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SEVERE RETINOPATHY OF PREMATURITY: REVIEW OF COMPLIANCE TO GUIDELINES, DEMOGRAPHICS AND ALTERNATIVE RISK FACTORS

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ABSTRACT

Introduction- Retinopathy of prematurity (ROP) has become one of the most common causes of preventable visual impairment in children worldwide. Effective screening, and compliance to the screening protocol is crucial to ensure timely management of this potentially blinding disease. The aims of this study were to evaluate the compliance of our centre to the local ROP protocol as well as to review the demographics and identify alternative risk factors involved in development of severe ROP.

Methods- 5-year retrospective review of infants with severe ROP requiring treatment in Sultan Abdul Halim Hospital, a tertiary referral centre in northern Malaysia. Medical records of all premature infants screened for ROP were cross referenced with the surgical registry for identification of infants who received treatment. Information including gestational age, birth weight and timing of treatment given were recorded and analysed.

Results- Between 2017 and 2021, 322 premature infants were screened and 26 (8.1%) infants were diagnosed with severe ROP which required treatment. Of these 26 infants, 77% underwent timely screening, and 74% received treatment within the recommended timeline. A new possible risk factor identified for development of severe ROP was a diagnosis of maternal COVID-19, though this is subject to further study.

Conclusion- The rate of timely screening and treatment provision of >70% suggests that the screening compliance at our centre is comparable to centres in developed countries. This indicates good adherence to the guidelines and a fairly low rate of delayed screening or treatment.

Key Words- Retinopathy of prematurity, screening, protocol, demographics, risk factors.

1. INTRODUCTION

Retinopathy of prematurity (ROP) has become one of the most common causes of preventable visual impairment or blindness in children worldwide, due to the increasing rate of survival in extremely premature infants (1). ROP occurs in response to retinal ischaemia, in the presence of an immature retinal vasculature, where normal retinal angiogenesis is replaced with hyperproliferative neovascular activity i.e. neovascularisation (2,3). This may then progress to retinal detachment which eventually leads to blindness if untreated (2,3). Several risk factors have been identified in the development of ROP, with the most significant being short gestation period, low birth weight, and the use of supplemental oxygen (4-6). ROP protocols provide information to ophthalmologists on screening criterias as well as treatment guidelines for premature infants with ROP. They are important tools that allow prompt recognition and management of ROP, thus improving the overall outcome. Many clinical studies have shown improved anatomic and visual outcome following treatment with cryotherapy or panretinal photocoagulation, in infants with severe ROP, while infants with threshold ROP have also been shown to gain significant benefit from early treatment (7). The protocols, especially screening criterias may differ between countries due to variability in demographics and differences in neonatal care practices (8-10). It is important that the local health authority identifies and incorporates risk factors or criterias unique to the local population into the guidelines, while at the same time routinely performing compliance assessments on neonatal centres, to ensure good adherence to protocols and effective management of this potentially blinding disease (8-10). The aims of this study were to evaluate the compliance of our centre to local ROP screening and management protocols, to review the demographics, and identify alternative risk factors involved in development of severe ROP.

2. METHODS

This was a retrospective study conducted at Sultan Abdul Halim Hospital in Malaysia, a tertiary referral centre with a neonatal intensive care unit (NICU) service. Electronic medical records were reviewed for all premature infants who were screened for ROP at the centre, over a period of 5 years, between January 2017 until December 2021. This data

was cross referenced with the Ophthalmology Department surgical registry for identification of infants with severe ROP, requiring treatment. Microsoft Excel was used to collect and analyse information including gestational age (GA), birth weight, age at screening and diagnosis, as well as the timing of treatment given post diagnosis. Antenatal risk factors, delivery details as well as post-natal particulars and management were also recorded. Examinations were carried out according to the Malaysian Clinical Practice Guidelines for ROP (2005) (11). All premature infants born less than 32 weeks and/ or with birth weight of less than 1500g were screened for ROP. Screenings were also carried out on premature infants born at more than 32 weeks of gestation or with birth weight more than 1500g, but who had unstable clinical conditions, and were deemed to be at high risk of developing ROP, as determined by the pediatrician or neonatologist in charge. The first ROP screening examination was performed on these infants at 31 weeks GA or 4-6 weeks postnatal age, whichever was later as proposed by the guidelines. Assessment was performed by two ophthalmologists and the stages of ROP were documented according to the International Classification of Retinopathy of Prematurity (2005), which divides the location of disease into three zones, five stages of severity and includes the description of plus disease manifestation (12). The treatment given was based on the Early Treatment for Retinopathy of Prematurity (ETROP) trial and criterion for treatment is threshold ROP, defined as stage 3 ROP with at least five contiguous clock hours or eight cumulative clock hours with plus disease (7,12). The Malaysian guidelines proposed that infants requiring treatment should be treated ideally within 48-72 hours of diagnosis with either laser treatment, cryotherapy, intravitreal anti-vascular endothelial growth factor (anti VEGF) or vitreo-retinal surgery if indicated (11). In this study, 25 infants received laser treatment while one infant was given both laser and intravitreal anti VEGF injection. Repeat examination were continued for all in 1 to 3-week intervals depending on severity until complete regression of ROP, with the treated eye deemed to have no further risk of visual loss or until complete vascularisation of the retina was seen.

3. RESULTS

A total of 322 premature infants were screened over the course of 5-years. Only 26 (8.1%) infants were diagnosed with severe ROP which required treatment. The rest of the infants (91.9%) were diagnosed as either stage 1-2 ROP which regressed, or did not develop ROP at all. Of the 26 infants with severe ROP, only 5 were females (19.2%) while the rest were male infants (80.8 %). The majority of these infants (n=23, 88.5%) were of Malay ethnicity while 3 infants (11.5%) were from the Indian ethnic group. The mean GA of these 26 infants was 28 weeks, with the youngest being born at 25 weeks and the oldest at 35 weeks. The birth weights ranged between 645g and 2280g, with the average being 1170g. Demographic details and characteristics are summarized in Table 1. The majority of these newborns (n=20, 77.0%) had their first screening within 4-6 weeks after delivery, at the GA of between 29 to 36 weeks (Figure 1). Mean GA at screening was 33 weeks. Six (23.1%) infants were screened beyond 7 weeks post-delivery, with the latest being screened at 11 weeks post-natal age or at 40 weeks GA. All of the infants were diagnosed with stage 3 ROP, with 7 infants (26.9%) also having features of Plus Disease. None had stage 4 or 5 ROP. Mean GA at diagnosis and commencement of treatment was 38 weeks, with the majority (n=20, 76.9%) being treated with indirect laser within 72 hours post diagnosis (Figure 2 and 3). Six infants (23.1%) were treated beyond the recommended treatment guidelines, i.e. more than 72 hours, with one infant being given treatment at 21 days after diagnosis. All of the infants required oxygen support post-delivery with 23 infants (88.5%) intubated while 3 (11.5%) were managed with non-invasive ventilation (NIV). An additional risk factor identified in this study was maternal diagnosis of COVID-19 which induced premature delivery. Two infants diagnosed with severe ROP were born of mothers infected with COVID-19 and they exceeded the screening criteria whereby both were born after 32 weeks and with birth weights of more than 1500g. The mean GA at termination of ROP management was 50.4 weeks with all infants being given appointment dates for follow up in the ophthalmology clinic, for refraction and general review.

4. DISCUSSION

The majority of premature infants screened in our centre did not develop severe ROP (91.3%). This result is fairly similar to studies conducted in other centres where up to 95% of infants screened did not have ROP which required treatment (8-10,13-15). This is despite greater numbers being screened and an increasing trend of premature birth each year, owing to advancement in medical care and technology (1). The majority of newborns with severe ROP requiring treatment in Sultan Abdul Halim Hospital were male patients. This is consistent with findings of other studies which suggest that boys are 14% more likely to be born preterm than girls (16,17). Premature male infants are also at a higher risk of death, with greater likelihood of getting infections, jaundice and congenital conditions (16,17). This subsequently leads them to being more likely to have preterm related disabilities such as learning problems, blindness, deafness and motor issues including cerebral palsy (16,17). The premature infants requiring treatment in this study were predominantly of Malay ethnicity, which is the largest ethnic group in Malaysia. The rest of the infants were

Indian and there were no premature infants from the Chinese ethnic group that required treatment. This distribution is inconsistent with the ethnic ratio recorded in the Population and Housing Census of Malaysia, which states the Chinese ethnic as the second largest ethnic group in Malaysia (18). However, this inconsistency could possibly be explained by the Chinese population having the highest average household income, which leads to better access to private maternal and neonatal facilities (18,19). Higher educational level among the Chinese ethnic group may also lead to better awareness on high-risk pregnancy, premature delivery and ROP in general (18-20). The Chinese population also has the lowest level of birth rates in comparison to any other ethnic group (18). Post-natal risk factors for ROP recorded in our study were similar to other reports, and these include high and prolonged oxygen requirement, severe respiratory distress syndrome, intraventricular haemorrhages, poor Apgar score, sepsis, anaemia requiring transfusion and multiple pregnancy (4-6). Low birth weight and younger gestational age appear to be the primary risk factors among infants requiring treatment at our centre, with 22 (84.6%) of these infants born either below 32 weeks and/or having a birth weight of less than 1500g. Our study recorded 4 infants (15.4%) with severe ROP who were born after 32 weeks or had a birth weight above 1500g, which is not consistent with and exceeded the screening criteria recommended by the national Malaysian ROP guidelines. It is worth noting that the Malaysian screening and treatment guidelines shared many resemblances to the UK protocol for ROP, with fairly similar screening criterias and treatment recommendations, as well as sources cited (11,21). However, few studies have questioned the efficacy of the UK ROP guidelines, or the western screening guidelines in general and their applicability to less developed nations (13,22-24). This is due to higher incidences of severe ROP requiring treatment in infants with birth weight of more than 1500g and of GA beyond 32 weeks, reported in countries with less advanced healthcare facilities (13,22-24). One study reported that 35% of infants with severe ROP in their centre exceeded the American screening guidelines, and concluded that infants with ROP recruited in their study were generally larger than those from high income countries, with wider range in terms of GA and birth weight (23). Another study of severe ROP reported an incidence of 20% in infants with birth weight above 1500g, and 9.4% in infants born beyond 32 weeks of gestation (24). Later presentation i.e. later screening is also seen in less developed nations with median screening age reported to be as late as 48 weeks post menstrual age, which is significantly associated with more advanced ROP (23). A possible explanation for development of ROP in these larger and more mature babies could be due the lack of standardised high-quality neonatal care compared with high-income countries (23,25). Apart from that, lack of awareness as well as difficulties for low-income mothers with sick infants to travel to tertiary screening centre in these less developed nations, might also be a reason for the data to be biased towards more mature infants (23-25). The maternal risk factors recorded in our study were consistent with other studies, and these include gestational diabetes, pregnancy induced hypertension or pre-eclampsia, and antepartum haemorrhage (4-6). An additional maternal risk factor identified in our study is maternal COVID 19, which induces premature delivery. Two infants with severe ROP requiring treatment in our study were born to mothers with COVID-19 and treated in the intensive care unit, with one of the infants also infected with COVID-19. Studies have shown that individuals who contract COVID-19 while pregnant face a higher risk of preterm birth, with data showing premature birth rate among mothers with COVID-19 diagnosis to be 11.8%, in comparison to just 8.7% in mothers without COVID-19 (26). The risk of very premature delivery i.e. at less than 32 weeks of gestation was 60% higher for mothers with COVID-19, while risk of giving birth at less than 37 weeks was reported to be 40% higher in those infected (26,27). And for those who also had co-morbidities such as hypertension, diabetes or obesity, the risk of pre term birth increased to 160%, in comparison to mothers without the infection (26,27). Although the risk of preterm birth in mothers with COVID-19 infection is well documented, direct correlation between this infection and the development of ROP in premature infants is yet to be proven. However, it should be emphasized that severe postnatal complications of extremely premature birth, as a result of maternal or foetal COVID-19 infection, such as poor Apgar score, hypothermia, hypoglycaemia and severe respiratory distress, all could lead to an exaggerated cytokine release, and that in itself is a known significant risk factor for the development of ROP (1,26-28). It is also worth noting that ROP screening might also be necessary for larger/ older infants of mothers with COVID-19, due to the aggressive nature of this illness and its tumultuous clinical course (11,21,26-28). Further studies are needed to evaluate whether ROP development is faster or more aggressive in premature infants diagnosed with COVID-19 or born to mothers with the illness. In our study, although the majority of infants were screened and treated in accordance to the standard guidelines, 6 infants with severe ROP (23.1%) had delayed screening while 6 infants (23.1%) also received delayed treatment (i.e. more than 72 hours after diagnosis) due to multiple reasons. One infant was transferred to another tertiary centre for surgical management of perforated NEC, while the rest were deemed to be either critically ill or extremely unstable for a safe ROP screening and treatment to be performed. Two late referrals were identified to be caused by lack of communication between the junior and senior medical officers as well as the support staff in charge of the babies.

Other possible reasons for non-adherence to screening and treatment guidelines include public holidays, changes in hospital or national policies, unexpected event such as the COVID-19 pandemic, lack of manpower/ specialist trained for ROP screening and limited vital resources such as ventilators and NICU bed (13,28). Few ways have been suggested to overcome delay or non-adherence to the guidelines and this include better liaison with the paediatric team and NICU, through frequent discussion and provision of information such as new updates in the policies on screening (13). Apart from that, it is recommended to have one person designated within the paediatric NICU team, to arrange for eligible preterm babies for ROP screening once they are admitted to the NICU, and to assign one ophthalmologist in charge who will oversee the ROP screening process (13). This will lead to a standardized ROP management while at the same time providing the paediatric team an easier and faster access to ophthalmology consultation, especially in difficult cases which requires special consideration (11,13,21). Other suggestions to improve compliance to screening guidelines include making proper arrangements, documentations and discharge planning especially when inter-hospital transfer is involved, as well as providing adequate training on ROP to medical officers and support staff in the NICU (11,13,21). All of the infants with severe ROP included in our study met the national screening indications for ROP and they fulfilled the ETROP criteria for early treatment. The majority of them (77%) underwent timely screening and received appropriate treatment in accordance to the Malaysian guideline. These infants were also given adequate subsequent follow up until discharge criteria were met. A nationwide audit performed in the UK to assess compliance rate to screening, showed that up to 77% of their ophthalmologist complied with the national guideline, while studies in other less developed countries recorded national compliance rate of between 47-73% (13,29,30). Therefore, we believed that the rate of screening compliance in our centre is acceptable, with good adherence to the guideline and a fairly low rate of delayed screening or treatment.

5. CONCLUSION

The results of our study suggest a possible need for evaluation of our current national screening protocol. A good percentage of our subject did not fit or exceeded the screening criteria. Therefore, there might be a need to incorporate new variables and additional factors such as socioeconomic status, COVID-19 or other more specific criteria relevant to our local population. The discussion however, must take into consideration the cost effectiveness and possible burden to our public health system, while at the same time aiming to optimize service and avoid unwanted delay or unnecessary screening. We would recommend a continuous evaluation or audit on ROP screening in all centres with neonatal service, to ensure optimum efficiency in screening and treatment provision, as well as maximum adherence to the national guideline.

Ethical consideration- This study adhered to the local guidelines by the Malaysian Medical Research and Ethics Committee and conducted in accordance to 1975 Helsinki Declaration, as revised in 1983.

Author Contributions - All authors contributed equally in planning and carrying out this study.

Conflict of interest - The authors have no conflict of interest to be declared.

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Table 1 Demographics (N=26)

Variables	N (%)
Gender	
Male	21 (80.8)
Female	5 (19.2)
Ethnicity	
Malay	23 (88.5)
Indian	3 (11.5)
Gestational age (weeks)	
<28	13 (50)
28-32	11 (42.3)
>32	2 (7.7)
Birth weight (g)	

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<1000	15 (57.7)
1001-1500	4 (15.4)
>1500	7 (26.9)
Gestational age + birth weight	
<32 weeks + ≤ 1500g	19 (73.1)
<32 weeks + >1500g	3 (11.5)
≥32 weeks + ≤1500g	0 (0)
≥32 weeks + ≥1500g	4 (15.4)

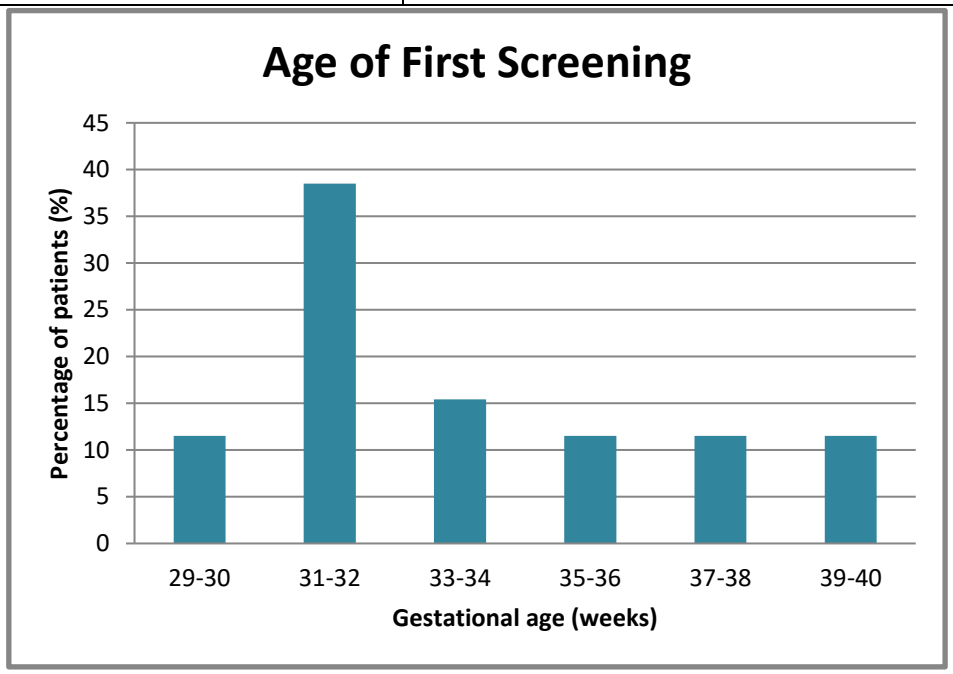

Figure 1. Age of first screening

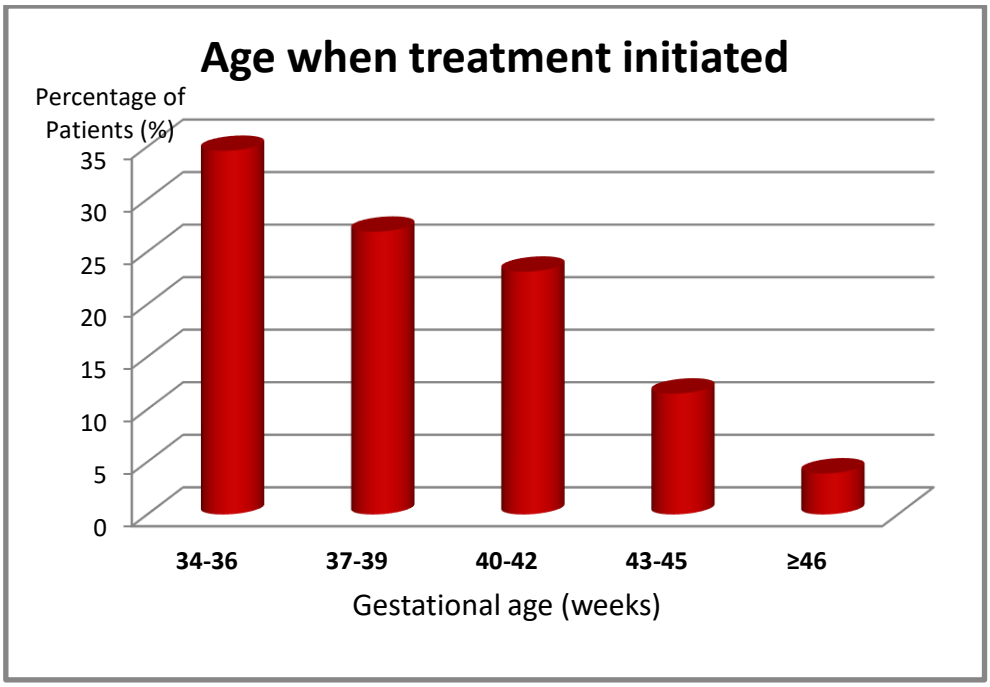

Figure 2. Age when treatment initiated.

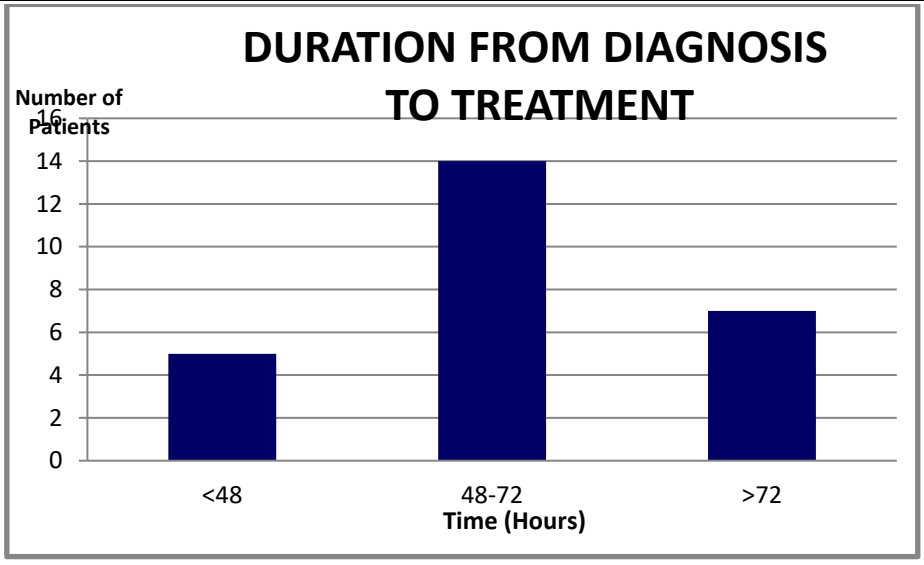

Figure 3. Duration from diagnosis to treatment

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