Ultrasonographic Findings in Eyes with Retinopathy of Prematurity in Malaysia

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SUMMARY

RetCam is an excellent screening tool for the detection of retinopathy of prematurity (ROP). However, affordability is a barrier when adopting the use of RetCam in developing countries. We aimed to describe different stages of ROP using ultrasonographic B-scan and to evaluate the association between funduscopic examinations and ultrasonographic B-scan findings in premature neonates with ROP in Malaysia. A descriptive cross sectional study was conducted in 90 eyes of 47 premature neonates with different stages of ROP in three tertiary hospitals in Malaysia. Experienced ophthalmologists performed detailed funduscopic examinations using binocular indirect ophthalmoscopy (BIO). A masked examiner performed a 10 MHz ultrasonographic B-scan evaluation with 12 meridian position images within 48 hours of clinical diagnosis. Data from the clinical examination and ultrasonographic findings were collected and analysed. We recruited 37 eyes (41.1%) with stage 1 ROP, 29 eyes (32.3%) with stage 2, 18 eyes (20.0%) with stage 3, and 3 eyes (3.3%) with stages 4 and 5 based on the clinical assessment. Ultrasonography correctly identified 3 (8.1%) stage 1 eyes, 17 (58.6%) stage 2 eyes, 13 (72.2%) stage 3 eyes, and 3 each (100%) of the stage 4 and 5 eyes. There was a significant association between the funduscopic signs and the ultrasound findings for stage 2 ROP and above (Fisher's exact test, p <0.001). In conclusion, all stages of ROP were detected and described with a 10 MHz ultrasonic B-scan system. A significant association was observed between funduscopic signs and ultrasonographic findings in premature Malaysian neonates with stage 2 ROP and above.

KEY WORDS:
Retinopathy of prematurity, funduscopic signs, B-scan ultrasonographic findings

INTRODUCTION

Premature neonates at risk of developing retinopathy of prematurity (ROP) are routinely screened with binocular indirect ophthalmoscopy (BIO). Those who are born with a birth weight less than 1500 grams, a gestational age ≤30 weeks, a birth weight between 1500 and 2000 grams, and an unstable clinical condition require serial funduscopic examinations until each eye is no longer at risk of developing vision-threatening ROP[1,2]. Infants are considered no longer at risk when they reach a postmenstrual age of 45 weeks or have full retinal vascularisation, the absence of pre-threshold disease, zone III retinal vascularisation without previous zone I or II ROP, or regression of ROP[1,2].

BIO is the gold standard for the detection of ROP[3,4]. However, the procedure requires pupillary dilation, the application of an eye speculum and a scleral indenter, and properly trained and skilful examiners. Furthermore, it is time consuming and can be stressful to premature neonates[5-7]. RetCam is a promising modality that has the potential to replace the use of BIO in ROP screening[8-10]. It eliminates the need to use topical dilating drops and scleral indenters. However, the price of the instrument appears to be the main barrier limiting its availability in the majority of hospitals, particularly in developing countries such as Malaysia.

In contrast, ophthalmic ultrasonography is a relatively less expensive diagnostic device that is available in most ophthalmology clinics worldwide. It is a potential diagnostic tool for ROP[11-15], and it allows visualisation of retinal images through closed eyelids. It also eliminates the need for topical dilating drops and the application of an eye speculum and indenter, and it causes less stress for premature infants when compared with BIO. This study aimed to describe specific ultrasonographic findings in various clinical stages of ROP and to evaluate the association between the funduscopic signs and ultrasonographic findings of ROP in premature Malaysian neonates.

MATERIALS AND METHODS

A total of 47 premature neonates (90 eyes) who fulfilled the selection criteria were recruited into the study. Three tertiary centres in Malaysia participated in this study: Hospital Universiti Sains Malaysia, Hospital Raja Perempuan Zainab II, Kota Bharu, and Hospital Kuala Lumpur. The study was conducted from September 2007 through October 2009 in accordance with the Declaration of Helsinki. The study protocol was approved by the Research and Ethical Committee of the School of Medical Sciences, Universiti Sains Malaysia. All parents/guardians were informed about the

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objectives, methods and implications of the study before obtaining consent for the participation of their neonates.

The inclusion criteria were premature neonates diagnosed with ROP by clinical assessment and consent provided by the parents/guardians. Premature neonates who had poor media and were unfit/too ill for clinical funduscopic assessments and/or ultrasonographic examinations were excluded from this study.

All of the neonates underwent thorough dilated funduscopic assessments conducted by senior ophthalmologist selected at each centre. The pupils were dilated using 0.5% cyclopentolate one hour prior to the examination. An eyelid speculum and a scleral indenter were used during the retinal examination. The clinical diagnoses were made based on the international classification[16].

Ultrasonographic examinations (10 MHz probes and the AVISO, Quantel Medical Inc.) were performed by identified masked personnel within 48 hours of the clinical diagnosis. Topical anaesthetic drops were instilled, and an adequate amount of hypoallergenic ultrasonic gel was used. The ultrasound probe was gently applied on the closed eyelids, and it was oriented in 12 clock-hour positions with the transducer marker pointing towards the centre of the eye (Fig. 1). Three ultrasonographic images were taken, and the best images were recorded digitally. Ultrasonographic findings were considered significant based on the descriptions by Jokl *et al*[12].

The obtained demographic and clinic data were entered into the data collection sheets. Two identified masked investigators were responsible for evaluating and analysing the ultrasonographic findings from all of the participating centres. The Statistical Package for Social Sciences for Windows version 18 was used for the data analysis. A p-value of < 0.05 was considered statistically significant. Fisher's exact test was used to calculate the significance level of the association between funduscopic signs and ultrasonographic findings at all stages of ROP ($p < 0.001$).

RESULTS

We recruited 90 eyes (47 premature neonates) from three tertiary centres in Malaysia. The eyes were analysed separately because the findings in each eye were independent and may not have been symmetrical. Table I summarises the demographic and clinical characteristics of the participating subjects. Both genders were equally affected, and 87.2% were of Malay ethnicity. Neonates born at less than 30 weeks gestation composed 72.3% of the study population, and 51.1% of the study population had a birth weight ranging from 1001-1530 grams. Pre-threshold ROP was observed in 73.4% of the examined eyes, threshold ROP was observed in 20%, and the remaining premature neonates had advanced ROP.

Table II summarises the clinical diagnoses based on the funduscopic signs and specific ultrasonographic findings observed in our subjects. Figures 2, 3 and 4 show the ultrasonographic findings observed in our patients, including shallow and broad retinal thickening, giant ridges, and partial and total retinal detachment.

Table III displays the association between the clinical diagnoses based on funduscopic signs and ultrasonographic findings. A high percentage, 91.9% (34 eyes), of premature neonates with stage 1 ROP observed during the funduscopic

Table I: Demographic and clinical characteristics

Characteristics	n (%)
Gender	
Male	22 (46.8)
Female	25 (53.2)
Race	
Malay	41 (87.2)
Chinese	3 (6.4)
Indian	1 (2.1)
Others	2 (4.3)
Period of gestation	
25-29 weeks	34 (72.3)
30-34 weeks	13 (27.7)
Birth weight (gram)	
< 750	2 (4.2)
751 – 1000	21 (44.7)
1001 – 1530	24 (51.1)
Clinical Stages of ROP*	
Stage 1	37 (41.1)
Stage 2	29 (32.3)
Stage 3	18 (20.0)
Stage 4	3 (3.3)
Stage 5	3 (3.3)

*calculated based on 90 eyes

Table II: Ultrasonographic findings in various stages of clinically diagnosed ROP

Funduscopic Signs	Ultrasonographic Findings				
	No finding	Shallow retinal thickening / ridge	Broad retinal thickening / giant ridge	Partial retinal detachment	Total retinal detachment
Stage 1 (n=37)	34 (91.9)	3 (8.1)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 2 (n=29)	12 (41.4)	17 (58.6)	0 (0.0)	0 (0.0)	0 (0.0)
Stage 3 (n=18)	5 (27.8)	1 (5.6)	12 (66.6)	0 (0.0)	0 (0.0)
Stage 4 (n=3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)	0 (0.0)
Stage 5 (n=3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)

Table III: Association of funduscopic signs and ultrasonographic findings

Funduscopic Signs	Identification of ROP by ultrasonography		p value
	Yes n (%)	No n (%)	
Stage 1 (n = 37)	3 (8.1%)	34 (91.9%)	
Stage 2 (n = 29)	17 (58.6%)	12 (41.4%)	
Stage 3 (n = 18)	13 (72.2%)	5 (27.8%)	<0.001
Stage 4 (n = 3)	3 (100.0%)	0 (0.0%)	
Stage 5 (n = 3)	3 (100.0%)	0 (0.0%)	

$p < 0.05$ (Fisher's exact test)

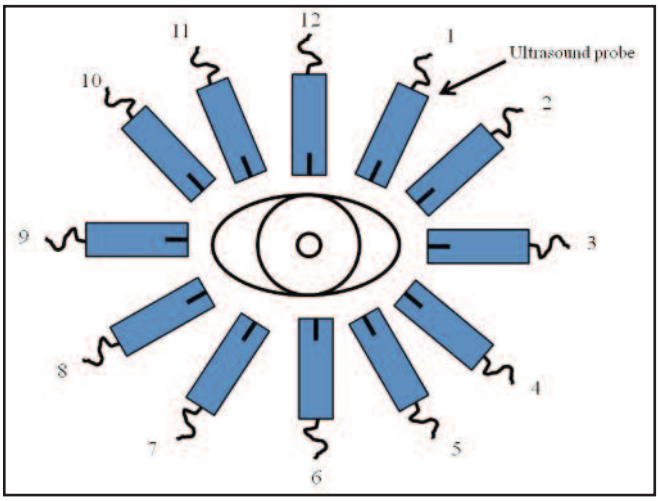

Fig. 1: The orientation of ultrasound probe in 12 clock hour positions with the transducer marker pointed toward the centre of eye, to get the meridians images.

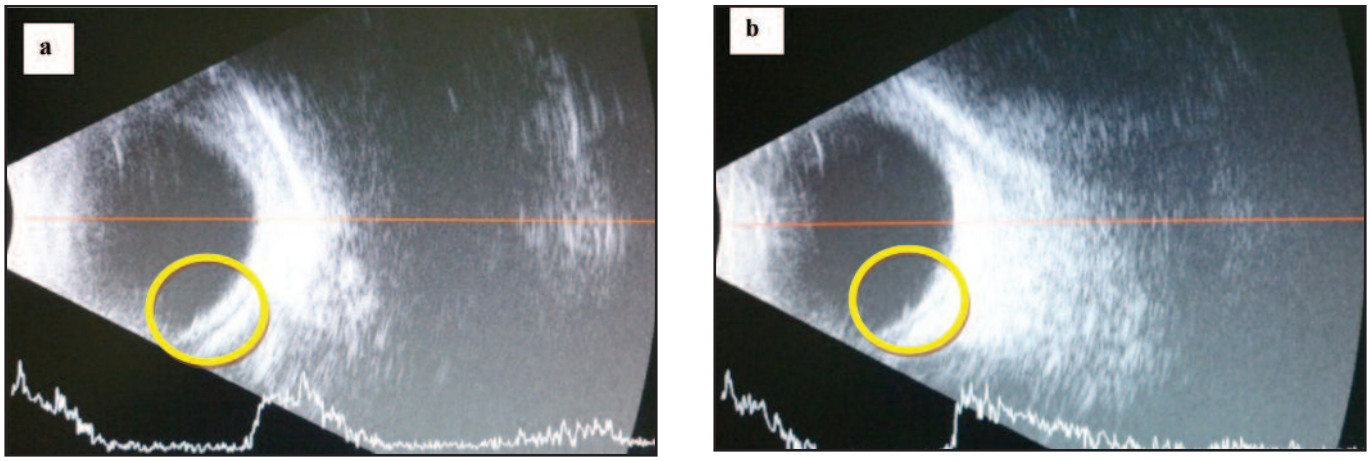

Fig. 2: Ultrasonographic findings observed in pre-threshold ROP. (a) Shallow retinal thickening corresponds with clinical stage 1 ROP. (b) Retinal thickening with ridge seen in patient with clinical stage 2 ROP.

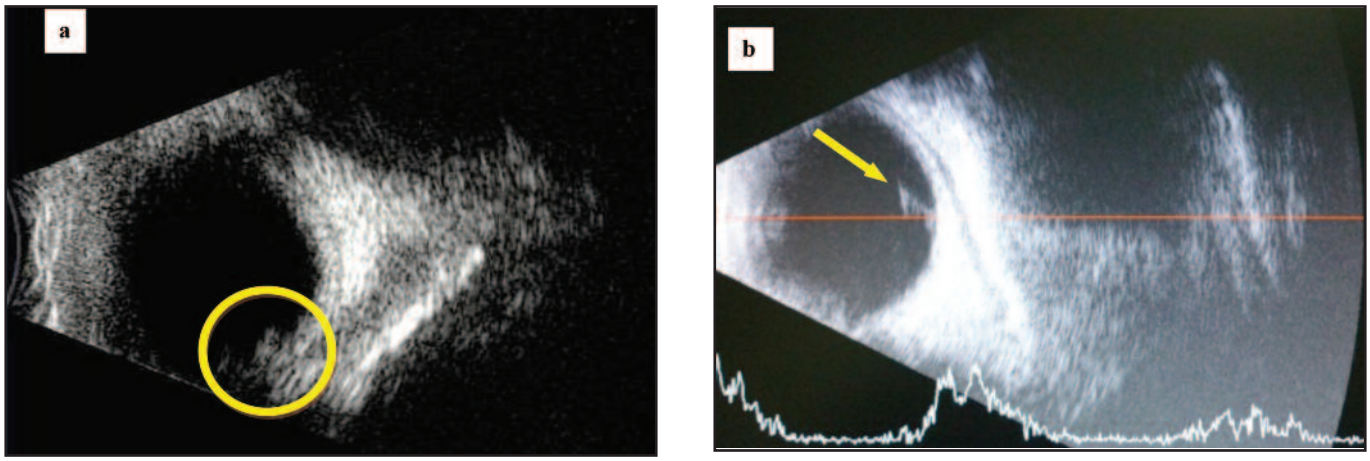

Fig. 3: Ultrasonographic findings observed in threshold ROP. (a) Stage 3 ROP shows a giant ridge with two apexes. (b) Stage 3 ROP shows a giant ridge with vitreous fibrous band traction (yellow arrow).

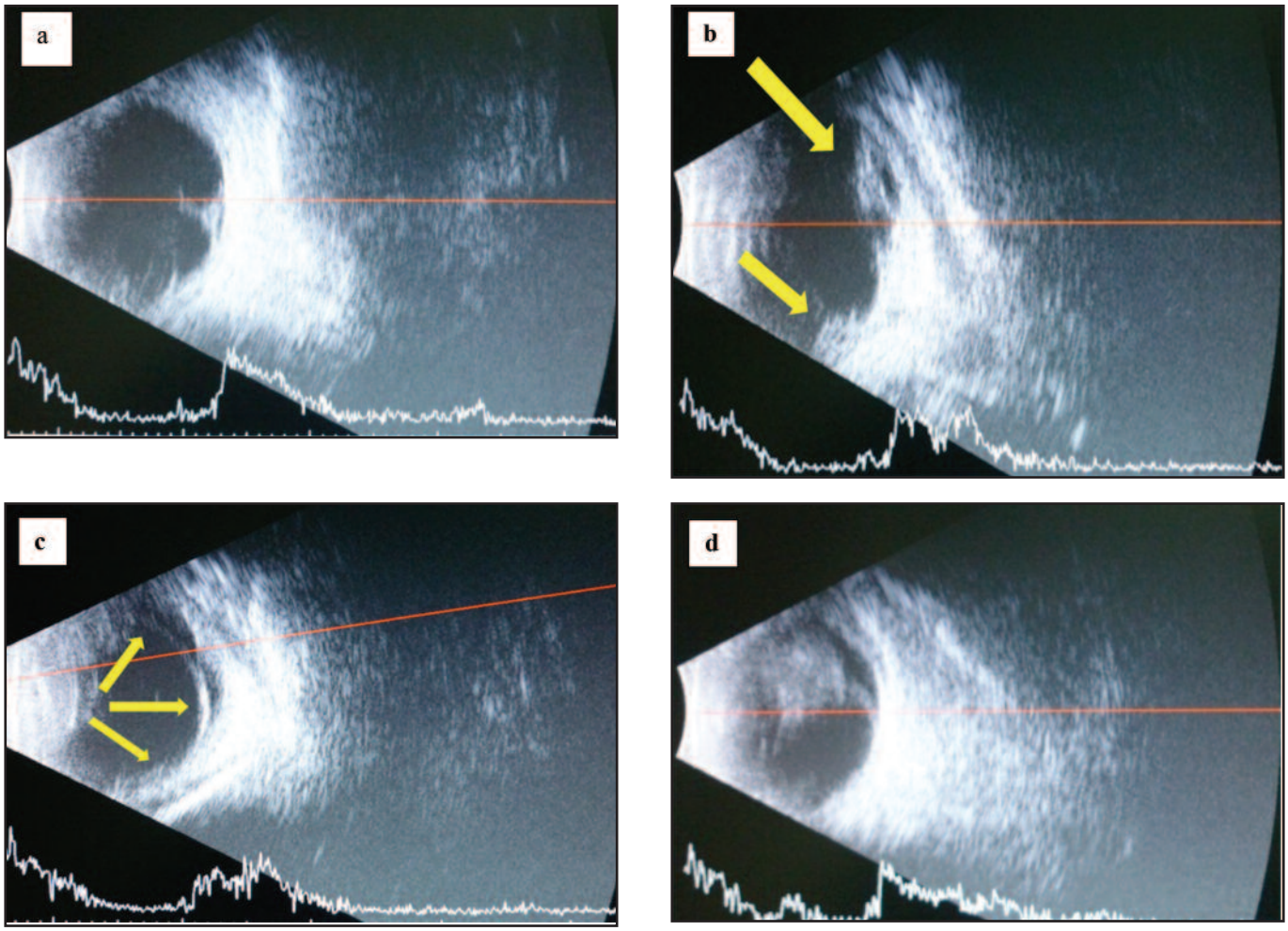

Fig. 4: Ultrasonographic findings observed in advanced ROP. (a) Stage 4a shows a partial retinal detachment as the retina is drawn anteriorly toward lens margin by vitreous condensation. (b) Stage 4b displays a more severe form of partial retinal detachment with donut appearance. (c) Stage 5 ROP shows a total retinal detachment. (d) Stage 5 ROP reveals a folded and scrolled retina into funnel shaped

examination revealed no detectable signs (termed a negative sign) in the ultrasonographic evaluations. Stage 2 and 3 ROP showed a higher percentage of detectable ultrasonographic features, at 58.6% and 72.2%, respectively. Stage 4 and 5 ROP displayed 100% agreement between the funduscopic signs and ultrasonographic findings. Fisher's exact test identified a significant association between the funduscopic signs and ultrasonographic findings ($p<0.01$) for stage 2 ROP and above.

DISCUSSION

The ultrasonographic findings in stage 4 and 5 ROP have been described in published case reports and series[11,14,15,17,19]. Jokl *et al* evaluated the use of ophthalmic ultrasonography for screening stage 2 and 3 ROP in 34 premature eyes using a 10 MHz probe[12] and stage 1 through 4 ROP in 38 premature eyes with a 20 Hz probe[13].

We chose to evaluate all stages of ROP using ophthalmic ultrasonography because the majority of eye clinics in Malaysia do not have access to a RetCam. We examined 84 eyes of premature neonates with stage 1 to 3 ROP and 6 eyes with stage 4 and 5 ROP throughout our study period.

Our study revealed that 91.9% of stage 1 ROP cases diagnosed during a clinical examination showed negative signs during the ultrasonographic examination. Only 3.1% (3 eyes) of the premature eyes with stage 1 ROP diagnosed during the clinical examination displayed the corresponding signs during the ultrasound assessment. Two eyes showed shallow retinal thickening, while one eye had a small triangular protrusion, suggestive of a ridge, in 1 of the 12 images taken.

In contrast to our findings, Jokl *et al* reported that 69.2% of eyes with stage 1 ROP showed agreement with ultrasonographic examinations using a 10 MHz probe[12]. However, the other study by Jokl *et al* did not evaluate ultrasonographic findings in stage 1 ROP using a 20 MHz probe[13].

The examiner's skill is crucial for obtaining a clear and good ultrasonographic image. The likelihood of misdiagnosing stage 1 ROP using ultrasonography (Fig. 2a) was greater than 90% in our study. We found it technically difficult to detect localised shallow retinal thickening in this group of patients. This is because the demarcation line in stage 1 ROP that represents hyperplasia of the spindle cells is too thin to be detected by the ultrasound beam[18].

We used a conventional 10 MHz handheld probe. This probe provides an axial resolution of approximately 200 µm and focuses on 20-25 mm of tissue. The focal zone falls near the retina in a contact examination that uses ultrasound gel on a closed eyelid[12]. The 20 MHz probe offers a higher resolution[13].

We observed a higher rate of detection by ultrasonography in stage 2 and 3 ROP (58.6% and 72.2%, respectively). Our patients with stage 2 ROP had findings of shallow retinal thickening and ridges (Fig. 2a and b), while stage 3 ROP displayed broad retinal thickening and giant ridges (Fig. 3a and b).

Jokl *et al* described the corresponding ultrasonographic findings in 2 of 11 eyes (18.2%) with stage 2 ROP and all 3 eyes (100.0%) with stage 3 ROP[12]. Our findings also parallel another observation by Jokl *et al*[13]. Brent *et al* described the presence of a ridge in stage 2 ROP and a neovascular frond in stage 3 ROP that were imaged with ultrasonography in their case series[11].

Stage 4 and 5 ROP were easily detected by ultrasonography in our study (Fig. 4). Three eyes showed evidence of partial retinal detachment, while another 3 eyes displayed signs of total retinal detachment. This included one eye (33.3%) that demonstrated an open posterior and anterior form configuration, while the other two eyes (66.7%) displayed a closed posterior and anterior form. Our findings support the existing role of ophthalmic ultrasonography in the detection of advanced stages of ROP[14,15,17,19].

In 1998, De Juan *et al* described the ultrasonographic appearance of 54 eyes with advanced ROP[19]. The configuration of retinal detachment and the existence of subretinal or choroidal haemorrhage were well described in their study[19]. Azad et al assessed the role of ultrasonography in the management of stage 5 ROP[17]. They noted that 53.3% (8 eyes) of the 83.3% of eyes diagnosed with stage 5 ROP with an anterior open funnel on B-scan ultrasonography had open access to the anterior surgical space and were scheduled for lensectomy[17].

CONCLUSION

Ultrasonography detected all stages of ROP in our subjects, although it was technically difficult to detect stage 1 ROP. A significant association was demonstrated between the funduscopic signs and ultrasonographic features in stage 2 ROP and above. The use of ultrasonography in the management of ROP will be advantageous for premature neonates with poor pupillary dilation and hazy media, particularly in countries with a limited number of trained paediatric ophthalmologists and limited RetCam availability.

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