCT findings among dengue patients. Our patients were recruited strictly based on inclusion and exclusion criteria. Slit-lamp and OCT machines used were standardized in the study. In addition, the fundus and OCT findings were re-checked by a consultant ophthalmologist to ensure the accuracy of the findings.

There are several limitations in this study which need to be addressed. Dengue affects all patients regardless of age group across Malaysia. However, this study was conducted at a single centre, and excluded outpatients, which may limit some of the findings. Moreover, patients may have unchecked or undiagnosed clinical or macular OCT findings prior to dengue fever. The immobility of the assessment tools requires sophisticated transport procedures. It is therefore difficult to conduct similar assessment on unstable or critically ill patients.

The prevalence of fundus findings in this study is 35%. It is higher compared to a study done by Kapoor *et al*.[13] The difference could be due to the inclusion of yellow subretinal dot as a manifestation of dengue-related complication, in the absence of any other causes. Yellow subretinal dot has been listed as one of the fundus findings of dengue as suggested by other studies.[18,19] Furthermore, absence of macular finding in the study done by Kapoor *et al*. could be another contributing factor of the lower prevalence.[13]

OCT finding in this study was detected in 13% of patients (30 eyes of 18 patients). However, there were 8% (17 eyes of 11 patients) of patients who had clinically abnormal macular findings. In other words, 5% (13 eyes of 7 patients) of the patients with OCT findings had no detectable clinical findings. These findings strongly suggest OCT is more sensitive in detecting dengue-related maculopathy.

A study done in Singapore by Su *et al*. in the year 2005 found 10% of dengue patients had clinical maculopathy,[18] while Chee in Singapore in year 2007[20] and Kapoor *et al.* in India[13] did not find any macular-related finding. The difference is most likely attributed by the different subtype of the DEN affecting different populations. In Singapore, the DEN-1 was predominant in the community in year 2005, whereas DEN-2 was predominant in year 2007. No individual dengue serotyping was performed. During our study period, DEN-1 had been the dominant serotype (60%).[2] It was similar to the study in Singapore in year 2005 in which the predominant (71.2%) dengue serotype was type 1.[20]

Similar to other studies,[12,21,22] our study found that vessel tortuosity was the most frequent fundus findings which was 20% (53 eyes) while diffuse retinal thickening (73%, 22 eyes) was the commonest macular OCT findings, followed by foveolitis (13%, 4 eyes) and cystoid macular oedema (10%, 3 eyes). However,

distinct from other studies,[11,19] macular haemorrhage, retinal vasculitis and retinal haemorrhage were unusual fundus findings in our study which only contributed 3.0% (8 eyes), 2.6% (7 eyes) and 0.4% (1 eye), respectively. One of the patients had macular OCT finding of submacular fluid which was never reported in previous studies. A study shows increased vascular permeability was observed in DEN-1, whereas more systemic haemorrhage was associated with DEN-2.[23] Based on the results, we postulate that DEN-1-infected patients have higher risk of maculopathy because of increased vascular permeability, whereas patients with DEN-2 has more risk of retinal haemorrhage.

Consistent with a study done by Su *et al*.,[18] our study found that there was a significant association between subjects having scotoma ($p < 0.001$) and abnormalities on Amsler grid testing ($p < 0.001$) with presence of OCT findings. However, we did not find significant difference of near or distance visual acuity between those with and without dengue maculopathy. This could be due to early cataract, under- or uncorrected refractive error in patients without dengue maculopathy.

In clinical management of dengue infection, blood investigations, traditionally full blood count, have been used as a screening and monitoring test for dengue infection. Among the available parameters, platelet count and haematocrit are frequently used to assist in dengue management. The risk factors of ocular complications following dengue infection have been studied. Some evidences showed that the severity of retinal abnormalities is related to the severity of thrombocytopenia.[13,21,24] However, our study showed there was no significant association detected between fundus findings with platelet count and haematocrit. The reason could be due to less retinal and macular haemorrhage in our fundus findings. In this study, we also did not find any significant association between the patients' demographics with fundus findings.

Similar to the other studies,[18,20] our study found that patients with dengue-related macular OCT findings were significantly younger than those without OCT findings ($p < 0.001$). Moreover, platelet and haematocrit had no impact on the presence of clinical dengue- related macular finding. Although the precise pathophysiology of dengue ophthalmic complications is still not elucidated, this study suggests that the possibility of younger age group has more robust immune-mediated process.[10,18,19] In addition, the delayed onset of dengue maculopathy in days 4 to 9 in our study favours the possibility of immune response in development of dengue maculopathy.

In multivariate logistic regression analysis, dengue without warning sign, Chinese ethnicity and absence of comorbidity were found to be the significant confounders in this study as far as OCT findings are concerned. The pathophysiology behind this association remains unknown. We believe that it is related to variable immune-mediated mechanism in patients with comorbid issues like

diabetes mellitus, hypertension and bronchial asthma or even among different ethnicities or different severity of dengue. However, none of the factors above showed any association with clinical fundus finding.

Results from our study show that it is not uncommon to have fundus or OCT findings in our population. Furthermore, the spectrum of fundus and macular OCT findings in our population can be varied. Platelet count and haematocrit level have little value as the predictors in dengue maculopathy. Instead, Amsler grid testing is still a useful and important test in the screening of dengue maculopathy. It may not be time and cost effective for eye screening in all dengue patients. However, fundus examination should be done in dengue patients with scotoma, near visual disturbance or abnormal Amsler finding.

We propose a larger multicentre study, looking at all dengue patients both admitted and those seen as outpatients, to provide further understanding of ocular manifestation of dengue fever. Furthermore, association between different serotype of *Aedes*-borne flavivirus and fundus and/or OCT finding should be investigated.

## Conclusion

In conclusion, our study reveals that the prevalence of clinical fundus and macular OCT findings among dengue inpatients was higher compared to other countries especially during dengue outbreaks. Furthermore, the spectrum of fundus and macular OCT findings in our population can be varied.

## References

1. Centers for Diseases Control and Prevention. DF fact sheet—CDC division of vector-borne infectious diseases. http://www.cdc.gov/dengue/epidemiology/. Accessed July 28, 2010.
2. WHO Western Pacific. Emerging disease surveillance and response. http://www.wpro.who.int/emerging_diseases/DengueSituationUpdates/en/. Accessed December 29, 2015.
3. Bernama. At least 20 dengue cases every day in Perak this year. https://www.malaysiakini.com/news/318043#ixzz4MsTXE6cE. Accessed November 1, 2015.
4. Loh BK, Bacsal K, Chee SP, et al. Foveolitis associated with dengue fever. Ophthalmologica. 2008;222(5):317-320.
5. Sanjay S, Wagle AM, Au Eong KG. Optic neuropathy associated with dengue fever. Eye. 2008;22:722-724.
6. Preechawat P, Poonyathalang A. Bilateral optic neuritis after dengue viral infection. J Neuroophthalmol. 2005;25:51-52.
7. Kanungo S, Shukla D, Kim R. Branch retinal artery occlusion secondary to dengue fever. Indian J Ophthalmol. 2008;56:73-74.
8. Yip VC, Sanjay S, Koh YT. Ophthalmic complications of dengue fever: a systematic review. Ophthalmol Ther. 2012;1:2. doi:10.1007/s40123-012-0002-z.
9. Gupta A, Srinivasan R, Setia S, Soundravally R, Pandian DG. Uveitis following dengue fever. Eye. 2009;23:873-876.
10. Chan DP, Teoh SC, Tan CS, et al; The Eye Institute Dengue-Related Ophthalmic Complications Workgroup. Ophthalmic complications of dengue. Emerg Infect Dis. 2006;12:285-289.

11. Teoh SC, Chan DP, Nah GK, et al. Eye institute dengue-related ophthalmic complications workgroup. A re-look at ocular complications in dengue fever and dengue haemorrhagic fever. Dengue Bull. 2006;30:184-193.
12. Teoh SC, Chee CK, Laude A, et al. Optical coherence tomography patterns as predictors of visual outcome in dengue-related maculopathy. Retina. 2010;30(3):390-398.
13. Kapoor HK, Bhai S, John M, Xavier J. Ocular manifestations of DF in an East Indian epidemic. Can J Ophthalmol. 2006;41:741-746.
14. Gilman J, Myatt MA. EpiCalc 2000 v1.02: A Statistical Calculator for Epidemiologists. Llanidloes, Mid Wales: Brixton Health; 1998.
15. World Health Organization. Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control. Geneva, Switzerland: World Health Organization; 2009.
16. Ministry of Health Malaysia. Clinical Practice Guidelines: Management of Dengue Infection in Adults; 2008.
17. Williamson DR, Albert M, Heels-Ansdell D, et al. Thrombocytopenia in critically ill patients receiving thromboprophylaxis: frequency, risk factors, and outcomes. Chest. 2013;144:1207.
18. Su DH, Bascal K, Chee SP, et al. Prevalence of dengue maculopathy in patients hospitalized for dengue fever. Ophthalmology. 2007;114:1743-1747.
19. Bacsal K, Chee SP, Cheng CL, Flores JV. Dengue-associated maculopathy. Arch Ophthalmol. 2007;125:501-510.
20. Chee E, Sims JL, Jap A, et al. Comparison of prevalence of dengue maculopathy during two epidemics with differing predominant serotypes. Am J Ophthalmol. 2009;148(6):910-913.
21. Malhotra R, Singh L, Bundela R, et al. Retinal profile: a clinical indicator of severity in dengue fever in a suburban Indian environment. Trop Doct. 2014;44(3):143-147.
22. Tan P, Lye DC, Yeo TK, et al. A prospective case-control study to investigate retinal microvascular changes in acute dengue infection. Sci Rep. 2015;5:17183. doi:10.1038/srep17183.
23. Balmaseda A, Hammond SN, Pérez L, et al. Serotype-specific differences in clinical manifestations of dengue. Am J Trop Med Hyg. 2006;74:449-456.
24. Carraro MC, Rossetti L, Gerli GC. Prevalence of retinopathy in patients with anemia or thrombocytopenia. Eur J Haematol. 2001;67:238-244.