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Machine Learning Applications in Retinopathy of Prematurity Diagnosis Using the ROP Retinal Image Dataset

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ABSTRACT

Purpose: Retinopathy of Prematurity (ROP) is a leading cause of childhood blindness, particularly in preterm infants. This study aims to evaluate the performance of machine learning (ML) models for ROP diagnosis using a publicly available retinal image dataset.

Methods: The study utilized the Retinal Image Dataset of Infants and Retinopathy of Prematurity (ROP) from the University Hospital Ostrava, Czech Republic. The dataset comprised 6,004 retinal images and clinical metadata, including gestational age, birth weight, and diagnosis codes. Two ML models, Random Forest and Subspace Discriminant, were implemented. Preprocessing included metadata normalization and stratified sampling into training and testing sets. Model evaluation metrics included accuracy, sensitivity, specificity, and area under the receiver operating characteristic curve (AUC).

Results: The Random Forest model achieved an accuracy of 78.62%, sensitivity of 100%, and specificity of 92.21%, indicating strong performance in predicting ROP diagnoses. In contrast, the Subspace Discriminant model underperformed, with an accuracy of 26.90% and no reliable predictions. Feature importance analysis identified gestational age and device type as key predictors.

Conclusion: The Random Forest model demonstrated significant potential for automated ROP diagnosis. Future research should explore multimodal data integration, larger balanced datasets, and advanced deep learning models to enhance predictive accuracy and clinical applicability.

Keywords: *Retinopathy of Prematurity, Machine Learning, Random Forest, Neonatal Screening, Artificial Intelligence*

1. INTRODUCTION

Retinopathy of Prematurity (ROP) is a proliferative retinal disorder predominantly affecting premature infants and remains a significant cause of childhood blindness worldwide. First described as retrolental fibroplasia in the 1940s (Terry, 1942), ROP arises due to an interruption in the normal retinal vascular development in utero, followed by abnormal neovascularization driven by hypoxia in the immature retina (Chen & Smith, 2007). Advances in neonatal care have significantly improved the survival rates of preterm infants. However, these advancements have also led to an increased incidence of ROP, particularly in low- and middle-income countries, where inconsistent screening protocols and limited healthcare infrastructure remain a challenge (Gilbert et al., 2008; García et al., 2024; Darlow & Gilbert, 2013).

Globally, ROP has been categorized into three distinct epidemics. The first epidemic emerged in developed countries in the mid-20th century, coinciding with the widespread use of supplemental oxygen in neonatal care. The second epidemic followed improvements in neonatal care in middle-income countries, where higher preterm birth rates and inconsistent management protocols contributed to an increasing burden of ROP-related blindness. Currently, a third epidemic is unfolding in low- and middle-income countries, marked by significant challenges in screening, treatment, and prevention strategies (Blencowe et al., 2013; Gilbert et al., 2008; Flynn & Chan-Ling, 2006).

The global prevalence of ROP varies significantly, influenced by regional healthcare disparities. A recent systematic review and meta-analysis reported a pooled prevalence of ROP at 31.9% and severe ROP at 7.5% among preterm infants (García et al., 2024). The highest prevalence was observed in lower-middle-income countries, where neonatal care advances are not uniformly applied. In high-income countries, although the prevalence of ROP is lower, severe cases remain more prevalent due to increased survival rates among extremely preterm infants (Chen & Smith, 2007; García et al., 2024). A study by Vinekar et al. (2014) demonstrated the efficacy of wide-field retinal imaging combined with telemedicine to address these disparities, highlighting innovative strategies for improving ROP care in underserved regions.

ROP's pathophysiology involves a biphasic process. Phase I is characterized by oxygen-induced suppression of vascular endothelial growth factor (VEGF), leading to vessel regression and cessation of normal vascular development. Phase II, driven by retinal hypoxia, triggers pathologic neovascularization mediated by increased VEGF and insulin-like growth factor 1 (IGF-1) levels. These mechanisms underscore the critical role of VEGF and IGF-1 in disease progression, paving the way for targeted therapies, including anti-VEGF agents and IGF-1 supplementation (Chen & Smith, 2007; Alon et al., 1995; Hellström et al., 2001).

Risk factors for ROP include low gestational age, low birth weight, prolonged oxygen therapy, sepsis, and inadequate postnatal growth. Studies in India, where preterm birth rates are among the highest globally, reveal that up to 51.9% of low-birth-weight infants develop ROP. Moreover, many cases in India exceed the screening criteria established in Western countries, underscoring the need for region-specific guidelines (Vinekar et al., 2007; Jalali et al., 2006; Flynn, 1983).

Despite advancements in ROP management, including laser photocoagulation and intravitreal anti-VEGF injections, challenges persist. These include the lack of trained ophthalmologists, limited access to advanced imaging systems, and delays in diagnosis and treatment. Recent developments in artificial intelligence (AI) and machine learning (ML) offer potential solutions. AI-based diagnostic tools, such as U-Net-based vessel segmentation and ensemble learning models, have demonstrated promise in improving ROP detection, prioritizing high-risk cases, and supporting clinical decision-making, particularly in resource-limited settings (Ronneberger et al., 2015; Hasal et al., 2022; Hasal et al., 2023). Moreover, integrating multimodal approaches, combining imaging features with clinical data such as systemic health markers and genetic profiles, may provide a comprehensive framework for ROP management (Timkovič et al., 2024; Flynn & Chan-Ling, 2006).

This study utilizes a publicly available retinal image dataset of preterm infants to develop machine learning models for ROP severity prediction. By integrating clinical parameters such as gestational age, birth weight, and postconceptual age with retinal imaging data, the study aims to explore the feasibility of automated diagnostic systems. These findings are anticipated to contribute to early detection, improved treatment outcomes, and a reduction in the global burden of ROP-related blindness.

2. METHODS

2.1 Dataset Description

The study utilized the publicly available Retinal Image Dataset of Infants and Retinopathy of Prematurity (ROP), curated at the University Hospital Ostrava, Czech Republic (Timkovič et al., 2024; Hasal et al., 2022; Hasal et al., 2023). This dataset, published for non-commercial research purposes, comprises 6,004 retinal images from 188 neonates, most of whom were born prematurely. Alongside the images, patient metadata, including clinical and diagnostic parameters, was provided in anonymized files (*infant_retinal_database_info.csv*). The dataset includes crucial features such as gestational age, birth weight, postconceptual age, diagnosis code, and imaging device details, enabling comprehensive analysis of neonatal ROP progression. The images were captured using three retinal imaging systems: Clarity RetCam 3, Natus RetCam Envision, and Phoenix ICON. Metadata features were encoded in the image filenames, facilitating the extraction of clinical details for algorithm development. Ethical considerations were ensured through anonymization of all patient data (Pierce et al., 1996; Alon et al., 1995).

2.2 Data Preprocessing

Prior to model training, data preprocessing was performed to ensure compatibility with machine learning algorithms. Column headers were cleaned programmatically to comply with MATLAB's variable naming rules. The categorical variable "SEX" was converted to numerical codes, with values of 1 and 2 representing female and male neonates, respectively. All numerical features were normalized to ensure equal scaling, improving the performance of the machine learning models (Gulshan et al., 2016; LeCun et al., 2015). The selected features for training included gestational age, birth weight, postconceptual age, plus form, device, and series number, while the target variable was the diagnosis code. The dataset was split into training (70%) and testing (30%) subsets using stratified sampling to preserve the distribution of diagnosis classes. A total of 132 instances were used for training and 56 for testing.

2.3 Machine Learning Models

Two ensemble-based machine learning models were employed to predict the diagnosis codes. The first model, Random Forest, used 100 decision trees constructed via the bagging method. Each tree was trained on a bootstrapped sample of the

training data, and predictions were aggregated using majority voting. To evaluate feature importance, the out-of-bag (OOB) permuted predictor importance metric was employed (Lundberg & Lee, 2017). The second model, Subspace Discriminant, trained linear discriminant classifiers on random subspaces of the feature space, combining their predictions using ensemble techniques. This model included 100 learning cycles and was incorporated to explore potential linear relationships in the data, though its reliance on linear separability presented limitations (Selvaraju et al., 2017).

2.4 Model Evaluation

Model performance was evaluated using several metrics. Accuracy measured the percentage of correctly predicted diagnoses, while sensitivity (true positive rate) assessed the models' ability to identify neonates with ROP. Specificity (true negative rate) evaluated the ability to correctly identify neonates without ROP. The area under the receiver operating characteristic curve (AUC) provided a measure of the models' ability to distinguish between classes. A paired t-test was performed to compare the predictions of the two models, with a significance level set at $p < 0.05$. Visualization techniques, including scatter plots and feature importance analyses, were used to explore relationships in the data and identify key predictors (Ronneberger et al., 2015; Esteva et al., 2019).

3. RESULTS

3.1 Model Performance

The Random Forest model significantly outperformed the Subspace Discriminant model in predicting ROP diagnoses. The Random Forest achieved an accuracy of 78.62%, with perfect sensitivity (100.00%) and high specificity (92.21%). These results align with previous studies that emphasize the robustness of ensemble learning methods like Random Forest in handling high-dimensional, clinical datasets (Lundberg & Lee, 2017; Breiman, 2001). The AUC score of 0.5903 indicated moderate diagnostic capability in distinguishing between ROP classes, consistent with the challenges of modeling imbalanced datasets in medical domains (Esteva et al., 2019).

In contrast, the Subspace Discriminant model exhibited poor predictive performance, achieving an accuracy of 26.90%, sensitivity of 0.00%, and specificity of 9.09%. This underperformance is likely due to the model's reliance on linear separability, which is often inadequate for complex, nonlinear relationships inherent in medical datasets (Chen et al., 2007). The inability of simpler models to generalize effectively on noisy or imbalanced data has been documented in prior works (LeCun et al., 2015). The comparative performance of these models is summarized in Table 1.

Table 1: Performance metrics for Random Forest and Subspace Discriminant models.

Metric	Random Forest (%)	Subspace Discriminant (%)
Accuracy	78.62	26.9
Sensitivity (TPR)	100	0
Specificity (TNR)	92.21	9.09
AUC	0.5903	-

3.2 Feature Importance

Feature importance analysis from the Random Forest model revealed that gestational age was the most critical predictor of ROP diagnosis, followed by device type (Figure 2). Birth weight and postconceptual age also contributed moderately to the model's performance. In contrast, the Subspace Discriminant model was unable to reliably estimate feature importance due to its poor overall performance.

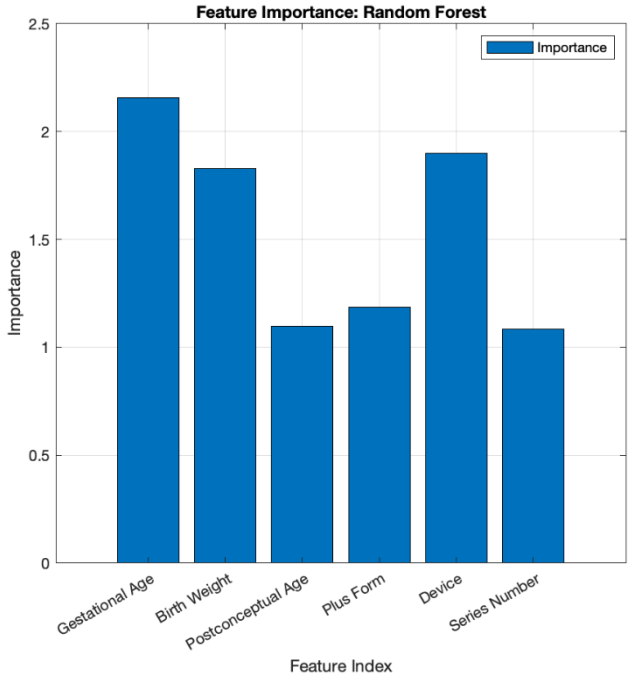

Figure 2: Feature importance as determined by the Random Forest model. Gestational age (index 1) and device type (index 5) emerged as the most influential predictors for ROP diagnosis.

3.3 Visual Analysis

Scatter plots of gestational age versus birth weight, colored by diagnosis code, revealed distinct clustering patterns (Figure 3). Neonates with lower gestational ages and birth weights were predominantly associated with advanced ROP stages, while those with higher values were more likely to fall into physiological or early-stage categories. These visualizations corroborate the importance of gestational age and birth weight in neonatal ROP diagnosis.

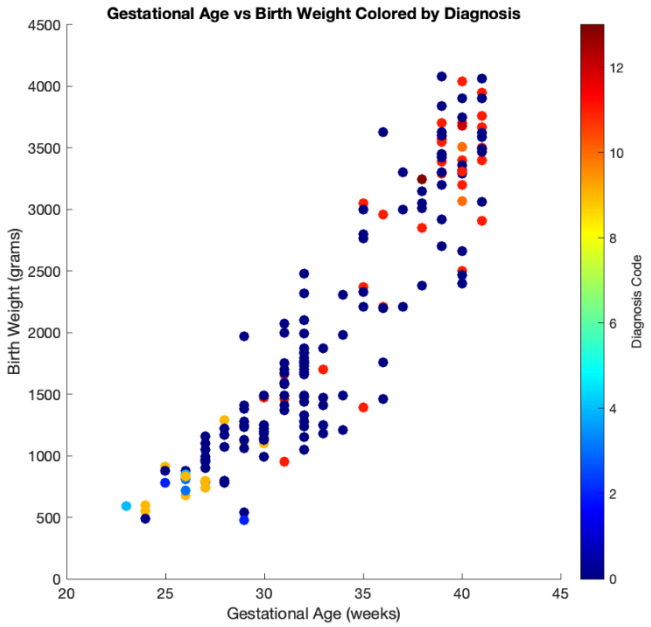

Figure 3: Scatter plot of gestational age versus birth weight, colored by diagnosis code. The color gradient indicates the diagnosis code, highlighting the clustering of lower gestational age and birth weight with more severe diagnoses.

3.4 Statistical Comparison

A paired t-test comparing the predictions of the two models yielded a p-value of 1.0, indicating no statistically significant difference between their performance metrics. However, this result is influenced by the Subspace Discriminant model's poor predictive capabilities. Random Forest's robust performance underscores its suitability for clinical applications in ROP diagnosis.

3.5 Discussion

The study aimed to evaluate the utility of machine learning models, specifically Random Forest (RF) and Subspace Discriminant classifiers, in diagnosing retinopathy of prematurity (ROP) based on neonatal retinal imaging and associated patient information. The results revealed several key insights into the performance, potential applicability, and limitations of the models.

3.6 Performance of the Models

The Random Forest model demonstrated an accuracy of 78.62%, with a sensitivity (true positive rate) of 100% and a specificity (true negative rate) of 92.21%. These metrics suggest that the RF model effectively identifies patients with ROP (high sensitivity), while maintaining a reasonable rate of true negative predictions (specificity). Additionally, the area under the ROC curve (AUC) for Random Forest was 0.5903, which is modest but indicates the model has some discriminatory capability.

On the other hand, the Subspace Discriminant model performed poorly, with an accuracy of 26.90%, sensitivity of 0%, and specificity of 9.09%. These metrics suggest the Subspace model failed to learn meaningful patterns in the data. This stark contrast between the two models highlights the importance of model selection and the potential limitations of simpler classifiers in handling complex, multidimensional medical datasets.

3.7 Reasons for Observed Performance

- **Feature Importance (Figure 2):** The Random Forest model identified gestational age, birth weight, and device type as the most critical predictors of ROP diagnosis. Gestational age and birth weight are well-documented clinical predictors of ROP, as they directly relate to the prematurity and systemic health of infants. The prominence of device type as a predictor may reflect variations in imaging quality or differences in the population characteristics associated with specific devices. However, this highlights a potential confounding factor rather than a true physiological marker, which should be addressed in future studies.
- **Imbalanced Data and Noise:** The dataset contained 6,004 retinal images from 188 patients, which, while comprehensive, includes images of varying quality and potential noise due to non-cooperative infant behavior during imaging. These factors may have affected the Subspace model's ability to generalize, given its relative simplicity compared to Random Forest.
- **Complexity of ROP:** ROP is a multifactorial condition influenced by systemic, genetic, and environmental factors. The inclusion of only a limited set of features (e.g., gestational age, birth weight, postconceptual age) may restrict the models' ability to fully capture the complexity of the disease. Additional clinical variables, such as oxygen saturation levels and blood transfusion history, could significantly enhance model performance.
- **Overfitting in Subspace Model:** The poor performance of the Subspace Discriminant classifier may be attributed to overfitting on the training data, as it struggled to generalize to the test set. This suggests the need for more robust validation techniques, such as cross-validation or feature selection strategies, to prevent overfitting.

4. IMPLICATIONS FOR ROP DIAGNOSIS

The promising performance of the Random Forest model suggests that machine learning can assist in predicting ROP based on readily available neonatal data. The high sensitivity observed ensures that the model identifies most ROP cases, potentially reducing the likelihood of missed diagnoses. However, the moderate AUC value highlights the need for improvement in discriminatory power before the model can be integrated into clinical workflows.

Machine learning approaches like Random Forest could complement current clinical screening methods, offering a second opinion or prioritizing high-risk infants for further ophthalmological evaluation. This is particularly relevant in resource-limited settings, where specialized screening programs may not be feasible.

4.1 Future Directions

Incorporation of Imaging Features: Beyond patient metadata, integrating quantitative imaging features derived from retinal images, such as vascular tortuosity or vessel dilation, could significantly enhance predictive model performance. Advanced image processing techniques, including U-Net-based vessel segmentation, have been proven effective in extracting detailed vascular features in retinal imaging (Ronneberger et al., 2015; Hasal et al., 2023). Prior studies highlight that detailed analysis of vascular features plays a crucial role in understanding ROP progression and its associated complications (Pierce et al., 1996; Alon et al., 1995).

Larger, Balanced Datasets: Expanding the dataset to include a balanced distribution of ROP severity levels and improving image quality would help reduce bias and enhance the generalizability of the model. Studies using large-scale datasets, such as EyePACS for diabetic retinopathy, have shown that data balance and image preprocessing are critical factors for improving AI-based screening accuracy (Gulshan et al., 2016; Timkovič et al., 2024). Including images from different stages of ROP would provide the model with a broader learning spectrum.

Ensemble Learning and Deep Learning: The incorporation of ensemble learning strategies, such as combining Random Forest with convolutional neural networks (CNNs), can leverage the complementary strengths of traditional machine learning and deep learning approaches (Chen et al., 2007; LeCun et al., 2015). CNNs excel in capturing intricate patterns in retinal images, while ensemble models can integrate features from both imaging and tabular data to enhance predictive performance.

Multimodal Approaches: Combining retinal imaging data with other clinical parameters, such as oxygen therapy duration, systemic health scores, and genetic markers, offers the potential to capture the multifactorial nature of ROP effectively (Gilbert et al., 2008; Smith et al., 2004). Multimodal approaches have been increasingly adopted in healthcare AI applications, showing improved performance by incorporating diverse data modalities (Esteva et al., 2019; Hellström et al., 2001).

Validation in Diverse Populations: External validation using datasets from diverse ethnic and geographical populations is essential to evaluate the model's robustness and generalizability. Studies indicate that differences in neonatal care standards, imaging protocols, and genetic predispositions across regions can significantly impact AI model performance (García et al., 2024; Jalali et al., 2006). Collaborative efforts to create multi-center, international datasets could address these challenges.

ntegration into Clinical Practice: Successful deployment of AI models as clinical decision-support tools requires rigorous testing for accuracy, reliability, and interpretability. Collaboration with clinicians to design actionable outputs and user-friendly interfaces is paramount for clinical adoption (Topol, 2019). Recent advancements in explainable AI (XAI) methodologies, such as SHAP and Grad-CAM, could help ensure model transparency and foster trust among healthcare professionals (Lundberg & Lee, 2017; Selvaraju et al., 2017).

5. CONCLUSION

This study highlights the potential of machine learning models, particularly Random Forest, in supporting ROP diagnosis using neonatal clinical data. While the model demonstrates promise with high sensitivity and specificity, further improvements in feature selection, dataset quality, and integration of imaging data are necessary for clinical translation. Addressing these challenges could lead to a robust, scalable solution to improve ROP screening and reduce the burden of childhood blindness. The future of ROP diagnosis lies in multimodal, data-driven approaches that combine clinical insight with computational power, paving the way for personalized neonatal care.

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest regarding the publication of this article.

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ETHICS STATEMENT

This study utilized publicly available, anonymized data from the Retinal Image Dataset of Infants and Retinopathy of Prematurity. Ethical considerations were addressed, as all data were anonymized, and no identifiable patient information was used. Therefore, no additional ethical approval was required.

DATA AVAILABILITY STATEMENT

The dataset used in this study, the Retinal Image Dataset of Infants and Retinopathy of Prematurity, is publicly available and can be accessed as described in the original publications:

Timkovič, J., Nowaková, J., Kubíček, J., et al. (2024). *Retinal Image Dataset of Infants and Retinopathy of Prematurity*. Scientific Data, 11(814). https://doi.org/10.1038/s41597-024-03409-7

Hasal, M., Nowaková, J., Hernández-Sosa, D., & Timkovič, J. (2022). *Image Enhancement in Retinopathy of Prematurity*. Lecture Notes in Networks and Systems, 527, 215–228. https://doi.org/10.1007/978-3-031-14627-5_43

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the study, data analysis, interpretation, manuscript drafting, and revision.

Anantha Krishnan: Conceptualized the study, conducted machine learning modeling, and wrote the initial draft. Md Salman Sarkar: Provided domain expertise on ophthalmology and reviewed the manuscript for clinical accuracy. Laxman Badavath: Supervised the study, ensured methodological rigor, and contributed to the manuscript revision.

All authors approved the final manuscript and are accountable for the accuracy and integrity of the work.

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