

Construction of a Retinopathy of Prematurity Onset Prediction Model Using the Random Forest Machine Learning Algorithm

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Research Article

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Abstract

Objective: This study aimed to refine and validate a previously developed Random Forest prediction model for the onset of Retinopathy of Prematurity (ROP), which was based on a machine learning approach.

Methods: A retrospective study was conducted on 150 neonatal cases who met the inclusion criteria and underwent ROP screening at the Department of Neonatology, Wuzhou Workers' Hospital, Guangxi, China, between January 2024 and September 2024. 1. Data on ROP-related risk factors and concurrent fundus screening results were collected by reviewing the electronic medical records (inpatient and follow-up outpatient) of the enrolled neonates. 2. The top 15 risk factors identified from five distinct machine learning models were analyzed to identify the common risk factors among them. 3. The Random Forest prediction model was validated.

Results: 1. Nine common risk factors were identified from the top 15 factors across the five machine learning models: oxygen therapy, oxygen concentration, gestational age, birth weight, anemia of prematurity, neonatal respiratory distress syndrome (NRDS), necrotizing enterocolitis (NEC), in vitro fertilization embryo transfer, and antibiotic use. 2. Validation of the Random Forest model using the dataset from Wuzhou Workers' Hospital showed good performance on the validation set: AUC: 0.892, accuracy: 77.9%, specificity: 99.3%, sensitivity: 62.9%, precision: 89.9%.

Conclusion: The Random Forest model, constructed using machine learning methods and incorporating predictive features such as oxygen therapy, oxygen concentration, gestational age, birth weight, anemia of prematurity, NRDS, NEC, in vitro fertilization embryo transfer, and antibiotic use, demonstrates good predictive value for ROP. This model holds potential for application in clinical screening of high-risk populations for retinopathy of prematurity.

Introduction

ROP is a developmental proliferative retinal vascular disease occurring in premature and low birth weight infants. ^[1] It has become one of the leading causes of visual impairment and blindness in newborns worldwide^[2]. ROP progresses rapidly, and the golden time window for effective treatment is narrow. Once the disease advances to the late stage, characterized by tractional retinal detachment, the blindness rate is extremely high, which severely affects the long-term quality of life of affected children. As an avoidable blinding eye disease, early screening, timely diagnosis, and appropriate treatment for premature infants with high-risk factors can effectively reduce the incidence of blindness due to ROP ^[3]. However, less than 5% of premature infants undergoing screening ultimately require treatment for ROP^[4]. Repeated, inefficient screenings for infants without clinical indications for treatment not only consume substantial medical resources but also cause psychological trauma to the preterm infants and impose a heavy economic burden on their families. Given the significant clinical insidious nature and progression risk of ROP, establishing an early screening system based on clinical prediction models has become

crucial for prevention and control. Previous research^[5] has confirmed that gestational age at birth, threatened preterm labor, fetal distress, birth weight, maternal thrombocytopenia, neonatal ischemic-hypoxic myocardial injury, mid-pregnancy, neonatal hyperkalemia, hyperlipidemia, mode of delivery, patent ductus arteriosus, twin pregnancy, neonatal hyperglycemia, electrolyte imbalance, neonatal hyperbilirubinemia, septic shock, umbilical cord around the neck, scarred uterus, oxygen concentration, neonatal respiratory distress syndrome, oxygen therapy, neonatal necrotizing enterocolitis, pulmonary hypertension, premature rupture of membranes, low birth weight, neonatal pneumonia, pregnancy-associated anemia, neonatal feeding intolerance, neonatal pulmonary hemorrhage, prenatal steroid use, antibiotic use, in vitro fertilization embryo transfer, anemia of prematurity, pregnancy with uterine fibroids, growth retardation, iron deficiency, thalassemia, gestational diabetes mellitus, high-risk pregnancy supervision, pregnancy complicated with mycotic vaginitis, neonatal sepsis, maternal electrolyte imbalance, pregnancy with hypoproteinemia, severe preeclampsia, and extremely low birth weight are independent risk factors for ROP, with the RF machine learning model identified as the optimal predictive model^[5].

Materials and Methods

1.1 Study Population

A retrospective study was conducted on 150 infants who underwent ROP screening in the Department of Neonatology at Wuzhou Workers' Hospital, Guangxi, China, between January 2024 and September 2024. The cohort included 67 girls (44.67%) and 83 boys (55.33%). The gestational age (GA) at birth ranged from 25 to 35 weeks (mean: 30.63 ± 2.68 weeks), and the birth weight (BW) ranged from 0.73 kg to 2.28 kg (mean: 1.53 ± 0.41 kg). Among them, 2 infants (1.3%) were small for gestational age, and 8 (5.33%) were from twin pregnancies. All infants had a history of oxygen therapy. This study adhered to the tenets of the Declaration of Helsinki and was approved by the Medical Ethics Committee of The First Affiliated Hospital of Guangxi Medical University, which granted a waiver for written informed consent (Ethics Approval No: 2024-K047-01). The inclusion criteria were defined according to the Chinese Guideline for Retinopathy of Prematurity Screening (2014)^[6] and the Chinese Expert Consensus on the Classification and Management of Retinopathy of Prematurity (2023)^[7]. Eligible neonates included: (1) those with a GA of < 32 weeks and/or a BW of < 2000 g; (2) those with severe systemic conditions or a significant history of oxygen therapy deemed high-risk by pediatricians.

Infants were excluded from the study based on the following criteria: (1) incomplete clinical data; (2) presence of severe congenital anomalies or chromosomal abnormalities; (3) coexisting ocular pathologies that could interfere with ROP screening or assessment (e.g., congenital cataract, congenital glaucoma, intraocular tumors, extensive retinal hemorrhage, familial exudative vitreoretinopathy, or congenital corneal leukoma); or (4) failure to complete the follow-up protocol until retinal vascularization or regression of ROP, as stipulated by the screening guidelines and expert consensus.

1.2 Study Design

1.2.1 Screening Criteria

The initial examination was initiated at 4–6 weeks after birth or at a postmenstrual age of 31–32 weeks. The screening intervals were as follows: (1) for Zone I with no ROP, or stage 1 or 2 ROP, examinations were conducted weekly; (2) for regressing ROP in Zone I, examinations could be performed every 1–2 weeks; (3) for stage 2 or 3 ROP in Zone II, examinations could be conducted weekly; (4) for stage 1 ROP in Zone II, examinations could be performed every 1–2 weeks; and (5) for stage 1 or no ROP in Zone II, or stage 1 or 2 ROP in Zone III, follow-up could be scheduled every 2–3 weeks

. Follow-up was terminated when any of the following criteria were met: (1) full retinal vascularization (the nasal retina reaching the ora serrata, and the temporal retina within one disc diameter of the ora serrata); (2) attainment of 45 weeks postmenstrual age without prethreshold or threshold ROP and with retinal vascularization extending into Zone III; or (3) regression of ROP.

1.2.2 Interpretation of Screening Results

The most severe ROP condition observed in each infant was recorded as the basis for classification. ROP lesions were classified according to the International Classification of ROP (ICROP) in terms of zone, stage, and the presence of plus disease ^[8].

Type 1 ROP: Defined as any ROP lesion in zone I with plus disease, stage 2 in zone II with plus disease, or stage 3 in zone II with plus disease. In the Early Treatment for ROP (ETROP) study, Type 1 ROP was considered an indication for treatment ^[9] and required intervention within 24–48 hours.

Type 2 ROP: Included stage 1 or 2 lesions in zone I, or stage 3 lesions in zone II without plus disease. In the ETROP study, Type 2 ROP was categorized as an observational lesion ^[9].

1.2.3. Data Collection

Data on potential risk factors and the screening results for ROP were collected by reviewing the electronic medical records (EMRs) during the hospitalization of the enrolled newborns and their follow-up outpatient visits. This process also involved tracking the progression of fundus findings during later follow-ups. Based on 46 independent risk factors identified in a previous study ^[5], information actually recorded in the EMRs was gathered and organized. The collected data, which may be associated with the occurrence and development of ROP, included the following aspects: Maternal factors (19 items): Mode of delivery, pregnancy combined with uterine fibroids, threatened preterm birth, fetal distress, prenatal steroid use, etc.

Neonatal factors (24 items): Gestational age, birth weight, anemia of prematurity, patent ductus arteriosus, neonatal sepsis, neonatal respiratory distress syndrome, etc.

Neonatal interventions (3 items): Oxygen therapy, antibiotic use, and oxygen concentration.

1.2.4. Screening of Risk Factors

Based on 46 risk factors identified in previous research and five machine learning models ^[5], we further extracted the most relevant features associated with the occurrence of ROP. The top 15 features ranked by feature importance were selected from the following five models using SHAP (SHapley Additive exPlanations) ^[10]: Random Forest (RF), Extreme Gradient Boosting (XGBoost), Light Gradient Boosting Machine (LightGBM), Decision Tree (DT), and Support Vector Machine (SVM). Venn diagrams were plotted to visualize the intersections of risk factors identified by these models. The nine risk factors common to all five methods were considered the final set of screened features.

1.2.5. Model Validation

The nine risk factors identified from the screening process were utilized to construct an optimal model based on the RF algorithm. The model was subsequently validated by applying it to cases retrospectively collected from Wuzhou Workers' Hospital for tracking and evaluation.

1.2.6. Observation Metrics

The performance of different models was evaluated using the following metrics: the Area Under the ROC Curve (AUC), accuracy, precision, sensitivity (recall), specificity, F1-score, and the Kappa coefficient.

1.2.7. Statistical Analysis

Statistical analyses were performed using R software (version 4.4.1) and Python (version 3.13.1). Continuous variables that were normally distributed are presented as the mean $\pm$ standard deviation ($\bar{x} \pm s$), while non-normally distributed measurement data are expressed as the median and interquartile range. Comparisons between groups for normally distributed continuous variables were conducted using the independent samples t-test. Categorical variables are described as absolute counts and percentages, and comparisons between groups were performed using the Pearson chi-square test or Fisher's exact probability test. All hypothesis tests were two-sided, and a P-value of less than 0.05 was considered statistically significant.

Results

2.1. Screening Results for ROP from Wuzhou Workers' Hospital

During the 9-week continuous screening period, 15 infants developed ROP, yielding an overall incidence of 10.00% (15/150). Among these cases, five infants (3.33%, 5/150) underwent treatment, including laser therapy or anti-VEGF therapy. The distribution of ROP by zones was as follows: zone III in 7 cases (4.67%), zone II in 4 cases (2.67%), and zone I in 4 cases (2.67%). According to the staging criteria, stage 1 disease was identified in 9 infants (6.00%), stage 2 in 2 infants (1.33%), and stage 3 in 2 infants (1.33%); no stage 4 or 5 disease was observed. Plus disease was present in 3 infants (2.00%), and aggressive posterior ROP (A-ROP) was identified in 2 cases (1.33%), as shown in Fig. 1.

2.2.1. Variable Importance Analysis Using RF

The 15 variables with the highest importance scores, in descending order, were as follows: oxygen concentration, oxygen therapy, gestational age, prenatal steroid use, low birth weight, pregnancy with anemia, in vitro fertilization–embryo transfer, neonatal respiratory distress syndrome, neonatal pneumonia, anemia of prematurity, birth weight, neonatal necrotizing enterocolitis, pregnancy complicated with fungal vaginitis, electrolyte disturbances, and antibiotic use (as shown in Fig. 2).

2.2.2. Feature Importance Analysis Using SVM

The 15 variables with the highest importance scores, ranked in descending order, were as follows: neonatal pulmonary hemorrhage, oxygen concentration, low birth weight, oxygen therapy, pregnancy complicated with fungal vaginitis, neonatal respiratory distress syndrome, in vitro fertilization–embryo transfer, antibiotic use, placental abruption, patent ductus arteriosus, anemia of prematurity, neonatal necrotizing enterocolitis, birth weight, mode of delivery, and neonatal hyperglycemia (as shown in Fig. 3).

2.2.3. Feature Importance Analysis Using XGBoost

The 15 variables with the highest importance scores, ranked in descending order, were as follows: oxygen concentration, gestational age, oxygen therapy, birth weight, prenatal steroid use, neonatal respiratory distress syndrome, neonatal pneumonia, in vitro fertilization–embryo transfer, pregnancy with anemia, anemia of prematurity, neonatal necrotizing enterocolitis, antibiotic use, patent ductus arteriosus, neonatal hyperglycemia, and mode of delivery (as shown in Fig. 4).

2.2.4. Feature Importance Analysis Using LightGBM

The 15 variables with the highest importance scores, ranked in descending order, were as follows: oxygen concentration, gestational age, oxygen therapy, prenatal steroid use, birth weight, anemia of prematurity, neonatal respiratory distress syndrome, pregnancy with anemia, neonatal pneumonia, in vitro fertilization–embryo transfer, neonatal necrotizing enterocolitis, antibiotic use, pregnancy complicated with fungal vaginitis, patent ductus arteriosus, and neonatal hyperglycemia (as shown in Fig. 5).

2.2.5. Feature Importance Analysis Using DT

The 15 variables with the highest importance scores, listed in descending order, were as follows: birth weight, oxygen therapy, oxygen concentration, pregnancy with anemia, in vitro fertilization–embryo transfer, prenatal steroid use, gestational age, neonatal necrotizing enterocolitis, neonatal pneumonia, neonatal hyperglycemia, antibiotic use, anemia of prematurity, neonatal respiratory distress syndrome, low birth weight, and patent ductus arteriosus (as shown in Fig. 6).

2.3. Construction of the Venn Diagram

A Venn diagram was utilized to identify the common features among the top 15 variables derived from the five methods mentioned above. The intersecting features included oxygen therapy, oxygen

concentration, gestational age, birth weight, anemia of prematurity, neonatal respiratory distress syndrome, neonatal necrotizing enterocolitis, in vitro fertilization–embryo transfer, and antibiotic use (as shown in Fig. 7). These nine predictors were ultimately selected for constructing the risk prediction model for ROP.

2.4. Univariate Analysis of the Nine Common Feature ROP Risk Factors

The results of the univariate analysis for continuous variables are presented in Table <link rid="tb2">1</link>. The mean gestational age and oxygen concentration in the ROP group were significantly lower than those in the non-ROP group (all $p < 0.001$). The birth weight in the ROP group was also significantly lower than that in the non-ROP group ($p = 0.001$). These findings indicate that infants who developed ROP were relatively less mature at birth and required higher oxygen concentrations compared to those who did not develop the condition

Table 1 1. Univariate Analysis of ROP Risk Factors (Continuous Variables, Mean ± SD)			
Risk Factor	ROP (no)(n = 135)	ROP(yes)(n = 15)	P
Gestational age (weeks)	30.71 ± 2.62	29.88 ± 3.16	<0.001
Birth weight (g)	1392.62 ± 558.49	1374.89 ± 386.34	0.001
oxygen concentration (%)	20 ± 8.56	32.69 ± 9.70	<0.001

Table 1 2. Univariate Analysis of ROP Risk Factors (Categorical Variables, n (%))			
Risk Factor	ROP (no)(n = 135)	ROP(yes)(n = 15)	P
Neonatal respiratory distress syndrome	38(28.1)	4(26.7)	0.008
antibiotic use	37(27.4)	5(33.3)	<0.001
in vitro fertilization–embryo transfer	23(17.0)	5(33.3)	0.04
anemia of prematurity	68(50.4)	2(13.3)	0.003
neonatal necrotizing enterocolitis	5(3.7)	1(6.7)	0.018
oxygen therapy	135(100)	15(100)	<0.01

The results of the univariate analysis for categorical neonatal factors are presented in Table 1–2. Neonatal respiratory distress syndrome, antibiotic use, in vitro fertilization–embryo transfer, anemia of prematurity, neonatal necrotizing enterocolitis, and oxygen therapy were significantly associated with the occurrence of retinopathy of prematurity (all $p < 0.05$).

Table 2
Validation Results of the Predictive Model

Metric	AUC	Accuracy	Precision	Specificity	Sensitivity	F1-Score	Kappa Coefficient
RF-Training Set ^[5]	1.000	0.997	0.997	0.997	0.997	0.997	0.994
RF-External Test Set	0.892	0.779	0.899	0.993	0.629	0.739	0.725

2.5 Model Validation

The nine risk factors screened above were incorporated into the RF machine learning model selected from a previous study ^[5], which served as the validation model. Data from 150 neonates at Wuzhou Workers' Hospital in Guangxi, along with their relevant risk factors, were used as the test set for the RF model. The test results are presented below (Fig. 8 – 2 and Table 2).

This study employed seven metrics to evaluate model performance. The comparison between the training set and the external test set showed decreases in AUC (1.00 vs. 0.892), F1-score (99.7% vs. 73.9%), Kappa coefficient (0.994 vs. 0.725), accuracy (99.7% vs. 77.9%), precision (99.7% vs. 89.9%), and sensitivity (99.7% vs. 62.9%) in the external test set, indicating slight overfitting and a minor decline in the reliability of positive class predictions, possibly influenced by class imbalance. Specificity remained high in the external test set (99.7% vs. 99.3%). Additionally, all AUC values exceeded the baseline of 0.80, demonstrating favorable model status. Combined with screening results from 150 newborns over nine consecutive weeks, 135 cases were diagnosed with non-vascularized retina in preterm infants, and none progressed to ROP after the screening period. The model predictions at the first week of screening for these 135 cases aligned with the actual outcomes (no ROP occurrence). However, the model could not accurately predict which infants diagnosed with ROP would not require further screening.

Discussion

3.1 Risk (Predictive) Factors for ROP

ROP is a developmental retinal vascular proliferative disorder that occurs in premature and low-birth-weight infants. Internationally recognized major risk factors for ROP include gestational age and birth weight ^[11], both of which are associated with the immaturity of retinal neural and vascular development at birth, making the retina vulnerable to injury. However, numerous studies suggest that the pathogenesis of ROP may involve multiple risk factors, such as a history of oxygen therapy, gestational hypertension, assisted reproductive technology, and anemia of prematurity, which also influence the onset of ROP ^[12–14]. Recent research further indicates that severe ROP is associated with necrotizing enterocolitis and the number of blood transfusions ^[15, 16]. To further explore potential risk factors and identify optimal indicator combinations for predicting ROP occurrence, we previously collected 109 potentially relevant

risk factors encompassing neonatal factors, maternal factors, and neonatal interventions ^[5]. Although numerous studies have investigated risk factors for ROP, most are based on small samples and analyzed using traditional logistic regression. While logistic regression is convenient to apply and interpret, its analytical capability is limited when dealing with numerous variables and intricate nonlinear relationships among them ^[17]. In this study, we employed machine learning algorithms to analyze risk factors for ROP. Using five machine learning algorithms, we selected the top 15 most significant risk factors. The factors consistently identified across all five algorithms included oxygen therapy, oxygen concentration, gestational age, birth weight, anemia of prematurity, neonatal respiratory distress syndrome, necrotizing enterocolitis, in vitro fertilization embryo transfer, and antibiotic use.

3.1.1 Oxygen Therapy, Oxygen Concentration, and ROP

In the treatment of high-risk preterm infants, oxygen therapy is essential for maintaining vital signs, preventing respiratory failure, and reducing hypoxia in critical organs such as the brain. However, oxygen therapy is a well-established contributing factor to ROP. Hypoxia, hyperoxia, and significant fluctuations in blood oxygen saturation are all associated with the development of ROP. The immature retinal vasculature of preterm infants is highly sensitive to hyperoxia. Excessive oxygen exposure may disrupt normal retinal vascular development by inducing abnormal expression of pro-angiogenic factors such as vascular endothelial growth factor (VEGF).

Studies have shown : that high-concentration oxygen therapy can lead to retinal vasoconstriction or obliteration, followed by hypoxia-triggered VEGF release, which promotes abnormal neovascularization and fibrosis, ultimately forming the typical pathological changes of ROP ^[18]. Clinical observations indicate : that higher oxygen concentrations and longer durations of oxygen therapy are significantly associated with increased incidence and severity of ROP ^[19, 20]. In this study, both oxygen therapy and oxygen concentration were closely correlated with ROP, and all infants diagnosed with ROP had a history of oxygen administration.

Retinal tissue in premature infants is highly susceptible to oxidative stress. This vulnerability arises from both the immature antioxidant system in preterm neonates and the high concentration of polyunsaturated fatty acids in the retina, which are sensitive to reactive oxygen species (ROS). Not all premature infants receiving long-term oxygen therapy develop ROP. In this study, among 150 neonates who received oxygen therapy, only 15 progressed to ROP. The tolerance to oxygen therapy varies among individuals, which may be associated with differences in their endogenous antioxidant levels ^[21]. For instance, vitamin E, a natural antioxidant, helps protect the retina against oxidative damage. Preterm infants may experience a severe deficiency of such vitamins; in these cases, even minimal oxygen exposure could increase the risk of ROP. Strict indications for oxygen use, along with appropriate concentration and timing, are critical in preventing severe ROP. However, some studies have shown that while restricted oxygen administration reduces the incidence of severe ROP, it may lead to increased mortality and higher rates of conditions such as cerebral palsy and congenital heart disease ^[22].

Although various measures can be taken to manage ROP, death is irreversible. Therefore, when implementing oxygen control strategies to prevent ROP, it is essential to balance the benefits and risks. When necessary, novel preventive measures should be explored.

3.1.2 Birth Weight, Gestational Age, and ROP

In this study, the mean birth weight of infants who developed ROP (1.37 ± 0.39 kg) was lower than that of the non-ROP group (1.39 ± 0.56 kg). Similarly, the mean gestational age of the ROP group (29.88 ± 3.16 weeks) was significantly lower than that of the non-ROP group (30.71 ± 2.62 weeks). Low birth weight and low gestational age showed a strong association with ROP. These two factors served as important indicators in our machine learning model and are internationally recognized as the most significant risk factors for ROP, forming the primary basis for screening criteria in various countries

. Higher gestational age and birth weight are protective factors against the occurrence and progression of ROP severity. A multicenter study found that each additional week of gestational age reduced the incidence of threshold ROP by 19% ^[23]. Another study reported that ROP affected 29% of infants born at less than 32 weeks gestation, and 65% of those born between 23 and 26 weeks ^[24]. Potential explanations include: low-birth-weight infants often present with immaturity of multiple organs (e.g., lungs, brain), necessitating interventions such as oxygen therapy and mechanical ventilation, which can further increase oxidative stress and the risk of vascular endothelial growth factor dysregulation. The immature retinal vasculature in very preterm infants is vulnerable to the extrauterine environment (e.g., hyperoxia, inflammation), predisposing them to abnormal vascular proliferation, thereby significantly increasing the incidence of ROP.

3.1.3 Anemia of Prematurity and ROP

Anemia of prematurity (AOP) has been reported to be significantly associated with ROP ^[25], which is consistent with the findings of the present study. AOP is characterized by a marked decrease in hemoglobin concentration after birth and impaired erythropoiesis due to insufficient production of erythropoietin (EPO). EPO, an important pro-angiogenic factor whose production is oxygen-regulated in both the kidney and the retina, has been implicated in retinal vascular stability in mouse models of ROP ^[26, 27]. Therefore, anemia resulting from low EPO levels may be linked to the development of ROP. Furthermore, blood transfusion, a common intervention for correcting anemia, may also potentially induce or exacerbate ROP. This risk is attributed to two main mechanisms. First, the iron load from transfusions might catalyze the formation of reactive oxygen species (ROS), thereby accelerating oxidative damage to the retina. Second, transfused blood products primarily contain adult hemoglobin (HbA), which has a lower oxygen affinity compared to fetal hemoglobin. This alteration can lead to a non-physiological hyperoxic environment in the immature retina, promoting the formation of oxygen free radicals and causing further retinal injury. However, it should be noted that some studies have reported that anemia is not an independent risk factor for ROP ^[28].

3.1.4 Neonatal Respiratory Distress Syndrome and ROP

Neonatal respiratory distress syndrome (NRDS) is a respiratory disorder primarily affecting preterm infants, caused by a deficiency of pulmonary surfactant. It manifests as a clinical syndrome characterized by respiratory distress shortly after birth, which progresses in severity. The incidence of NRDS increases with decreasing gestational age. Due to pulmonary immaturity, preterm infants are susceptible to NRDS and often require prolonged oxygen therapy or mechanical ventilation. The immature retina is highly sensitive to high concentrations of oxygen. In hyperoxic environments, retinal vessels constrict; upon cessation of oxygen supplementation, relative hypoxia occurs, triggering upregulation of VEGF and leading to retinal neovascularization. Notably, significant fluctuations in partial pressure of oxygen during oxygen therapy may exacerbate retinal vascular injury and increase the risk of ROP. One study indicated that NRDS is a factor associated with an increased incidence of ROP, with affected children exhibiting a 2.5-fold higher ROP incidence compared to the control group^[29]. Another study reported a significant increase in ROP among infants with respiratory distress syndrome born at 34–36 weeks of gestation^[30]. The findings of this study are consistent with these reports, as all infants included had a history of prolonged oxygen exposure and lower gestational ages. However, some studies have found no significant correlation between NRDS and the occurrence of ROP^[31].

3.1.5 Necrotizing Enterocolitis and ROP

Necrotizing enterocolitis (NEC) is a life-threatening condition in premature infants, characterized primarily by intestinal mucosal ischemia, hypoxia, and infection, leading to localized or diffuse necrosis of the small intestine and colon. Clinical manifestations include abdominal distension and bloody stools, which may progress to peritonitis, sepsis, and even death in severe cases. Preterm infants with a gestational age of less than 32 weeks and birth weight under 1500 grams are at high risk, primarily due to their immature intestinal development, which increases susceptibility to external insults such as hypoxia and infection. Oxidative stress resulting from hypoxia or oxygen therapy in preterm infants may exacerbate intestinal ischemia and dysregulate vascular tone, thereby elevating the risk of NEC. NEC is frequently complicated by sepsis or systemic infection. The release of inflammatory mediators, such as endotoxins and leukotrienes, may propagate a systemic inflammatory response that accelerates the progression of ROP. In the present study, all five neonates diagnosed with NEC were born at less than 32 weeks of gestation and weighed below 1500 grams; among them, one infant developed ROP. Machine learning model screening identified NEC as an independent factor for ROP occurrence. Numerous studies have reported that NEC is a significant independent risk factor for ROP^[32, 33]. Another study indicated that NEC predisposes infants to complications such as sepsis and other ischemic-hypoxic conditions, and therapeutic interventions like blood product transfusions may also increase the risk of ROP^[34].

3.1.6 In Vitro Fertilization-Embryo Transfer and ROP

In vitro fertilization-embryo transfer (IVF-ET), commonly known as test-tube baby technology, has been reported to potentially increase the risk of ROP. Some studies suggest that mothers undergoing IVF-ET are generally older and often present with additional risk factors contributing to infertility, which may

lead to a higher incidence of multiple pregnancies^[35]. These factors collectively could contribute to the development of ROP. In the present study, a strong correlation was observed between IVF-ET and ROP, with an incidence rate of 18% (5/28) among the affected infants. Notably, all mothers who underwent IVF-ET in this cohort were of advanced maternal age. Another systematic analysis of 179 preterm infants born via IVF-ET indicated that IVF-ET is a risk factor for threshold ROP, potentially attributable to exposure of gametes and embryos to various physical manipulations, pharmacological agents, and other potential harmful factors during the culture process^[36]. McKibbin et al. proposed that IVF contributes to an increased incidence of ROP primarily by elevating the risks of prematurity, low birth weight, and multiple gestations^[37]. In contrast, Friling et al. argued that IVF is not an independent risk factor for ROP and does not predict the severity of the condition^[38].

3.1.7 Antibiotic Use and ROP

Antibiotic exposure in premature infants can significantly alter the composition and diversity of the gut microbiota, leading to the proliferation of potential pathogens such as (*Enterococcus* and *Staphylococcus*). Dysbiosis of the gut microbiota may trigger a systemic inflammatory response via the "gut-retina axis," promoting abnormal retinal vascular proliferation and thereby increasing the risk of ROP. Additionally, antibiotics may suppress the immunomodulatory effects of the normal microbiota, impairing the infant's ability to regulate oxidative stress and vascular endothelial growth factors, which in turn affects retinal vascular development. In the present study, 5 out of 15 infants with ROP had a history of prolonged antibiotic use, indicating a close association between antibiotic exposure and ROP occurrence. An animal study demonstrated that antibiotic administration exacerbated ischemic-hypoxic retinopathy^[39]. Humberg et al. reported that extensive antibiotic use significantly influenced the incidence of ROP^[40]. However, other studies found no significant correlation between antibiotic exposure, including duration of use, and the development of ROP^[41, 42]. While existing evidence partially supports a potential link between antibiotic exposure and ROP risk, the specific mechanisms and clinical implications require further investigation.

3.2 Machine Learning-Based Prediction Model for the Risk of ROP Onset

ROP is one of the leading causes of childhood blindness worldwide, imposing significant psychosocial and economic burdens on affected individuals and their families. Early screening and regular monitoring are critical for the clinical diagnosis and management of ROP. Typically, ophthalmologists can make rapid diagnoses during each screening using fundus photography equipment. Even non-ophthalmologists can operate devices such as the RetCam3 to capture fundus images, which can then be transmitted remotely to specialized ophthalmologists for diagnosis. However, the high cost of RetCam3 equipment makes it unaffordable for many hospitals at the municipal level and below in China. Additionally, the use of binocular indirect ophthalmoscopy requires specialized training and has a long learning curve, leading to difficulties in implementing screening programs in many healthcare settings. Moreover, the majority of neonates who meet current screening criteria do not develop ROP, and among

those who do, less than 10% require treatment. Therefore, it is clinically essential to develop prediction models capable of early risk stratification for ROP. This study aims to construct an onset prediction model based on basic clinical characteristics of infants to improve screening efficiency, enhance the accuracy of identifying high-risk populations, reduce unnecessary screenings, and optimize resource allocation, thereby alleviating pressures on healthcare systems.

In the current era of big data, the enhanced completeness of clinical data collection has made it possible to process vast amounts of information through machine learning methods and develop programmed prediction models, which has emerged as a new approach to improving clinical diagnostic and therapeutic efficiency. Machine learning not only enables the construction of complex models but also supports clinical decision-making based on data derived from these models. When the dataset is sufficiently large, the accuracy of machine learning algorithms tends to be higher. In this study, to ensure the validity of the prediction model for the onset of ROP, we initially screened important features associated with ROP using Lasso regression analysis in a prior investigation ^[5]. Subsequently, seven machine learning models were compared and evaluated, with the results indicating that the model constructed using the RF algorithm demonstrated the best predictive performance, while the AUC values of the other models all exceeded 0.85. Furthermore, this study conducted a secondary screening of predictive risk factors by applying five machine learning algorithms to identify the top 15 overlapping features via Venn diagrams. This process yielded nine key features: oxygen therapy, oxygen concentration, gestational age, birth weight, anemia of prematurity, neonatal respiratory distress syndrome, necrotizing enterocolitis, in vitro fertilization-embryo transfer, and antibiotic use, all of which were incorporated into the ROP risk prediction model. External validation using external hospital medical records was subsequently performed, further confirming the model's robust performance—none of the 135 premature infants without diagnosed ROP were missed.

Conclusions

In summary, the RF model developed using machine learning methods—incorporating predictive features such as oxygen therapy, oxygen concentration, gestational age, birth weight, anemia of prematurity, neonatal respiratory distress syndrome, necrotizing enterocolitis, in vitro fertilization-embryo transfer, and antibiotic use—demonstrates favorable predictive value for ROP. This model shows potential for clinical application in screening high-risk populations for ROP.

Declarations

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Author contributions

Funding acquisition, project administration, resources, supervision, MLH; Conceptualization, validation, writing review, supervision and editing, YY and LLL; data curation, formal analysis, software, visualization, and writing original draft, YY; investigation, methodology, YL. All authors have read and agreed to the published version of the manuscript.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics declarations

This study adhered to the principles of the Declaration of Helsinki and was approved by the Medical Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (Ethics Approval No.: 2024-K047-01), which waived the requirement for written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Figures

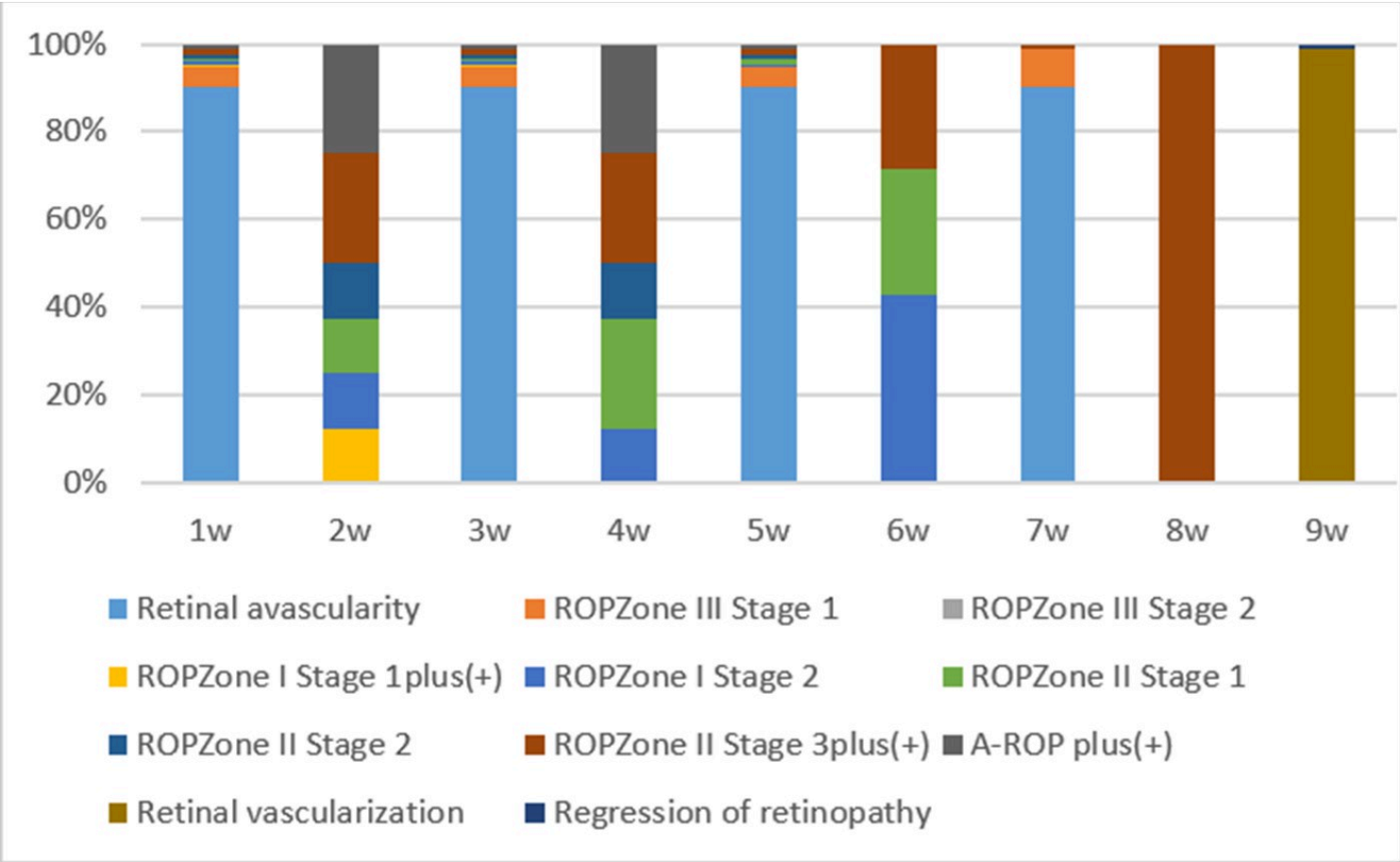


Figure 1

Staging and Zoning Distribution of ROP Cases in 150 Neonates Screened Over 9Weeks Across Sequential Time Points (%)

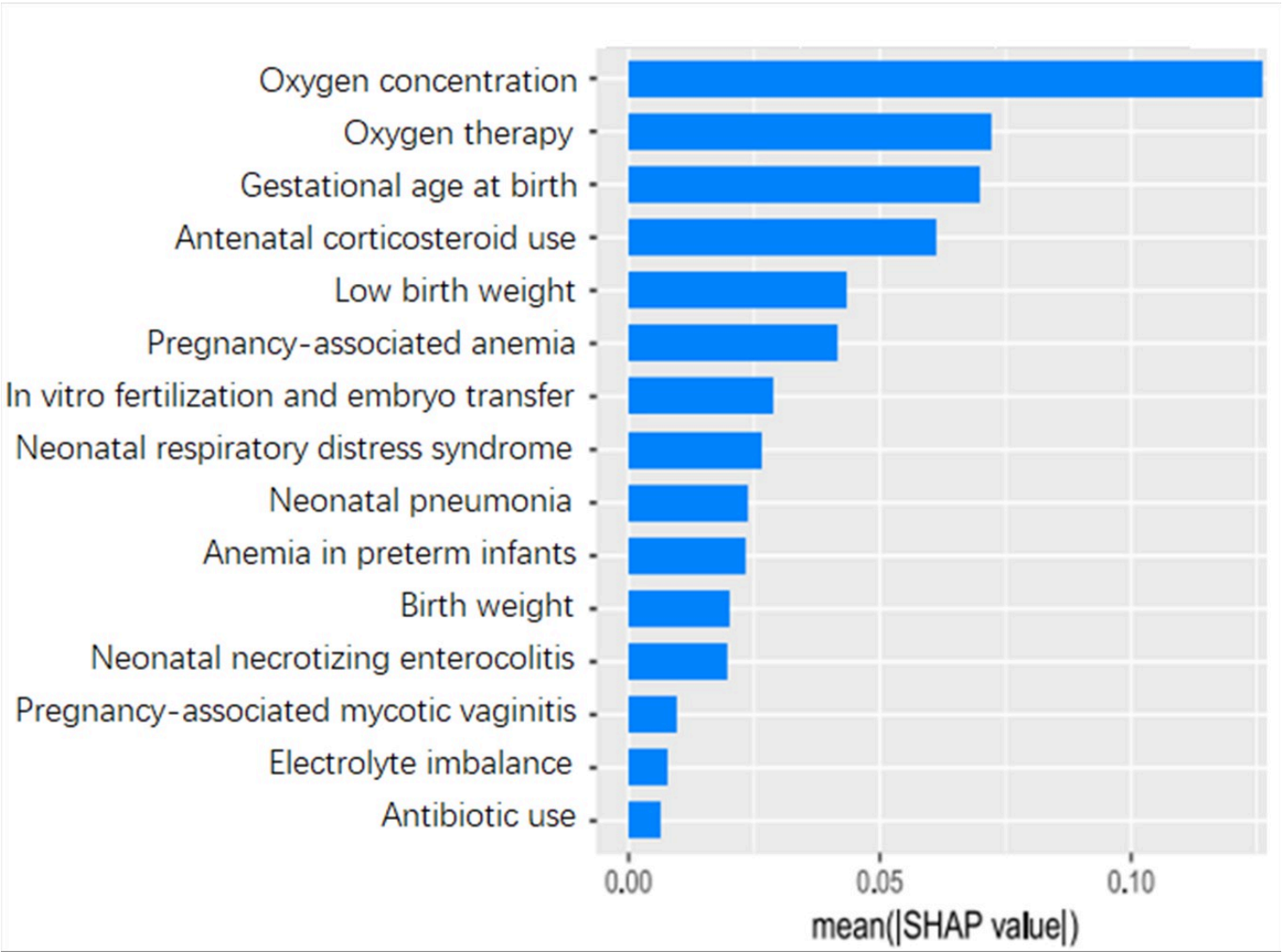


Figure 2

Variable Importance Ranking RF

SVM Feature Importance Ranking

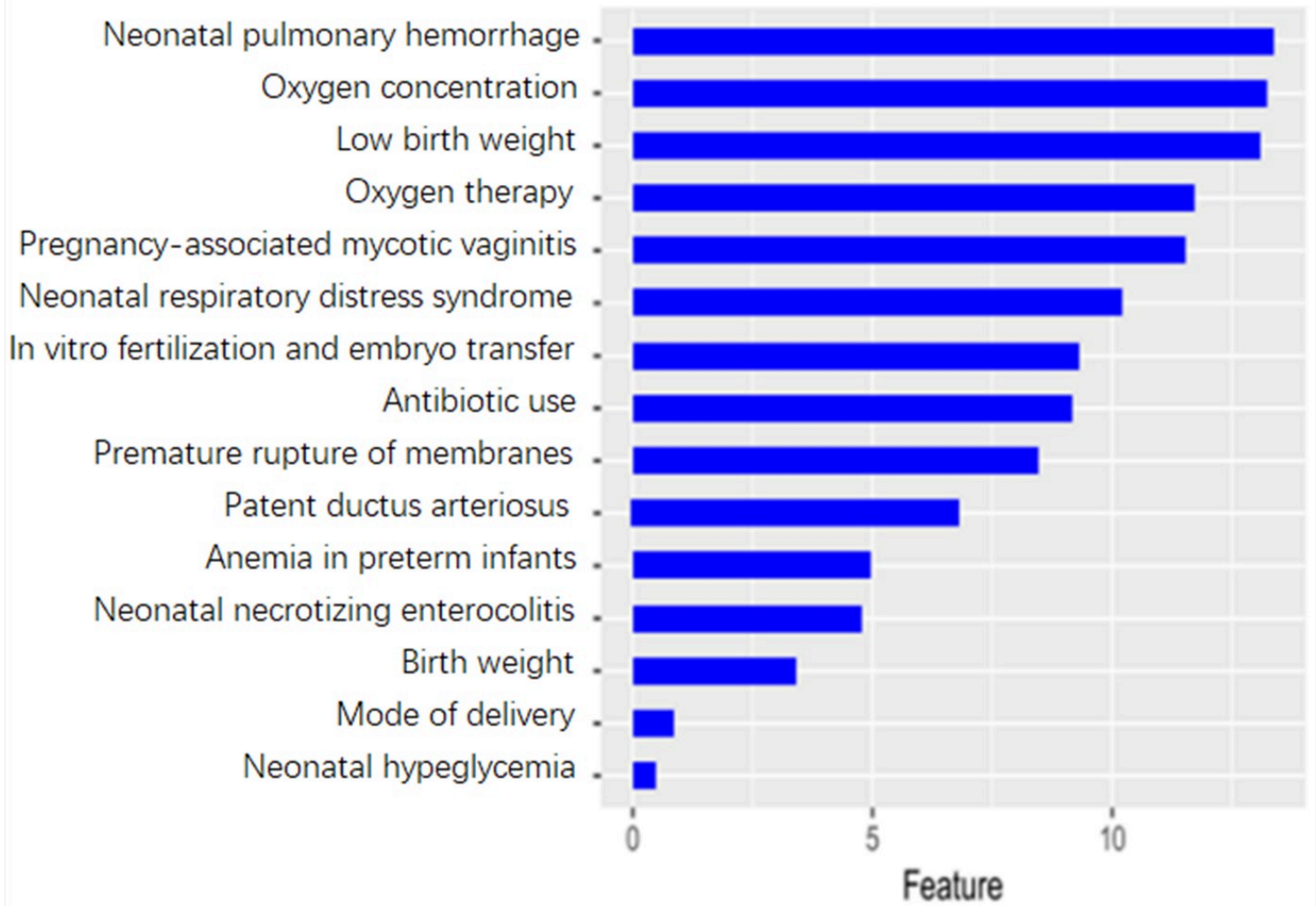


Figure 3

Variable Importance Ranking (SVM)

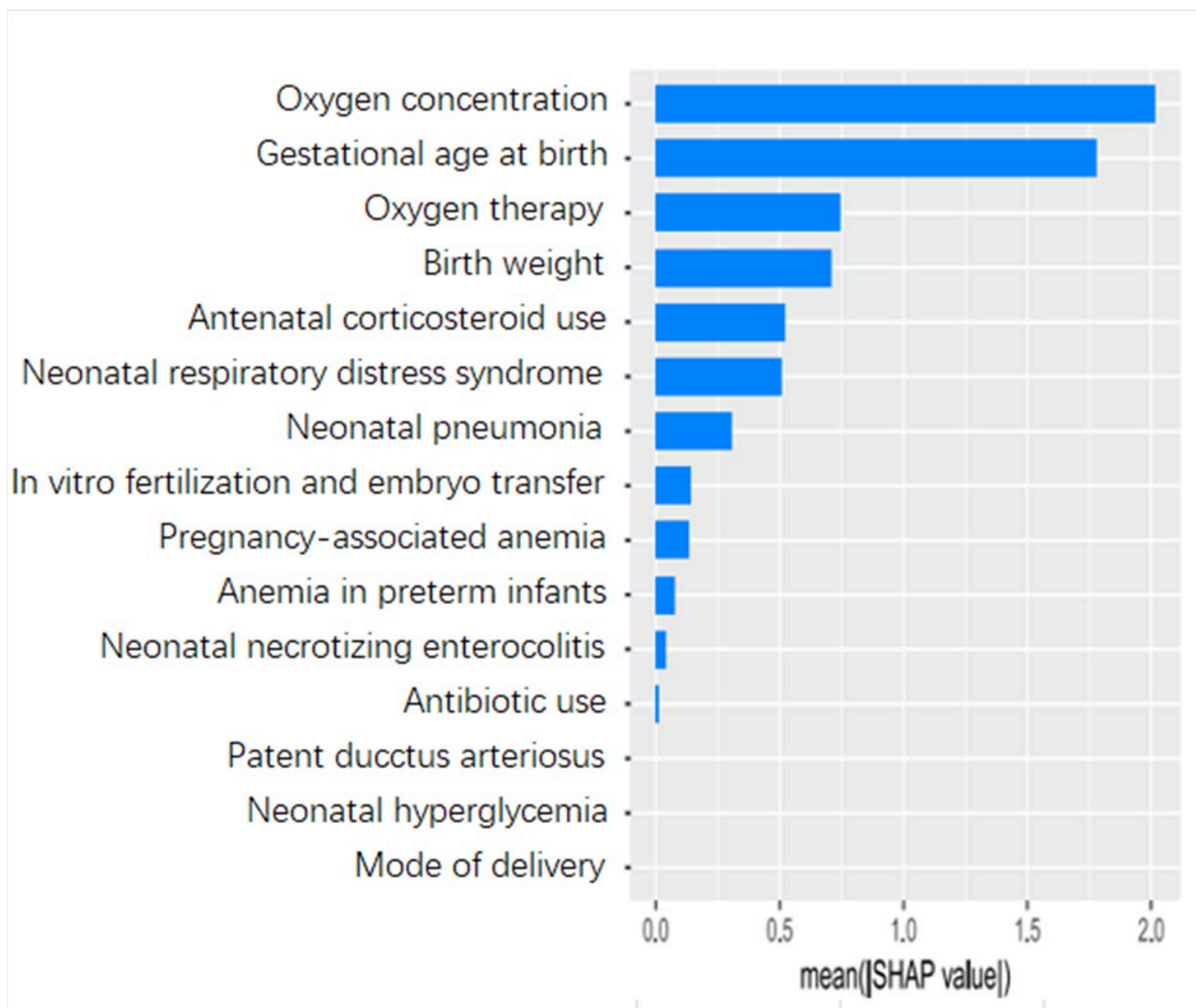


Figure 4

Variable Importance Ranking (XG Boost)

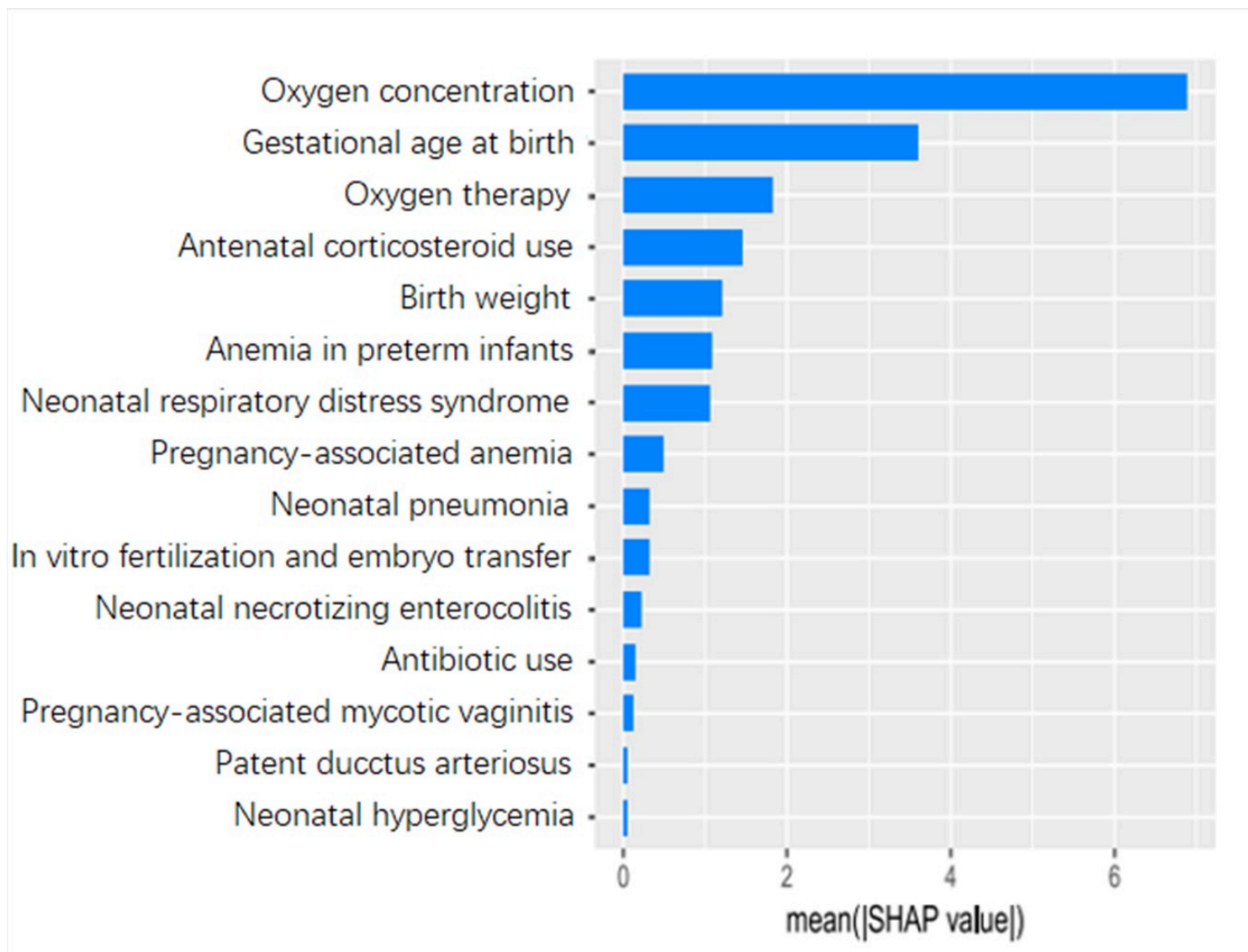


Figure 5

Variable Importance Ranking (Light GBM)

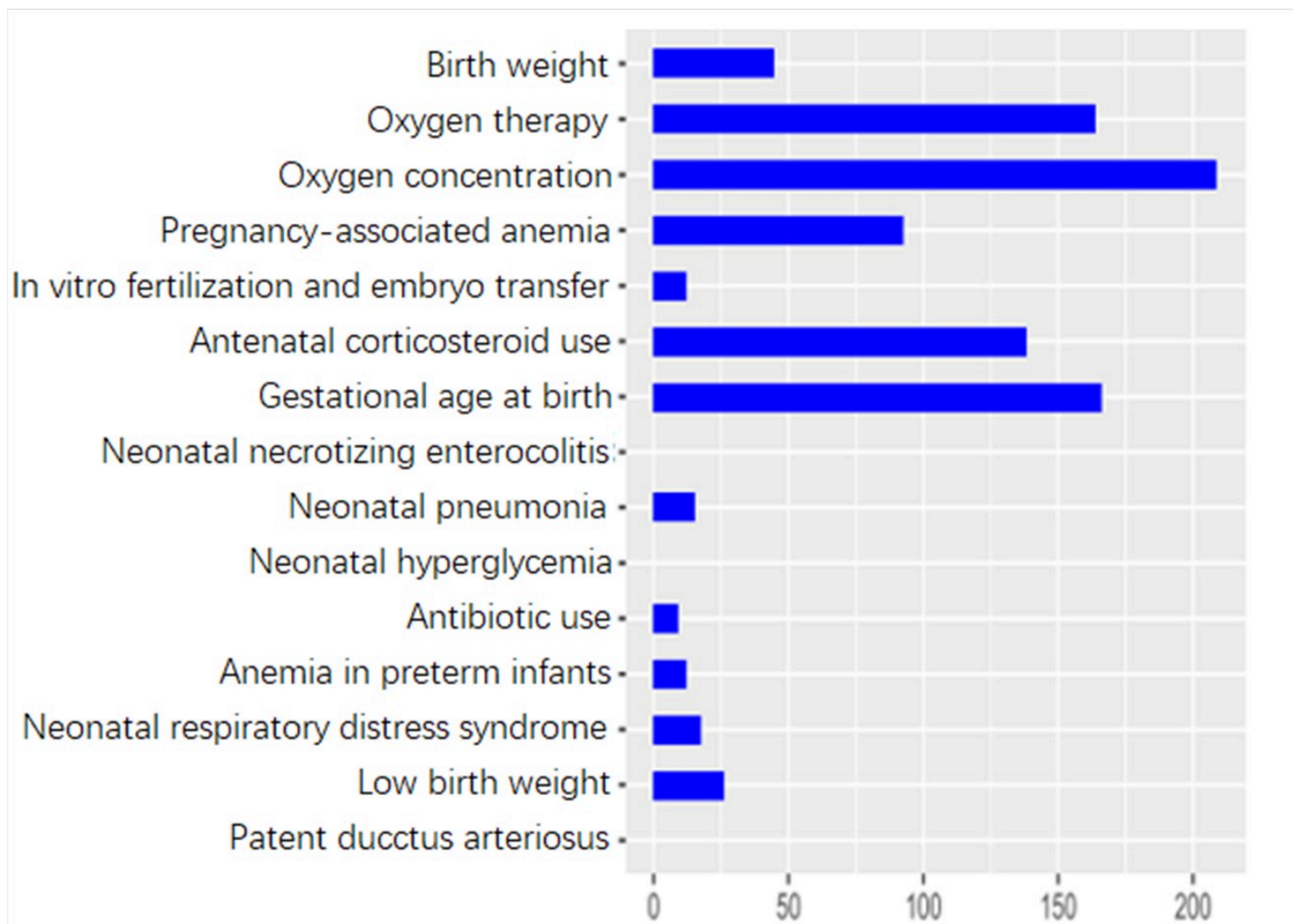


Figure 6

Variable Importance Ranking (DT)

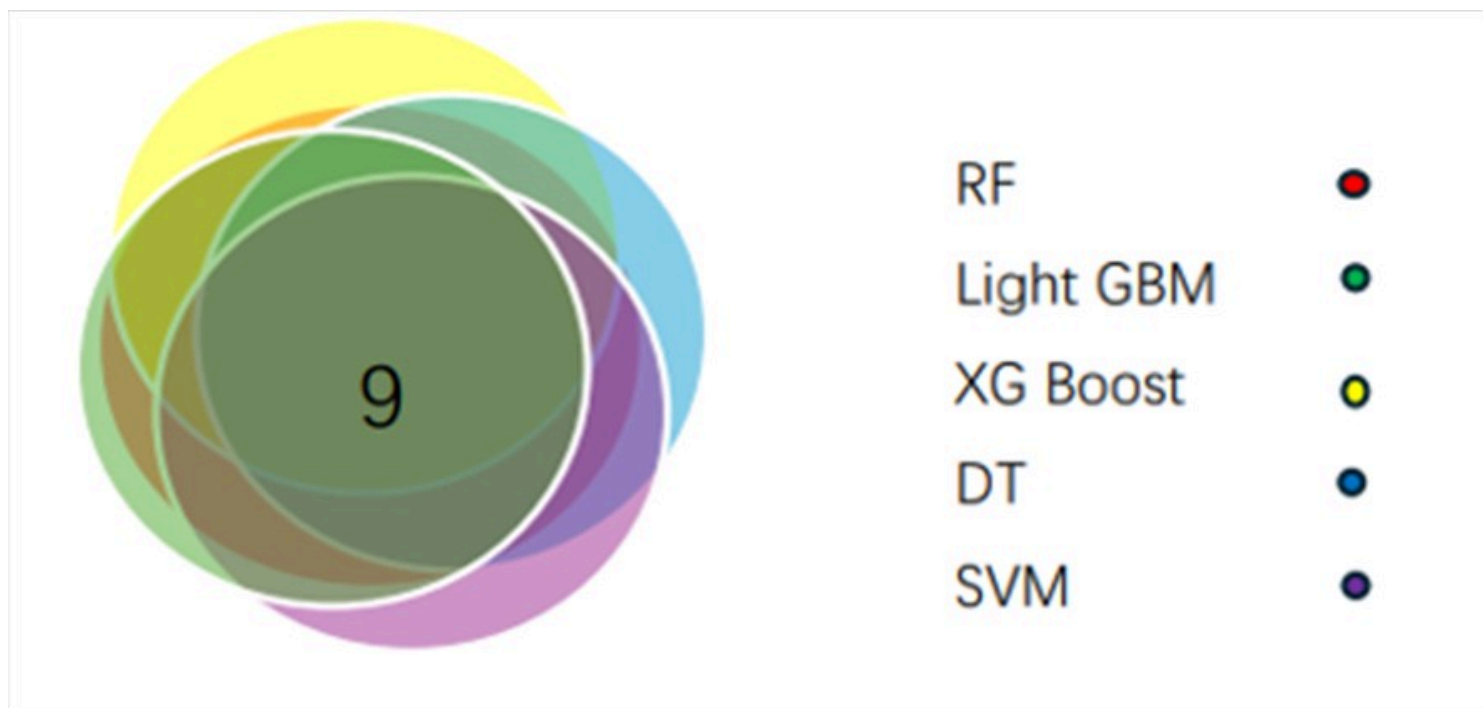


Figure 7

Venn Diagram of Five Machine Learning Algorithms for Selected Final Variables

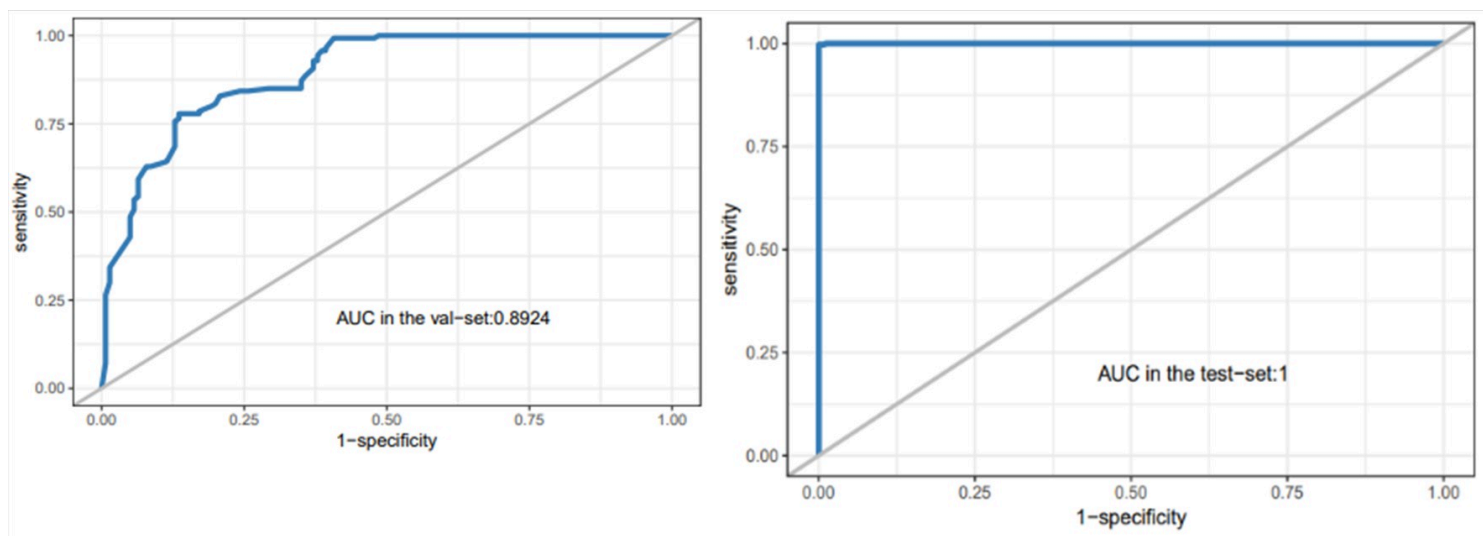


Figure 8

1. AUC of the RF^[5] Model on the Original Training Set
2. AUC of the RF Model on the External Test Set