Retinopathy of Prematurity Is a Biomarker for Pathological Processes in the Immature Brain

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Keywords
- Neurodevelopmental impairment
- Retinopathy of prematurity
- Extremely preterm
- Neurovascular unit

Abstract
Introduction: Retinopathy of prematurity (ROP) is considered a neurovascular disease. We investigated whether ROP, mild or severe, is associated with neurodevelopmental impairment (NDI) in extremely preterm children. Methods: We conducted a multicenter retrospective cohort study in southern Taiwan. A total of 394 children <28 weeks of gestation who survived to discharge from 2011 to 2018 received neurodevelopmental assessment at corrected age of 24 months. Severe ROP was defined as ROP of stages 2 plus or worse, or recipients of retinal therapy, and mild ROP as stage 1 or 2 in at least one eye. NDI was defined as cognitive or motor impairment using the Bayley Scales of Infant and Toddler Development, moderate to severe cerebral palsy, or profound hearing loss. Results: Among the 374 children validated for analysis, 157 children (42%) had non-ROP, 145 (39%) mild ROP, and 72 (19%) severe ROP. As ROP severity increased progressively from non-ROP, to mild ROP, and to severe ROP, the rates of NDI increased from 25%, to 46%, and to 61%. The multivariable logistic regression showed that the model included three levels of ROP, and neonatal morbidities achieved better overall performance for NDI than the model that included neonatal morbidities alone. Compared with non-ROP, mild ROP and severe ROP had adjusted odds ratios of 1.90 (95% CI: 1.10–3.28) and 2.75 (95% CI: 1.33–5.67) for NDI, respectively. Conclusion: Mild ROP and severe ROP are independent neonatal morbidities associated with NDI. Neurodevelopmental follow-up of extremely preterm children with any stage of ROP is needed.
Introduction

Despite the medical advances with increasing survival, infants born extremely preterm remain at high risk of neurodevelopmental impairment (NDI) at follow-up [1]. Retinopathy of prematurity (ROP) is viewed as an arrest of retinal vascular development with pathological compensatory vascularization. ROP develops in 60% of extremely preterm babies with gestational age (GA) <28 weeks. Around 70% of ROP is mild and resolves spontaneously without treatment [2]. Before effective screening and treatment became available, approximately 5% of extremely preterm infants were bilaterally blind, and 50% of them were multi-disabled [3]. With the combination of improvements in neonatal care, widespread screening, and timing retinal therapy, there have been significant decreases in blinding ROP (<1%) in developed countries. However, the incidence of ROP has not declined because of the increasing survival of extremely and periviable preterm infants [1].

During development, the vasculature, neuronal circuits, and astrocyte networks integrate to form the neurovascular unit (NVU). The neurons and vasculature have intertwined time courses of proliferation, migration, and differentiation and share a common array of signaling molecules that regulate development [4, 5]. Although the pathogenic hallmark is abnormal retinal vessels, ROP may be considered an NVU disease involving both vascular and neural components [2, 6]. Several studies have shown long-term visual dysfunction with severe ROP even when vascular alterations have regressed [7, 8]. Infants with severe ROP have a high rate of NDI extending into adolescence [9–12]. In line with these data, preterm infants with severe ROP had thinner retinal nerve fiber layer and delayed white matter maturation associated with NDI [13, 14]. ROP may be part of a spectrum that includes altered development of NVU in both the retina and brain [6].

Although ROP is defined according to different stages of vascularization, the disease is a continuous process [2]. Most previous studies have focused exclusively on comparing the NDI of severe ROP and nonsevere ROP [10, 11]. However, very few studies have examined the outcomes of the spectrum of ROP, which includes non-ROP, mild ROP, and severe ROP. It is possible that ROP, mild as well as severe, is a biomarker for pathological processes not only in the retina but also in the brain. Here, we investigated whether among extremely preterm infants, as compared with a non-ROP group, the mild ROP and severe ROP groups are, respectively, associated with a higher risk of NDI, independent of neonatal risks or morbidities.

Participants and Methods

The preterm children follow-up network registered 552 infants who were born with GA <28 weeks and admitted to the NICUs of 4 tertiary centers located in southern Taiwan between January 2011 and August 2018 [15]. After discharge, the extremely preterm survivors were longitudinally followed up for neurodevelopmental status at the university hospital. Among the 442 infants who survived to discharge, 5 infants died after discharge; 14 were lost to follow-up; 29 moved to other cities; and 394 (89%) received neurodevelopmental examinations at corrected age (CA) of 24 months. After excluding the children who had brain malformations or genetic syndromes (n = 10), parents with mental disorders (n = 5), brain damage after discharge (n = 4), or severe visual impairment with visual acuity less than 20/200 in both eyes (n = 1), 374 children were included for analysis (Fig. 1). The children who had follow-up assessment (n = 374) and those who were lost to follow-up (n = 43) were comparable in terms of demographics, neonatal risks, and morbidities (online suppl. Table S1; for all online suppl. material, see www.karger.com/doi/10.1159/000526652). The preterm infants were included after written consent obtained from their parents. The Institutional Review Board of National Cheng Kung University Hospital approved this study.

ROP Screening and Treatment

The first ROP screening was performed at 31 weeks’ postmenstrual age. Eyes without ROP were re-examined biweekly until full vascularization of the retina. Those with ROP were examined every week until regression occurred or treatment was required. The highest stage of ROP recorded was assigned to each infant [16]. The average number of eye examinations received per infant was 4.3 (SD: 2.5). Severe ROP was defined as unilateral or bilateral ROP of stages 2 plus or worse, or as recipients of retinal therapy, and mild ROP defined as stage 1 or 2 disease in at least one eye [17]. The treatment followed the recommendations of the Early Treatment for Retinopathy of Prematurity Cooperative Group [18].

Predictor Variables

Small for GA was defined as birthweights lower than the 10th percentile for sex and GA for Taiwanese infants [19]. Events in the perinatal and neonatal period included respiratory distress syndrome (RDS), hemodynamically significant patent ductus arteriosus (hs-PDA), sepsis, necrotizing enterocolitis (NEC), postnatal steroid use for evolving or active bronchopulmonary dysplasia (BPD), severe intraventricular hemorrhage (IVH grade III or any grade of IVH plus periventricular hemorrhage), and cystic periventricular leukomalacia (cPVL). The percentages of duration requiring O2 supplements during hospital stay delivered either by invasive mechanical ventilation (IMV), nasal cannula, nasal continuous positive airway pressure or noninvasive positive pressure support, and the percentages of duration under IMV during hospital stay to keep the oxygen saturation at 88–95% by pulse oximetry were recorded.

Neurodevelopmental Assessment

Neurodevelopment was assessed at CA 24 months using the Bayley Scales of Infant and Toddler Development, third edition (BSID-III), with 3 composite scores on cognitive, language, and motor scales. NDI was defined as any of the following: cognitive
impairment (defined as cognition composite scores <85), motor impairment (motor composite scores <85), moderate to severe cerebral palsy (Gross Motor Functional Classification Scale level ≥2), or profound hearing loss requiring amplification in both ears [1].

**Fig. 1.** Patient recruitments and follow-up assessments.

**Statistical Analyses**

Neonatal risk factors, morbidities, and outcomes were compared among the different ROP groups using χ² tests or Fisher’s exact test for the categorical variables and analysis of variances for the continuous variables and Kruskal-Wallis tests as an alternative
if the normality assumption is violated. Tukey HSD and Bonferroni adjustment as post hoc tests were used to explore the pair-wise differences in continuous and categorical variables between groups. The association between ROP and outcomes was analyzed using a logistic regression, adjusted for the selected risk factors. After univariate analysis, all candidate factors were included in the multivariate analysis. Stepwise procedures were adopted as model selection algorithm for the multivariate model using Akaike information criterion. In addition, the likelihood ratio test was applied for the goodness-of-fit of two competing statistical models. A $p$ value <0.05 was considered statistically significant.

**Results**

Among the 374 extremely preterm children followed up at CA 24 months, 157 infants (42%) had non-ROP, 145 (39%) had mild ROP, and 72 (19%) had severe ROP. Fifty-eight of the 72 infants with severe ROP received retinal treatment, including cryotherapy in 2 infants, laser photocoagulation in 3, and anti-vascular endothelial growth factor (VEGF) in 53 (Fig. 1).

**Different Neonatal Risks among the Non-ROP, Mild ROP, and Severe ROP Groups**

Compared with the non-ROP group, the mild and severe ROP groups were significantly lower in GA; had higher rates of RDS requiring surfactant therapy, postnatal steroid use, severe IVH and cPVL; showed higher percentages of duration under IMV during hospital stay and more negative delta $z$ scores of body weight from birth to discharge; and stayed longer in the hospital. The severe ROP group had significantly lower GA and birth body weight, male gender, low 5-min Apgar scores, RDS requiring surfactant therapy, postnatal steroid use, severe IVH, NEC, cPVL, BPD, lower body weight growth, and a higher percentage of duration under IMV during hospital stay and more negative delta $z$ scores of body weight from birth to discharge; and stayed longer in the hospital. The severe ROP group had significantly lower GA and birth body weight and displayed high rates of hs-PDA requiring intervention, postnatal steroid use, and BPD; longer durations of hospital stay; and higher percentages of duration requiring O$_2$ or IMV during hospital stay compared with the mild ROP group. The subgroup of severe ROP who required retinal therapy like the severe ROP group has similar differences in demographics, neonatal morbidities, and at discharge status comparing with the non-ROP or mild ROP groups (Table 1). However, this subgroup had significantly lower GA and postnatal body weight growth and more BPD than infant with severe ROP without retinal treatment (online suppl. Table S2).

**NDI Outcomes after Different Severities of ROP**

At CA 24 months, as ROP severity increased from non-ROP, mild ROP to severe ROP, there was a gradient of increases in the rate of NDI, with 25% in non-ROP, 46% in mild ROP, and 61% in severe ROP (Table 2).

Compared with the non-ROP group, the mild ROP and severe ROP groups and the severe ROP subgroup requiring retinal therapy had significantly higher rates of NDI, cognitive impairment, and motor delay. The mild ROP, severe ROP, and the severe ROP subgroup with retinal therapy were comparable in the rates of NDI, cognitive impairment, and moderate or severe cerebral palsy. The severe ROP subgroup requiring retinal therapy showed a significantly higher rate of motor delay than the non-ROP and mild ROP groups. The severe ROP group and the severe ROP subgroup requiring retinal therapy also displayed significantly smaller head sizes than the non-ROP and mild ROP groups (Table 2). In severe ROP group, infants with retinal treatment had a significantly higher rate of motor impairment than infants without treatment (online suppl. Table S2).

The composite scores of BSID-III were negatively associated with ROP severity (online suppl. Table S3). The severe ROP and mild ROP groups had significantly lower cognitive and motor composite scores compared with the non-ROP group. After adjusting for GA and male gender, the severe ROP and mild ROP groups had significantly lower cognitive ($-5.1$ and $-3.7$, respectively), language ($-3.8$ and $-1$, respectively), and motor ($-3.8$ and $-3.1$, respectively) mean composite scores compared with the non-ROP group.

**The Effects of ROP Severity and Neonatal Risks on NDI Outcome**

The univariate logistic regression model showed that lower GA and birth body weight, male gender, low 5-min Apgar scores, RDS requiring surfactant therapy, postnatal steroid use, hs-PDA requiring intervention, severe IVH, NEC, cPVL, BPD, lower body weight growth, and a higher percentage of duration under IMV during admission were associated with NDI (online suppl. Table S4). Severe and mild ROP were also the significant risk factors for NDI. Further multivariable logistic regressions of three models showed the respective contributory role of mild ROP and severe ROP to the NDI. Male, GA, hs-PDA requiring intervention, NEC, and cPVL were the risk factors for NDI in the model without including ROP classification. Male, hs-PDA requiring intervention, NEC, and cPVL were the risks factors for the model that included severe ROP/nonsevere ROP classification. In contrast, in model 3, hs-PDA requiring intervention, NEC, cPVL, and both mild ROP and severe ROP were the risk factors for NDI (Table 3). Compared with non-ROP, mild ROP and severe ROP had adjusted odds ratios of 1.90 (95% confidence interval [CI]: 1.10–3.28) and 2.75 (95% CI: 1.10–3.28).
**Table 1. Differences in the demographics, neonatal exposures, and morbidities among extremely preterm groups of non-ROP, mild ROP, and severe ROP**

| Variables | Total, N = 374 | Non-ROP, N = 157 | Mild ROP, N = 145 | Severe ROP, N = 72 | p value | Severe ROP with retinal therapy, N = 58 |
|-----------|----------------|------------------|-------------------|-------------------|---------|-------------------------------------|
| **Demographics/perinatal period** | | | | | | |
| GA, weeks, mean (SD) | 26.5 (1.5) | 27.1 (1.1)a | 26.5 (1.3)b | 25.2 (1.5)c | <0.001 | 24.9 (1.4)c |
| Birthweight, g, mean (SD) | 939 (226) | 1,005 (204)a | 951 (232)b | 771 (174)b | <0.001 | 757 (165)b |
| Male, n (%) | 215 (57) | 83 (53) | 83 (57) | 49 (68) | 0.097 | 39 (67) |
| Preeclampsia, n (%) | 61 (16.3) | 28 (17.8) | 24 (16.6) | 9 (12.5) | 0.595 | 5 (8.6) |
| Chorioamnionitis, n (%) | 48 (12.8) | 16 (10.2) | 22 (15.2) | 10 (13.9) | 0.415 | 8 (13.8) |
| Maternal education ≥college, n (%) | 175 (47) | 81 (52) | 63 (43) | 31 (43) | 0.285 | 24 (41.4) |
| Small for GA, n (%) | 58 (16) | 26 (17) | 16 (11) | 16 (22) | 0.090 | 10 (17.2) |
| Multiple gestation, n (%) | 94 (25) | 40 (25) | 37 (26) | 17 (24) | 0.947 | 15 (25.9) |

**Neonatal period**

| Variables | Total, N = 374 | Non-ROP, N = 157 | Mild ROP, N = 145 | Severe ROP, N = 72 | p value | Severe ROP with retinal therapy, N = 58 |
|-----------|----------------|------------------|-------------------|-------------------|---------|-------------------------------------|
| 5-min Apgar score <7, n (%) | 86 (23) | 31 (20) | 30 (21) | 25 (35) | 0.034 | 19 (32.8) |
| RDS requiring surfactant therapy, n (%) | 192 (51) | 52 (33)a | 94 (65)b | 62 (84)b | <0.001 | 38 (65.5)b |
| Postnatal steroid use, n (%) | 64 (17) | 11 (7)a | 25 (17)b | 28 (39)c | <0.001 | 24 (41.4)c |
| hs-PDA requiring intervention, n (%) | 207 (55) | 80 (51)a | 76 (52)b | 51 (71)b | 0.031 | 43 (71.4)b |
| Severe IVH, n (%) | 47 (13) | 3 (2)a | 29 (20)b | 15 (21)b | <0.001 | 12 (20.7)b |
| Bacteremia, n (%) | 76 (20) | 21 (13)a | 31 (21)a,b | 24 (33)b | 0.002 | 20 (34.5)b |
| NEC, n (%) | 47 (13) | 13 (8) | 23 (16) | 11 (15) | 0.103 | 10 (17.2) |
| cPVL, n (%) | 28 (7) | 4 (3)a | 16 (11)b | 8 (11)b | 0.009 | 7 (12.1)b |

**At discharge**

| Variables | Total, N = 374 | Non-ROP, N = 157 | Mild ROP, N = 145 | Severe ROP, N = 72 | p value | Severe ROP with retinal therapy, N = 58 |
|-----------|----------------|------------------|-------------------|-------------------|---------|-------------------------------------|
| PMA, weeks, mean (SD) | 38 (4) | 37 (3)a | 38 (4)b | 40 (4)c | <0.001 | 40 (4)c |
| Hospital stay, days, mean (SD) | 83 (32) | 71 (25)a | 83 (32)b | 107 (30)c | <0.001 | 110 (30)c |
| % of duration requiring O2 supplements during hospital stay, mean (SD) | 80 (14) | 78 (15)a | 80 (13)a,b | 85 (14)b | <0.001 | 86 (13)b |
| % of duration under IMV during hospital stay, mean (SD) | 12 (16) | 5 (11)a | 13 (15)b | 23 (20)c | <0.001 | 22 (20)c |
| Body weight, kg, mean (SD) | 170 (45) | 55 (35)a | 62 (43)b | 53 (74)b | <0.001 | 46 (79)b |
| Head circumference, cm, mean (SD) | −1.65 (1.05) | −1.24 (0.81)a | −1.91 (0.99)b | −2.05 (1.32)b | <0.001 | −2.24 (1.33)b |

NDI, n (%) | 39 (25)a | 66 (46)b | 44 (61)b | <0.001 | 37 (64)b |
| Cognitive impairment,* n (%) | 23 (15)a | 47 (32)b | 30 (42)b | <0.001 | 25 (43)b |
| Moderate or severe cerebral palsy, n (%) | 4 (2.5)a | 14 (9.7)b | 11 (15.3)b | <0.001 | 11 (19.0)b |
| Motor impairment,* n (%) | 26 (17)a | 42 (29)b | 32 (46)b | <0.001 | 30 (53)c |
| Profound hearing impairment, n (%) | 1 (0.6) | 3 (2.1) | 3 (4.2) | 0.354 | 2 (3.4) |
| Body weight, kg, mean (SD) | 11.8 (1.6)a | 11.3 (1.6)b | 11.0 (1.6)b | <0.001 | 10.9 (1.5)b |
| Head circumference, cm, mean (SD) | 47.6 (1.8)a | 47.2 (1.9)a | 46.5 (1.7)b | <0.001 | 46.3 (1.6)b |

* Cognitive and motor impairment by Bayley Scales of Infant and Toddler Development, third edition. # p values refer to trends across the non-ROP, mild ROP, and severe ROP groups. a, b, c The groups marked with the same a or b or c represent no difference between the groups; the groups marked with different a, b, c denote statistical significance between groups (at <0.05 level).

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**Table 2. The effects of early life mild ROP and severe ROP on neurodevelopment and growth outcomes at 24 months of CA**

| Outcomes | Non-ROP, N = 157 | Mild ROP, N = 145 | Severe ROP, N = 72 | p value | Severe ROP with retinal therapy, N = 58 |
|----------|-------------------|-------------------|-------------------|---------|-------------------------------------|
| NDI, n (%) | 39 (25)a | 66 (46)b | 44 (61)b | <0.001 | 37 (64)b |
| Cognitive impairment,* n (%) | 23 (15)a | 47 (32)b | 30 (42)b | <0.001 | 25 (43)b |
| Moderate or severe cerebral palsy, n (%) | 4 (2.5)a | 14 (9.7)b | 11 (15.3)b | <0.001 | 11 (19.0)b |
| Motor impairment,* n (%) | 26 (17)a | 42 (29)b | 32 (46)b | <0.001 | 30 (53)c |
| Profound hearing impairment, n (%) | 1 (0.6) | 3 (2.1) | 3 (4.2) | 0.354 | 2 (3.4) |
| Body weight, kg, mean (SD) | 11.8 (1.6)a | 11.3 (1.6)b | 11.0 (1.6)b | <0.001 | 10.9 (1.5)b |
| Head circumference, cm, mean (SD) | 47.6 (1.8)a | 47.2 (1.9)a | 46.5 (1.7)b | <0.001 | 46.3 (1.6)b |

* Cognitive and motor impairment by Bayley Scales of Infant and Toddler Development, third edition. # p values refer to trends across the non-ROP, mild ROP, and severe ROP groups. a, b, c The groups marked with the same a or b or c represent no difference between the groups; the groups marked with different a, b, c denote statistical significance between groups (at <0.05 level).
1.33–5.67) for NDI, respectively. The model 3 had significantly better overall performance as compared to model 1 and model 2, as shown by Akaike information criterion and Log likelihood ratio test. There was no significant difference between model 1 and model 2.

**Discussion**

In this study of different levels of ROP severity in extremely preterm children, we showed a gradient of increased rates of NDI at CA 24 months across children without ROP, children with mild ROP, and children with severe ROP. ROP, mild as well as severe, was associated with a higher risk of NDI, independently of other morbidities. The model that included mild and severe ROP achieved better overall performance for NDI than the models that did not. The findings suggest that ROP, mild or severe, is a biomarker for pathological processes not only in the retina but also in the brain.

Several studies have shown an association between ROP and later NDI [9–12]. The majority of studies compared infants with severe ROP to those without severe ROP and did not separate mild ROP from non-ROP. Thus, the outcome impact of mild ROP has not been emphasized. One previous study found the severity of ROP related to functional disability at 5.5 years of age. But unfavorable visual outcome rather than ROP stages had the
greatest predictive effect [3]. The blinding ROP has decreased significantly since the improvements in neonatal care [1]. Therefore it might be believed that ROP is no longer associated with NDI. However, the most common cause of visual impairment in preterm children nowadays is brain damage causing cerebral visual impairment [20]. Our results indicate that infants with any ROP retain high risk of NDI (46–61%). Furthermore, when we defined ROP as non-ROP, mild ROP, and severe ROP, we observed that the rates of NDI increased as ROP worsened in severity. Therefore, different severity of ROP may represent the spectrum of pathological processes that are visible in the retina but also proceeding in the brain.

Several features of NVU development in immature retinal and brain have links to common pathways that in turn may be affected by insults associated with extreme prematurity [6]. Our data showed that compared to the non-ROP group, the mild ROP and severe ROP shared many adverse exposures and morbidities in the neonatal period, which included severe RDS, postnatal steroid use, severe IVH, cPVL, longer duration under IMU, and lower body weight gain. Extremely preterm birth coincides with a critical time window of NVU development in the retina as well as in the brain [6]. These data suggest that unfavorable exposures that promote the development of ROP, even mild, may also associate with deviating NVU development in immature brain.

Studies have shown that clinical risks, including severe brain injury, NEC, BPD, and severe ROP, are significantly associated with NDI outcomes [12, 21]. Our data emphasized the predictive power for NDI was significantly increased in the model that included both mild and severe ROP than the models without ROP or with severe/non-severe ROP. Severe ROP and mild ROP had a 2.75 and 1.90 times higher aOR, respectively, for NDI than those without ROP. Even though those infants with mild ROP have relatively lower risk of NDI than severe ROP, they represent a much larger proportion of extremely preterm infants. Early identification of those infants at risk for NDI is vital to achieve interventions to maximize developmental potential.

Our data showed severe ROP with retinal therapy had a higher rate of motor impairment than severe ROP without therapy. However, it was difficult to attribute the impairment to the direct effect of retinal treatment because infants with retinal treatment had significantly lower GA and body weight gain and more BPD than those without treatment [22].

There are concerns that the BSID-III underestimates developmental delay [23]. Cognitive development in infants is a dynamic process. More accurate predictions of cognitive outcomes may be obtained from the developmental trajectories rather than from a single time point measurement [24]. Definite visual outcome measurements were limited in these young toddlers. Cerebral visual impairment can occur in association with NDI in infants with ROP [25]. It is possible that some participants might have subnormal visual acuity, restriction or subnormal sensitivity of visual field function, or eye motility problems contributing to the low BSID scores [7]. Follow-up assessment using more sophisticated methods for children with ROP is important.

In conclusion, we found that mild ROP and severe ROP are both independent neonatal morbidities associated with NDI. The model including different levels of ROP severity achieved better overall performance for NDI than the model that did not. Close neurodevelopmental follow-up in extremely premature infants with any ROP is important.

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Statement of Ethics

The study was approved by the Institutional Review Boards of National Cheng Kung University Hospital (approval number [A-BR-108-013]). The preterm infants were included after written consent was obtained from their parents. There is no figure or video of any recognizable patient in this manuscript.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Chao-Ching Huang participated in the design of the study, prepared the data, provided the interpretation of the data, and drafted the initial manuscript; Chi-Hsiang Chu participated in the design of the study, conducted the statistical analyses, and co-drafted the initial manuscript with Chao-Ching Huang; Yen-Kuang Lin participated in the statistical analyses and the interpretation of the data; Yung-Chieh Lin participated in preparing the data; Hsiu-Mei Wang participated in interpretation of the data; Ying-Chao Chang conceptualized and designed the study, drafted the final manuscript, and collaborated with Chi-Hsiang Chu and Yen-Kuang Lin to review the statistical analyses.

Data Availability Statement

The data analyzed in this study were obtained from Premature Baby Foundation of Taiwan, and the authors did not obtain permission to publicly share these data. Researchers interested in using the data must apply for an acceptance from Premature Baby Foundation of Taiwan (pbf@pbf.org.tw).

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