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Original Article

Retinopathy of Prematurity in Late Preterm Twins with a Birth Weight Discordance: Can it be Predicted by Artificial Intelligence?

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Abstract

Objectives: The objective is to predict the development of retinopathy of prematurity (ROP) in discordant twins using a machine learning approach.

Methods: The records of 640 twin pairs born at 32–35 weeks gestational age (GA) with birth weight (BW) discordance were evaluated retrospectively. The infants' gender, GA, postmenstruel age at examination, BW, discordance rate, ROP Stages and Zones, and treatment options were recorded. The variables were used to develop a model to predict the development of ROP. Machine learning models were used for algorithm training and 10-fold cross-validation (CV) was applied for validation. The main measures were reported as sensitivity, specificity, receiver operating characteristic curve, and the area under the curve.

Results: A total of 640 twin pairs underwent ophthalmic examination, of which 55 (4.3%) were ROP. The infants' GA was 33.56±1.01 weeks (32–35 weeks) and BW was 1996±335 g (1000–3400 g). The mean discordance rate of the infants was 11.8±9.7% (0.0–53.9%). Using operating points, the Decision Tree algorithm detected ROP prediction with 71% sensitivity and 80% specificity in CV, while the Multi-Layer Perceptron algorithm detected 70% sensitivity and specificity. In addition, the X-Tree and Random Forest algorithms detected ROP prediction with 84% and 80% specificity, respectively.

Conclusion: The results of this study support that BW discordance may be effective in the development of ROP in preterm twins and that artificial intelligence models can predict the development of ROP in accordance with clinical findings.

Keywords: Artificial intelligence, machine learning, preterm, retinopathy of prematurity, twin

Introduction

Retinopathy of prematurity (ROP), still one of the leading causes of childhood blindness worldwide, is a proliferative vascular disorder of the developing retina that develops in premature infants with early gestational age (GA) and low birth weight (BW). Due to the developments in neonatal care, the survival rate of premature infants and therefore the number of infants at risk for ROP is increasing worldwide (1,2). In addition to low BW and early GA, preterm comorbidities such as respiratory distress syndrome, intraventricular hemorrhage,

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necrotizing enterocolitis and sepsis, medical interventions such as mechanical ventilation and blood transfusion, maternal factors such as preeclampsia and chorioamnionitis are also associated with the development of ROP (3,4). On the other hand, recent studies have shown that more mature infants in developing countries may develop ROP due to exposure to risk factors and may require treatment (5-8). Although it is still a controversial issue that multiple pregnancies are a risk factor for ROP, it has been reported that ROP may develop in multiple pregnancies due to the increased risk of preterm birth and low BW (9-11). Since twin pairs have the same GA and similar maternal and prenatal environment, twin studies are important in evaluating the impact of BW and risk factors on the development of ROP. Twin discordance caused by the weight difference between fetuses in twin pregnancies is relatively common in multiple pregnancies. Discordance between twins was rated as a 15–25% difference in BW by the American College of Obstetricians and Gynecologists (12). However, due to the differences in the discordance rates of the studies, the results of the studies evaluating the relationship between twin BW discordance and ROP may contradictory (13-15).

In recent years, the use of predictive models that can guide the prediction of infants at high risk of developing ROP based on clinical findings has been increasing. Reid and Eaton. noted that machine learning, one of the artificial intelligence (AI) applications, focuses more on ROP in pediatric ophthalmology and produces results that will rival clinicians (16).

The purpose of our study was to predict the development of ROP in discordant twins using a machine learning approach (MLA).

Methods

The Ethical Review Committee approved this study (2023/01), which performed in line with the standards of the Declaration of Helsinki for research involving human subjects.

The study included 640 twins born at 32–35 weeks GA with BW discordance from April 2010 to April 2022. Neonates with inadequate data, congenital eye anomaly, and twin–twin transfusion syndrome were excluded from the study. The infants' gender, GA, post menstruel age (PMA) at examination, BW, discordance rate, ROP Stages and Zones, and treatment options were recorded. The discordance rate between the BW of twin pairs was calculated for each twin pair as" BW difference/larger twin BW ×100%.

Premature infants with GA <34 weeks and BW ≤1700 g or GA ≥34 weeks and BW>1700g, whose clinical course was unstable during their hospitalization, were screened for ROP according to the national screening guideline (17). ROP screening of premature infants was first performed at the 4–6 weeks after birth. Pupils were dilated by applying 0.5% tropicamide (Tropamid, Bilim Pharmaceuticals, Türkiye) and 2.5% phenylephrine (Mydfrin, Alcon, USA) 2 or 3 times every five minutes. Topical anesthesia with 0.5% proparacaine hydrochloride (Alcaine, Alcon, USA) was applied just before the examination. Fundus examination was performed using a binocular indirect ophthalmoscope and a 20-diopter lens using a pediatric eye speculum and scleral depressor. According to the International Classification of ROP, third edition (ICROP-3), ROP examination findings of the infants were evaluated (18). Control examinations were scheduled at 1 or 2-week intervals according to the ROP findings. Infants with normal retinal vascularization were evaluated by calling them for a 6th month follow-up.

Statistical Analysis

Statistical analyzes were performed with Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA) version 25.0. Categorical data were presented as numbers (n) and percentage (%) and descriptive data as mean±standard deviation. Machine learning algorithms were used to predict the development ROP in discordance twins. The data of the infants included in the study were recorded as a dataset and divided into two subgroups for modeling (training) and testing. The variables of gender, GA, BW, discordance rate, and PMA at examination were used to develop a model to predict the development of ROP in twin pairs. X-tree, Random Forest (RF), Decision Tree (DT), K-Nearest Neighborhoods (KNN), Support Vector Machine (SVM), Multi-Layer Perceptron (MLP) and Naive Bayes machine learning models were used for algorithm training. The performance of the predictive model was evaluated using cross-validation (CV) to maximize model fit in the dataset. At each iteration, 90% of the data is used for training (n=1152 infants) and 10% for validation (testing) (n=128 infants), ensuring that each variable in the dataset is estimated exactly once. Finally, model performance was evaluated using the test set. Model evaluation was reported as sensitivity and specificity and was graphically described via the receiver operating characteristic (ROC) curve. In addition, the quantitative performance of the model was summarized by the area under the curve (AUC). A summary of the study procedure is shown in Figure 1.

Results

A total of 640 twin pairs (1280 preterm infants) underwent ophthalmic examination retrospectively, of which 615 (48%) were female and 665 (52%) were male. The infants' GA was 33.56±1.01 weeks (32–35 weeks) and BW was 1996±335 g (1000–3400 g). The examination was performed at a mean PMA of 38.79±2.31 weeks (range: 35.0–53.4 weeks). The mean discordance rate of the infants was 11.8±9.7 % (0.0–53.9%).

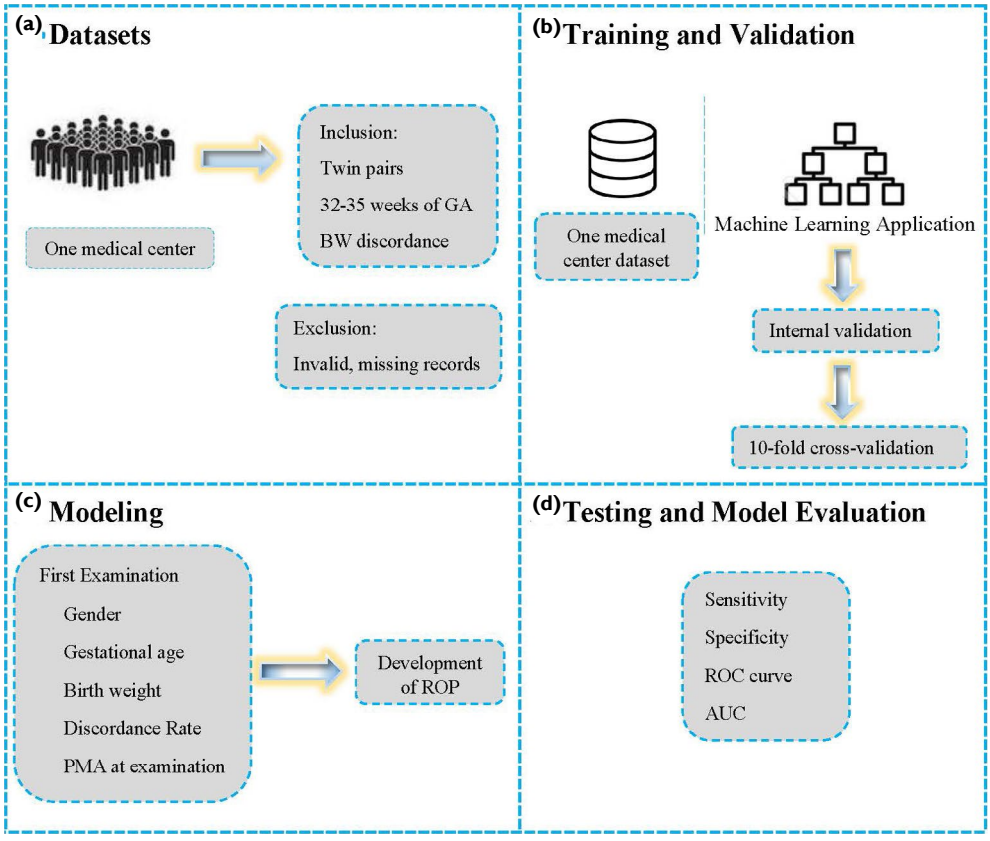

Figure 1. A summary of the study procedure. **(a)** One ophthalmic center records were included. Only twin pairs born at 32–35 weeks of gestation with birth weight (BW) discordance were included in the study. **(b)** The variables such as gender, gestational age, BW, discordance rate, and postmenstruel age at examination were used to develop a model. **(c)** We used machine learning models for algorithm training and 10-fold cross-validation for validation. **(d)** Model evaluation was reported as sensitivity and specificity and was graphically described via the receiver operating characteristic curve and the quantitative performance of the model was summarized by the area under the curve.

Bilateral ROP was found in 52 of the infants included in the study and unilateral ROP was found in 3 of them. Of the 55 (4.3%) infants detected ROP, 93 eyes of 48 infants had stage I ROP and 14 eyes of 7 infants had stage II ROP. Again, 41 eyes of 21 infants had ROP in zone II and 66 eyes of 34 infants had ROP in zone III. Plus disease and also treatment requirement was not found in infants with ROP. Demographic data and ROP findings of infants are presented in Table 1.

Among the machine learning algorithms used for analysis such as X-tree, RF, DT, KNN, SVM, MLP and Naive Bayes, DT, and MLP algorithms more prominently showed higher performance in predicting ROP development. Therefore, the analyzes are mostly reported based on DT and MLP algorithms. Using operating points, the DT algorithm detected ROP prediction with 71% sensitivity and 80% specificity, while the MLP algorithm detected ROP prediction with 70% sensitivity and specificity, in CV. On the other hand, the X-Tree and RF algorithms detected ROP prediction with 84% and 80% specificity, respectively. A ROC and also AUC of the predictive models, representing the relationship between sensitivity and specificity is shown in Figure 2.

Discussion

To the best of our knowledge, this is the first study to evaluate ROP development using AI algorithms in late preterm discordant twins. In the present study, we observed that machine learning algorithms were able to predict ROP with 70% sensitivity and 80% specificity in twin infants born at 32–35 weeks of gestation with BW discordance.

In the study of Zloto et al., in which they investigated the effect of BW on the development of ROP in preterm discordant twins born before 34 weeks GA, ROP was found to be significantly higher in small twins (8.9%), and it was stated that BW was the primary factor in the ROP development independent of GA (19).

In this study, discordance was defined as a BW difference of ≥20%, and the mean discordance rate was 35%. As a result, it was stated that the significant discordance between

Table 1. Demographic data and ROP findings of infants

Gestational age (weeks)	
Mean±SD (Range)	33.56±1.01 (32–35)
Birth weight (g)	
Mean±SD (Range)	1996±335 g (1000–3400 g)
Gender	
Female (n, %)	615 (48)
Male (n, %)	665 (52)
PMA at examination (weeks)	
Mean±SD (Range)	38.79±2.31 (35.0–53.4)
Discordance Rate	
Mean±SD (Range)	11.8±9.7 (0.0–53.9)
Zone	
Zone II (n, %)	21 (1.64)
Zone III (n, %)	34 (2.65)
Stage	
Stage I (n, %)	48 (3.75)
Stage II (n, %)	7 (0.54)

PMA: Postmenstrual age; SD: Standard deviation.

the twins was effective in the development of ROP and allowed the role of BW to be evaluated.

In the study of Fellow et al., in which 26 discordant twins were analyzed, including BW, GA, gender, and highest ROP stage, discordance was defined as 15%. While the rate of advanced-stage ROP was 38% in low BW babies, this rate was 23% in high BW babies. Furthermore, while treatment requirement was found in two infants with high BW, ROP regressed spontaneously in twins with lower BW (15).

Contrary to these studies, Wang et al. and Woo et al. found no significant difference in the development of ROP between twin pairs in their study with infants with a discordance rate <15% (14,20).

In our study, no minimum value for the discordance rate was recorded. While ROP was detected in 4.3% of the patients, no treatment was required and spontaneous regression was observed in all patients. Considering the studies in the literature, these results suggest that the inclusion of mature infants in the study may cause this situation (5-8,15).

In recent years, the use of predictive models that can guide disease prediction and follow-up based on clinical findings has been increasing. As seen previously in the literature, most ML applications in pediatric ophthalmology have focused on ROP (16). Nisha et al. observed that machine learning algorithms can measure the differences in decision-making between ROP experts and trainees, thus increasing the

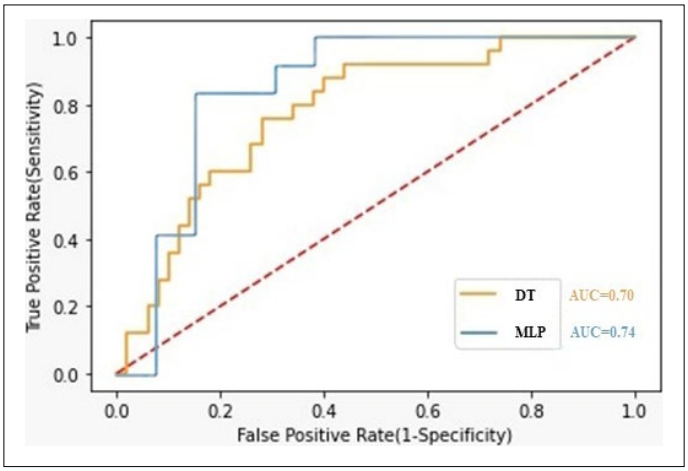

Figure 2. A receiver operating characteristic curve and area under the curve of the predictive models.

accuracy of diagnosis and helping to control the training process (21). In another study, retinal vasculature in a model of oxygen-induced retinopathy was automatically assessed using an MLA (22).

Advances in retinal imaging have facilitated the emergence of AI-based assessments for ROP (23). Previously, fundus images were manually segmented to evaluate features such as vessel diameter and tortuosity, but with recent developments, convolutional neural networks-algorithms that do not require subjective feature descriptions have been used. Tan et al. detected plus disease with 97% sensitivity and 98% negative predictive value, which is important in the diagnosis of ROP disease with the model they developed (24). It has also been shown that ROP detection can be predicted with higher sensitivity and specificity as the algorithms used progress (25,26). In the SUNDROP study, in which 608 preterm infants were evaluated, the sensitivity was 100% and the specificity was 99.8% in the detection of cases with ROP requiring treatment when compared with indirect binocular ophthalmoscopy (27).

Today, although AI applications based on the evaluation of retinal images are prominent in ROP, MLA based on automatic grading of retinal images, which reduces the subjectivity of fundus examination, continues to be used. In our study, we predicted the development of ROP in twin pairs with BW discordance using machine learning algorithms and found 70% sensitivity and 80% specificity in ROP prediction. Because the infants included in the study were in the late preterm period and the incidence of ROP decreased as BW and GA increased, may have caused our estimation rates to be lower than other studies in the literature (25-27). However, this is an expected result.

The limitations of our study are the retrospective design, small sample size, and absence of perinatal risk factors that may affect the development of ROP. Since twins with BW

discordance are a special group, evaluations were made on a small sample size. It may be remarkable to evaluate the performance of the prediction algorithm in premature infants with large sample sizes and diversified data. In addition, the small number of infants with ROP included in the study may also have affected the evaluation results.

Conclusion

The results of this study support that BW discordance may be effective in the development of ROP in preterm twins and that AI models can predict the development of ROP in accordance with clinical findings.

Disclosures

Ethics Committee Approval: The Ethical Review Committee approved this study (2023/01), which performed in line with the standards of the Declaration of Helsinki for research involving human subjects.

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Conflict of Interest: None declared.

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