ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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Performance of Artificial Intelligence in the Detection of Retinopathy of Prematurity Based on Clinical Risk Factors and Ophthalmic Examination Findings: A Observational Research-Descriptive Research

Klinik Risk Faktörleri ve Oftalmik Muayene Bulgularına Dayalı Prematüre Retinopatisinin Tespitinde Yapay Zekanın Performansı: Gözlemsel Araştırma-Tanımlayıcı Araştırma

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ABSTRACT Objective: To assess the predictive value of risk factors and ophthalmic examination findings for the development of retinopathy of prematurity (ROP) using artificial intelligence (AI) models. **Material and Methods:** A total of 453 premature infants between 22-33 weeks of gestation screened for ROP were evaluated retrospectively. The infants' perinatal risk factors (multiple births, small for gestational age, neonatal sepsis, etc) and ophthalmic examination findings were recorded. Random Forest model were trained with 10-fold cross validation using these variables to predict ROP. Accuracy, specificity, receiver operating characteristic curve, and area under the curve metrics were used to evaluate algorithm performance. **Results:** The model trained on all variables achieved 85% accuracy and 90% specificity in predicting ROP. On the other hand, the model trained on gestational age (GA), birth weight (BW) and perinatal risk factors achieved higher accuracy (87%) and specificity (90%) in predicting ROP compared to the model trained on GA and BW alone (76% accuracy and 82% specificity). When each variable was evaluated individually, the most effective factors were found to be total days on oxygen, GA, multiple birth and BW, respectively. In addition, the model was able to detect infants with stage II ROP (90% accuracy, 96% specificity) and zone III ROP (93% accuracy, 99% specificity) with higher accuracy and specificity. **Conclusion:** In addition to prematurity, exposure to perinatal risk factors is important in the development of ROP, and the evaluation of the effect of these factors using AI may support ROP specialists in the clinical management of infants.

Keywords: Artificial intelligence; retinopathy of prematurity; preterm; machine learning

ÖZET Amaç: Bu çalışmanın amacı, yapay zekâ (YZ) modelleri kullanılarak prematüre retinopatisi [retinopathy of prematurity (ROP)] gelişiminde risk faktörleri ve oftalmik muayene bulgularının öngörücü değerinin değerlendirilmesidir. **Gereç ve Yöntemler:** ROP açısından tarama yapılan, 22-33 haftalık gebeler arasında doğan 453 prematüre yenidoğanın muayene bulguları geriye dönük değerlendirildi. Yenidoğanlara ait perinatal risk faktörleri (çoklu doğum, gestasyonel yaşa göre küçük doğum, neonatal sepsis vb.) ve oftalmolojik muayene bulguları kaydedildi. Bu değişkenler kullanılarak 10 katlı çapraz doğrulama ile ROP'u tahmin etmek için Rastgele Orman modeli eğitildi. Algoritma performansını değerlendirmek için doğruluk, özgüllük, alıcı işletim karakteristiği eğrisi ve eğrinin altındaki alan ölçümleri kullanıldı. **Bulgular:** Tüm değişkenler kullanılarak eğitilen modelin, ROP'u tahmin etmede %85 doğruluk ve %90 özgüllüğe ulaştığı görüldü. Gebelik yaşı (GY), doğum ağırlığı (DA) ve perinatal risk faktörleri ile eğitilen modelin, yalnızca GY ve DA ile eğitilen modele kıyasla (%76 doğruluk ve %82 özgüllük) ROP'u tahmin etmede daha yüksek doğruluk (%87) ve özgüllük (%90) elde ettiği tespit edildi. Her değişken tek tek değerlendirildiğinde en etkili faktörlerin sırasıyla toplam oksijen günü, GY, çoklu doğum ve DA olduğu bulundu. Ayrıca, modelin evre II ROP'lu (%90 doğruluk, %96 özgüllük) ve bölge III ROP'lu (%93 doğruluk, %99 özgüllük) bebekleri daha yüksek doğruluk ve özgüllükle tespit edebildiği görüldü. **Sonuç:** Prematüritenin yanı sıra perinatal risk faktörlerine maruziyet ROP gelişiminde önemlidir ve bu faktörlerin etkisinin YZ kullanılarak değerlendirilmesi, ROP uzmanlarına yenidoğanların klinik takibinde destek sağlayabilir.

Anahtar Kelimeler: Yapay zekâ; prematüre retinopatisi; prematüre; makine öğrenimi

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Retinopathy of prematurity (ROP), which can often be prevented with early diagnosis and treatment, remains one of the leading causes of childhood blindness. With advances in neonatal care, particularly in low- and middle-income countries, the survival of very preterm infants and the incidence of ROP has increased significantly.[1-3] The risk of ROP is influenced by multiple antenatal, perinatal and postnatal factors, including multiple births (MB), being small for gestational age (SGA), duration of mechanical ventilation, bronchopulmonary dysplasia (BPD), red blood cell (RBC) transfusions, patent ductus arteriosus (PDA), chorioamnionitis, neonatal sepsis, necrotizing enterocolitis (NEC) and intraventricular hemorrhage, as well as prematurity.[4,5]

Clinical diagnosis of ROP may vary due to interobserver variability.[6-8] This variability has encouraged the use of artificial intelligence (AI)-based diagnostic tools that rapidly identify fundus images requiring further evaluation, thereby improving diagnostic accuracy, efficiency, and objectivity.[9,10] In recent years, significant advances have been made in the field of AI and several studies have shown promising results. AI can be broadly categorized into machine learning (ML) and its subset, deep learning (DL). DL algorithms, which are widely used in the analysis of complex medical images, have been successfully applied to detect retinal diseases such as diabetic retinopathy, glaucoma, age-related macular degeneration, and cataracts.[11-14] In ROP, most ML and DL studies have focused on identifying plus and preplus disease.[15,16] while models incorporating clinical features such as ROP stage and zone, alongside risk factor analysis, are relatively rare.[17,18]

The purpose of our study were (1) to evaluate perinatal risk factors and ophthalmic examination findings as a predictive variable for ROP development, (2) to predict ROP stage and zone of ROP from these variables and (3) to evaluate the algorithm's ability to discriminate ROP stages and zones by comparing infants with and without ROP.

MATERIAL AND METHODS

This retrospective study was approved by the Ethical Review Committee (date: April 5, 2023; no: AEŞH-EK1-2023-071) and adhered to the tenets of the Declaration of Helsinki for research involving human subjects. Informed consent was obtained from the parents or legal guardians of all participants.

DATA SETS

A total of 453 premature infants who underwent ROP screening between January 2021-December 2022 based on national screening guideline were retrospectively evaluated.[19] ROP screening was performed using a binocular indirect ophthalmoscope with a 20 D and/or 28 D lens. The data were evaluated by two experienced ophthalmologists (EKY, CK) who had experience with ROP. Of these, 277 infants were excluded due to incomplete data. In addition to demographic information and ophthalmic examination findings (ROP stage, zone and presence of plus disease), perinatal risk factors were recorded. These included MB, SGA (<10th percentiles), duration of invasive mechanical ventilation (days), BPD [(oxygen requirement >36 weeks postmenstruel age (PMA)], RBC transfusions (more than twice), PDA requiring treatment, chorioamnionitis, neonatal sepsis (culture positive), NEC (≥modified Bell's stage 2), total days on oxygen (TDoO). The ophthalmic examination findings were documented based on the International Classification of ROPs, 3rd edition.[20]

Infants with "type I ROP" received laser photocoagulation (LPC) based on the Early Treatment for Retinopathy of Prematurity study.[21] As indicated in the Bevacizumab Eliminates Angiogenic Threads of ROP study, intravitreal bevacizumab (IVB) treatment was administered to infants with zone I ROP, and also posterior zone II ROP, in whom the ROP line was posteriorly close to the zone I.[22]

DEVELOPMENT OF ML ALGORITHM

For algorithm training, Random Forest (RF), Decision Tree (DT), X-tree, Support Vector Machine, Multi Layer Perceptron, K-Nearest Neighborhoods and Naive Bayes ML models were used. Analyses were reported according to RF because of its significantly higher performance in predicting ROP development among the algorithms. The determining factors in choosing this architecture are that it could work effectively with both categorical and continuous

data, that noise and errors in the data do not affect the generalization ability, and that it was a model that reduces the risk of overfitting since it is created by combining multiple DT models. The dataset comprising demographic, ophthalmological, and perinatal data was divided into modeling (training) and validation (testing) sets. Model performance was evaluated using 10-fold cross-validation (CV). The samples were randomly divided into 10 equally sized sub-samples in each segment to ensure homogeneity. Therefore, in each trial, 90% of the data was used for training (n=408 infants) and 10% for testing (n=45 infants). In this way, each subset was used as both training and test data, thus a homogeneous distribution was achieved and the risk of memorization of the model was reduced. A summary of model is shown in Figure 1.

STATISTICAL ANALYSIS

The SPSS (SPSS Inc., Chicago, Illionis, USA) version 25.0 program package was used for statistical analysis. Descriptive data were presented as mean±standard deviation and categorical data as numbers (n) and percentage (%). Model evaluation

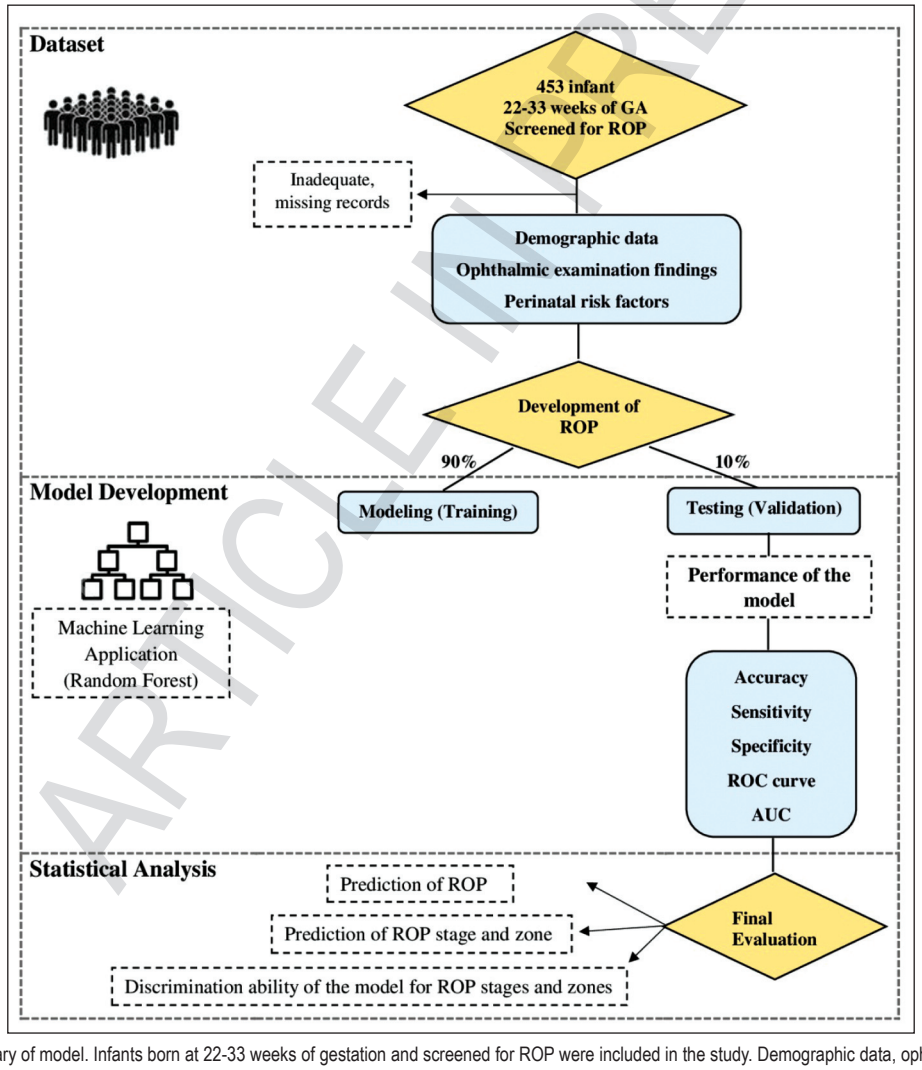

FIGURE 1: A summary of model. Infants born at 22-33 weeks of gestation and screened for ROP were included in the study. Demographic data, ophthalmic examination findings and perinatal risk factors of the infants were used to develop a model. Machine learning model was used for algorithm training and 10-fold cross validation for validation. Performance of the model was expressed as accuracy, sensitivity and specificity and also graphically described via the ROC curve and summarized by the AUC for predicting ROP development and the algorithm's ability to predict and discriminate ROP stages and zones.

GA: Gestational age; ROP: Retinopathy of prematurity; ROC: Receiver operating characteristic; AUC: Area under the curve

was expressed as accuracy and specificity for predicting ROP development also ROP stages and zones. On the other hand, the effect of each variable on the accuracy value for ROP prediction was calculated using the feature selection (all box x) method. Furthermore, the algorithm's ability to discriminate ROP stages and zones by comparing infants with and without ROP was analyzed graphically via the receiver operating characteristic (ROC) curve produced by plotting between true positive rate (sensitivity) and false positive rate (1-spesificity) and summarized by the area under the curve (AUC).

RESULTS

CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF INFANTS

The study included 453 infants with a mean gestational age (GA) of 30±2 weeks and a mean birth weight (BW) of 1513±443 g. Among them, 140 (93.3%) had bilateral ROP and 10 (6.7%) had unilateral ROP. LPC was administered to 6 infants (1.3%) with Type I ROP at a mean PMA of 36.09±2.31 weeks and all of these infants had plus disease. No infant in the cohort received IVB treatment. Notably, there were no infants of advanced ROP (stage III-V or zone I) during follow-up. Spontaneous regression of ROP was observed in 144 (96%) infants followed up with a diagnosis of Type 2 ROP. Demographic data of the infants, ophthalmic examination findings, and risk factors that may be potential predictors for the development of ROP are shown in Table 1.

TABLE 1: Demographic data, ophthalmic examination findings and perinatal risk factors of infants

GA (weeks)	$\bar{X}$±SD	30±2
	(Range)	(22-33)
BW (g)	$\bar{X}$±SD	1513±443 g
	(Range)	(525-2,880 g)
Gender	Female (n, %)	211 (46.6%)
	Male (n, %)	242 (53.4%)
PMA at examination (weeks)	$\bar{X}$±SD	34.67±2.45
	(Range)	(27.57-38.86)
Zone	Zone II (n, %)	120 (80%)
	Zone III (n, %)	30 (20%)
Stage	Stage I (n, %)	87 (58%)
	Stage II (n, %)	63 (42%)
Type 1 ROP (required treatment)	n, %	6 (1.3%)
PMA at treatment (weeks)	$\bar{X}$±SD	36.09±2.31
	(Range)	(32.14-38.86)
Perinatal risk factors		
Multiple births	n, %	204 (45%)
SGA<10th Percentile	n, %	79 (17.4%)
Duration of invasive mechanical	$\bar{X}$±SD	3.5±13.5
ventilation (days)	(Range)	(0-192)
BPD (oxygen requirement>36 weeks PMA)	n, %	259 (57.1)
RBC transfusions (more than twice)	n, %	41 (9%)
PDA requiring treatment	n, %	88 (19.4%)
Chorioamnionitis	n, %	10 (2.2%)
Neonatal sepsis (culture positive)	n, %	6 (1.32%)
NEC (≥stage 2)	n, %	4 (0.9)
Total days on oxygen	$\bar{X}$±SD	20.2±32.0
	(Range)	(0-271)

GA: Gestational age; SD: Standard deviation; BW: Birth weight; PMA: Postmenstrual age; ROP: Retinopathy of prematurity; SGA: Small for gestational age; BPD: Bronchopulmonary dysplasia; RBC: Red blood cell; PDA: Patent ductus arteriosus; NEC: Necrotizing enterocolitis

PERFORMANCE OF THE ML MODEL FOR ROP PREDICTION

The results showed that the trained model evaluated using 10-fold CV could achieve 0.85 accuracy, 0.90 specificity, and 0.83 AUC to detect infants with ROP. Models using only GA and BW showed 0.76 accuracy and 0.82 specificity, while models trained with perinatal risk factors had 0.73-0.82. The highest AUC value (0.85) was obtained when the model was trained using selected features, including GA, BW, and perinatal risk factors, achieving an accuracy of 0.87 and a specificity of 0.90. Gender and PMA at examination were found to be the least predictive. Of the models using each perinatal risk factor, the model using MB and TDoO together showed an accuracy of 0.72 and a specificity of 0.84. In addition, we found 0.83 accuracy and 0.89 specificity in the model using MB, TDoO, GA and BW together (Figure 2).

As shown in Table 2, evaluation of each variable's effect on model accuracy revealed that TDoO (19.93) contributed most positively to ROP prediction. In contrast, variables such as PMA at examination (-8.77), chorioamnionitis (-2.09), and NEC (-2.09) were found to negatively impact the model's accuracy. This suggests that excluding these variables may enhance model performance, potentially by reducing overfitting or eliminating irrelevant noise.

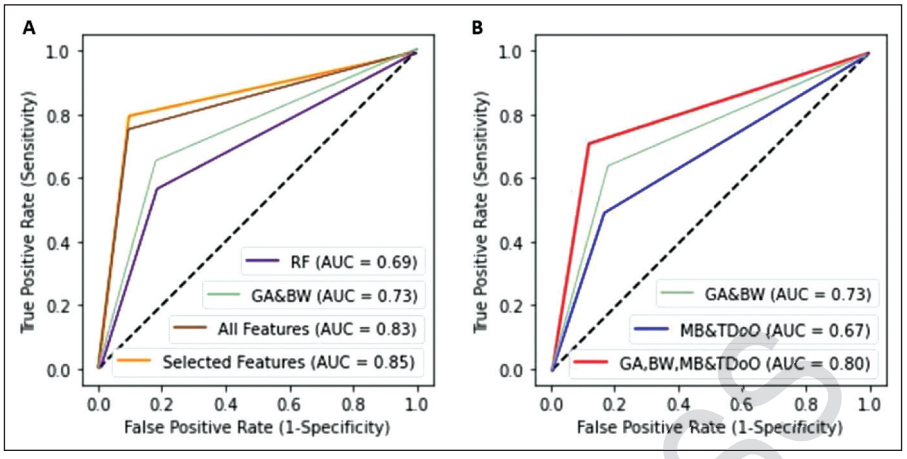

FIGURE 2: The ROC curves and AUC values of the trained model for ROP prediction. (A) Brown line (all features) defines the analysis with all variables such as gender, GA, BW, PMA at examination, and perinatal RF. Yellow line (selected features) defines the analysis with variables except gender and PMA at examination. Green line defines the analysis with GA and BW. Purple line defines the analysis with only perinatal RF. (B) Red line defines the analysis with GA, BW, MB and TDoO. Blue line defines the analysis with MB and TDoO. Green line defines the analysis with GA and BW.
RF: Risk factors; AUC: Area under the curve; GA: Gestational age; BW: Birth weight; TDoO: Total days on oxygen

TABLE 2: The effect of each variable on the accuracy value for ROP prediction

Variables	Accuracy
GA (weeks)	**17.74**
BW (g)	**15.45**
Gender	2.29
PMA at examination (weeks)	-8.77
Perinatal risk factors	
Multiple births	**15.55**
SGA< 10th Percentile	0.09
Duration of invaziv mechanical ventilation (days)	2.39
BPD (oxygen requirement > 36 weeks PMA)	6.77
RBC transfusions (more than twice)	6.77
PDA requiring treatment	4.58
Chorioamnionitis	-2.09
Neonatal sepsis (culture positive)	6.77
NEC (≥ stage 2)	-2.09
Total days on oxygen	**19.93**
ROP prediction	**85.44**

GA: Gestational age; BW: Birth weight; PMA: Postmenstrual age;
SGA: Small for gestational age; BPD: Bronchopulmonary dysplasia;
: Red blood cell; PDA: Patent ductus arteriosus; NEC: Necrotizing enterocolitis;
ROP: Retinopathy of prematurity

Besides, when all variables were used, the models achieved an accuracy and specificity of 0.76-0.79 for predicting the stage of ROP, and 0.81-0.84 for predicting the zone of ROP, respectively. Model achieved relatively higher performance in predicting zone of ROP.

The accuracy and specificity values for the model's ability to predict ROP severity were 0.85-0.90, respectively, in discriminating between ROP versus no ROP, 0.82-0.94 between stage I ROP versus stage II and no ROP, and 0.90-0.96 between stage II ROP versus stage I and no ROP. On the other hand, the accuracy and specificity values of the model for the ability to predict the zone of ROP were 0.85-0.90 respectively, to discriminate between ROP versus no ROP, 0.87-0.93 for zone II ROP versus zone III and no ROP and 0.93-0.99 for zone III ROP versus zone II and no ROP. However, as shown in Figure 3, the AUC value for zone III ROP versus zone II and no ROP was only 0.51, indicating poor discriminatory ability, whereas the AUC for zone II ROP versus zone III and no ROP was 0.80, suggesting a better classification performance for zone II cases.

The ROC curve and AUC values of the model for the discrimination of ROP stages and zones are shown in Figure 3. Due to the small number of infants requiring treatment, this group of infants was not included in the analysis.

DISCUSSION

To the best of our knowledge, publications with AI models focusing on and analyzing risk factors as a predictive variable in the development of ROP, as

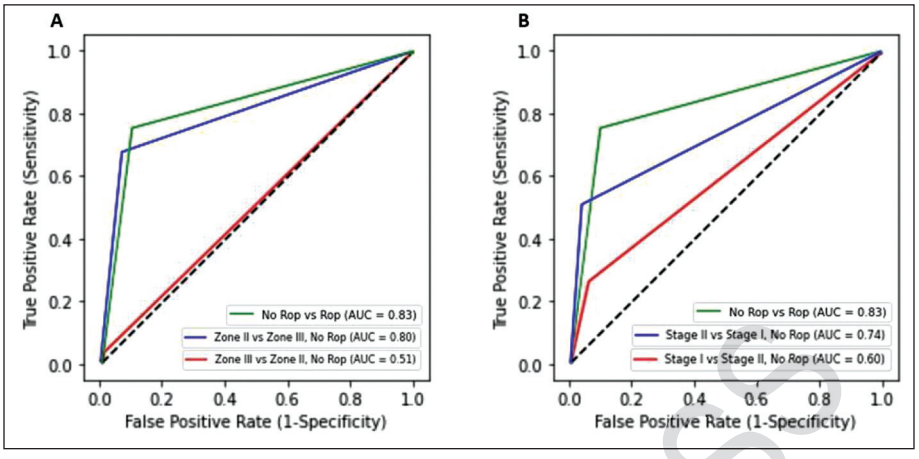

FIGURE 3: The ROC curves and AUC values of the model's discrimination ability for ROP zone **(A)** and stage **(B)**.
ROP: Retinopathy of prematurity; AUC: Area under the curve

well as ophthalmic examination findings such as pre-plus-plus disease, ROP stage and zone, are rare.[17,18] In this study, the model achieved high accuracy and specificity when trained with ophthalmic examination findings and perinatal risk factors. Moreover, the accuracy and specificity of the model increased when trained with GA, BW, and perinatal risk factors alone.

Chen et al. demonstrated that oxygen exposure can be quantified as a predictive variable for the development of ROP requiring treatment and aggressive ROP using ML (RF model).[23] In our study, when we used TDoO exposure and MB as perinatal risk factors, the RF model achieved 0.72 accuracy and 0.84 specificity.

Although AI has been explored for early detection of neonatal conditions such as sepsis, BPD, PDA, and NEC, their roles in ROP prediction remain unclear.[24-28]

In our study, we found that perinatal risk factors such as culture-positive neonatal sepsis, PDA requiring treatment, duration of invasive mechanical ventilation, BPD and blood transfusion had positive effects on the prediction of ROP, but not as much as the TDoO and MB. Conversely, we observed that SGA was almost ineffective in predicting ROP, while NEC and chorioamnionitis had a negative effect on predicting ROP. One possible explanation is that these conditions, being severe systemic illnesses, may have led to early mortality or loss to follow-up before ROP could develop or be documented. Additionally, the low frequency of these diagnoses in the dataset may have limited the model's ability to learn meaningful patterns associated with them.

Agrawal et al. developed a model to predict zones I, II and III from fundus images where the macula may not be visible and found 98% accuracy with 2 different imaging systems. Furthermore, they noted that infants could be classified as "high risk" and "low risk" based on the zones of the vascularized retina, which could help decide on a screening and follow-up program.[29]

Tong et al. predicted the stage of ROP and plus disease with an accuracy of 0.957 and 0.896, respectively, with the DL-based model. They also noted that the model was able to distinguish stage I to stage V infants with ROP with an accuracy of 0.876, 0.942, 0.968, 0.998 and 0.999, respectively.[30]

Li et al. in the system they developed for early diagnosis and quantitative analysis of ROP stages, trained system achieved 95.93% sensitivity and 96.41% specificity with normal images, while these values are 90.21-97.67% for stage I ROP, 92.75-98.74% for stage II ROP, and 91.84-99.29% for stage III ROP. As a result, it was stated that the system achieved high accuracy in the diagnosis of stage I-III ROP and that quantitative analysis of disease characteristics could be effective in physicians' classification decisions.[31]

Huang et al. reported that with the algorithms they developed for automatic detection of early-stage ROP using fundus images, they were able to predict infants without ROP with 96.14% sensitivity and 95.95% specificity, infants with stage I ROP with 91.82% sensitivity and 94.50% specificity, and infants with stage II ROP with 89.81% sensitivity and 98.99% specificity. They stated that the proposed model provided high accuracy in the diagnosis of early-stage ROP and has the potential to assist in ROP screening.[32]

In our study, trained model achieved relatively higher performance in detecting zone of ROP (with 0.81 accuracy and 0.84 specificity) than stage of ROP (with 0.76 accuracy and 0.79 specificity). In addition, when we evaluated the ability of the model to determine the stage and zone of ROP, we found that the model was able to discriminate stage II and zone III ROP with higher accuracy and specificity (0.90-0.96 for stage II ROP and 0.93-0.99 for zone III ROP, respectively). However, as shown in Figure 3, the AUC value for zone III ROP versus zone II and no ROP was only 0.51, indicating poor discriminatory ability, whereas the AUC for zone II ROP versus zone III and no ROP was 0.80, suggesting a better classification performance for zone II cases. This means that while accuracy and specificity reflect performance at a specific threshold, the AUC provides a more comprehensive assessment of the model's discriminative ability to distinguish zone II ROP from other conditions across all possible thresholds.

Among the limitations of our study are its retrospective design, small sample size and absence of more advanced ROP, such as stage III-V ROP and zone I ROP. Due to these factors, the distribution in the dataset may change and the performance of the model in predicting the development and severity of ROP may be affected. Due to the current limitations, it may not be appropriate to generalize our results. Studies with larger numbers of infants are needed to evaluate the impact of all these factors on the ROP prediction with AI.

Technological advances are making AI a more current topic in the medical field. AI can enable testing of the efficiency, accuracy and objectivity of ROP diagnosis according to objective disease severity thresholds. Introducing AI algorithms into clinical practice can reduce workload and support ophthalmologists' decision-making processes in ROP management.

CONCLUSION

In addition to prematurity, exposure to perinatal risk factors is important in the development of ROP, and evaluating the effects of these factors with AI may benefit ROP specialists.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Eşay Kıran Yenice, Caner Kara, Dilek Ulubaş Işık, İstemi Han Çelik, Mustafa Yenice, Çağatay Berke Erdaş;* ***Design:*** *Eşay Kıran Yenice, Caner Kara, Dilek Ulubaş Işık, İstemi Han Çelik, Mustafa Yenice, Çağatay Berke Erdaş;* ***Control/Supervision:*** *Eşay Kıran Yenice, Caner Kara, Dilek Ulubaş Işık, İstemi Han Çelik, Mustafa Yenice, Çağatay Berke Erdaş;* ***Data Collection and/or Processing:*** *Eşay Kıran Yenice, Caner Kara, Dilek Ulubaş Işık, İstemi Han Çelik;* ***Analysis and/or Interpretation:*** *Eşay Kıran Yenice, Caner Kara, Dilek Ulubaş Işık, İstemi Han Çelik, Mustafa Yenice, Çağatay Berke Erdaş;* ***Literature Review:*** *Eşay Kıran Yenice;* ***Writing the Article:*** *Eşay Kıran Yenice, Caner Kara, Dilek Ulubaş Işık, İstemi Han Çelik, Mustafa Yenice, Çağatay Berke Erdaş;* ***Critical Review:*** *Eşay Kıran Yenice, Caner Kara, Dilek Ulubaş Işık, İstemi Han Çelik, Mustafa Yenice, Çağatay Berke Erdaş;* ***Materials:*** *Eşay Kıran Yenice, Caner Kara, Dilek Ulubaş Işık, İstemi Han Çelik, Mustafa Yenice, Çağatay Berke Erdaş.*

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