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Predicting Neonatal Risk of Patent Ductus Arteriosus: A Machine Learning Analysis of Maternal Pathology, Medication, and Neonatal Health Indicators Using Random Forest and XGBoost Models

Ana Maria Cristina Jura [1,2], Daniela Eugenia Popescu [1,2,*], Cosmin Cîtu [1], Marius Biriș [1], Corina Pienar [3], Corina Paul [3], Oana Maria Petrescu [4], Andreea Teodora Constantin [5], Alexandru Dinulescu [5] and Ioana Roșca [5,6]

[1] Department of Obstetrics and Gynecology, "Victor Babeş" University of Medicine and Pharmacy, Eftimie Murgu Sq. No. 2, 300041 Timişoara, Romania
[2] Medici's MedLife Hospital Timișoara, Ciprian Porumbescu street no. 9, 0356 911, Timișoara, Romania
[3] Department of Pediatrics, 2nd Pediatrics Clinic, "Victor Babes" University of Medicine and Pharmacy, 300041 Timisoara, Romania
[4] Pediatric Cardiology, Clinical Hospital of Obstetrics and Gynecology "Prof. Dr. P.Sirbu", 060251 Bucharest, Romania
[5] University of Medicine and Pharmacy "Carol Davila", 020021 Bucharest, Romania
[6] Neonatology Department, Clinical Hospital of Obstetrics and Gynecology "Prof. Dr. P.Sirbu", 060251 Bucharest, Romania
* Correspondence: popescu.daniela@umft.ro

Abstract: Background: Patent ductus arteriosus (PDA) is common in newborns, being associated with high morbidity and mortality. While maternal and neonatal conditions are known contributors, few studies use advanced machine learning (ML) as predictive factors. This study assessed how maternal pathologies, medications, and neonatal factors affect the risk of PDA using traditional statistics and ML algorithms: Random Forest (RF) and XGBoost (XGB). **Methods:** A retrospective 3 year cohort study of 201 NICU neonates assessed maternal and neonatal factors. Logistic regression (LR) and chi-square analyses identified significant predictors, while ML models enhanced predictive accuracy and pinpointed key PDA factors. **Results:** LR identified prolonged rupture of membranes (>18 hours) as the most significant predictor (OR: 13.03, p<0.001). The ML models identified gestational age, maternal anemia, prenatal care level, birth weight, prolonged rupture of membranes, medication usage, diabetes, pregnancy-induced hypertension, SARS-CoV-2 infection, and cervical cerclage as key predictors. The RF model had 76.3% accuracy, moderate sensitivity (47.4%), and high specificity (90%). XGB performed better with 81.4% accuracy, an AUC of 0.872, sensitivity of 92.5%, and specificity of 57.9%. **Conclusion:** This study shows that maternal and neonatal factors significantly influence the risk of PDA. ML, particularly XGBoost, enhances predictive abilities, guiding targeted interventions and improving neonatal outcomes.

Keywords: congenital heart disease; cardiac abnormalities; personalized diagnosis and treatment; machine learning; neonatal intensive care unit; maternal pathology; persistent ductus arteriosus; maternal medication; pregnancy complications

1. Introduction

Persistent ductus arteriosus (PDA) is a common disorder in newborns and a significant predictor of morbidity and mortality. Several studies have been conducted to identify potential factors associated with delayed ductal closure in term newborns [1], but reports of maternal factors associated with early PDA in newborns are limited [2,3].

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The ductus arteriosus (DA) is a fetal structure that connects the main pulmonary artery and the aorta. Its main function is to shunt blood flow away from the pulmonary circulation, given that the vascular resistance in the pulmonary circulation is high, and toward the aorta, closer to the peripheral organs with lower vascular resistance. To provide flow-dependent vasodilation capability and the large variability in postnatal shunt size necessary for adapting to the systemic vascular resistance, the DA's structure is characterized by a uniformly developed middle layer of longitudinal smooth muscle cells, which acquire the capability of constriction after birth [4]. In the human fetus, the previously described DA function results in left-to-right shunting of oxygenated blood from the aortic arch to the main pulmonary artery. After birth, the basic switch from a shunt to a reentry system and the consequent closure of the DA lead to right-to-left shunting of deoxygenated blood from the main pulmonary artery to the aorta, thereby increasing the amount of oxygenated blood sent toward the body [5].

Traditionally, there is a tendency to treat neonatal PDA, and attention is urgently required. However, those treated pharmacologically alone are limited and there are more complicated outcomes [6]. Compared to mothers with pathologic pregnancy, the risk of PDA is also higher for these newborns. However, there are few studies of PDA association with pathologic pregnancy such as non-infectious inflammatory diseases and autoimmune-related diseases [7,8]. Although the outcome is neonatal hypoxia, the mother's illness has not been relevant. Focusing on the fact that the fetus responds to maternal symptoms of hypoxia, the fetus of pathologic pregnancy, including maternal trauma, may exacerbate fetal damage by maternal hypoxia [9].

Maternal hypertension impacts fetal circulatory development, potentially resulting in hypertrophy of left-heart structures and affecting the risk of patent ductus arteriosus due to modified blood flow and vascular resistance [10–12]. Also, it is known that gestational diabetes and type 1 diabetes in pregnancy are linked to hyperglycemia, which may affect the cardiac development of neonates, raising the risk of PDA in offspring [13,14]. Maternal thyroid dysfunction, especially hypothyroidism, may impair fetal vascular physiology [15], potentially postponing ductus arteriosus closure and elevating the risk of patent ductus arteriosus due to heightened prostaglandin levels and alterations in vascular resistance [16,17]. Other potential maternal contributing factors to PDA include infections, particularly urinary tract infections during pregnancy [18,19], but also viral infections during pregnacy, and maternal anemia, specifically iron deficiency anaemia [20–23].

Machine learning enables machines to learn from a training dataset and predict outcomes for new data. It uses statistical theory to build mathematical models, aiming to derive inferences from samples [24]. Decision trees are classification techniques in data mining and machine learning, using a straightforward algorithm easily understood by researchers. As white-box models, they offer non-parametric flexibility, handle heterogeneous data, and classify sequential data without needing normalized features. They also require less execution time for classification than other methods [25]. The Random Forest (RF) predictive model, based on decision trees, is a behavioral analysis tool that manages extensive data sets from modern supply chain operations, especially in healthcare [26]. The RF model is highly precise among common data classification algorithms and can handle extensive datasets with specific parameters. It efficiently manages diverse variables, making it suitable for complex tasks like health supply chain management. If a class is less prevalent, datasets can be automatically balanced [27]. The Extreme Gradient Boosting (XGBoost) model is prominent in machine learning for its generalizability, low overfitting risk, and high interpretability. It excels in predictive medicine tasks using tabular data like electronic health records and is used in critical care scenarios [28].

The study seeks to identify critical predictive features and evaluate the relative efficacy of algorithms by analysing an extensive dataset of maternal and neonatal health indicators, focussing on accuracy, sensitivity, specificity, and additional diagnostic metrics. The primary objective is to develop a dependable predictive instrument to aid healthcare professionals in the early detection of neonates at elevated risk for PDA, thereby enabling prompt interventions and enhancing neonatal care outcomes.

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2. Materials and Methods

A retrospective analysis was conducted based on a cohort of both preterm and term newborns who were hospitalized in the Neonatal Intensive Care Unit (NICU) in the Clinical Hospital of Obstetrics and Gynecology "Prof. Dr. Panait Sârbu" of Bucharest, Romania. We included all newborns admitted to NICU between 01.01.2021 to 31.12.2023, over a period of three years. Ethical approval was obtained from the Research Ethics Committee of the Clinical Hospital of Obstetrics and Gynecology "Prof. Dr. Panait Sârbu" of Bucharest, no. 16516/11.12.2024 The dataset included a total of 201 cases with detailed maternal and neonatal variables.

Inclusion criteria consisted of neonates born at the Clinical Hospital of Obstetrics and Gynecology "Prof. Dr. Panait Sârbu" and admitted to NICU within the study period along with documented maternal health data. Exclusion criteria were cases with missing critical data, such as gestational age, birth weight, APGAR score, maternal pathology or medication use during pregnancy.

2.1. Variables and Data Preprocessing

Data were preprocessed to convert categorical variables into a suitable format for analysis. Key predictor variables included maternal age, prenatal care level, specific maternal pathologies such as hypertension, diabetes, infections, and medications taken during pregnancy (antibiotics, antihypertensives, steroids). Neonatal outcomes included PDA diagnosis as the primary target variable (binary variable indicating presence or absence of PDA). For predictor variables we included maternal and medication variables, as follows:

- **Maternal Pathologies**: Conditions such as hypertension, diabetes, anemia, infections (e.g., GBS, SARS-CoV-2), and pregnancy complications (e.g., preeclampsia, prolonged rupture of membranes).
- **Medication During Pregnancy**: Administration of medications including aspirin, nifedipine, antibiotics, and insulin.

Missing values were handled using the imputation method, and outliers were reviewed to ensure data consistency.

2.2. Statistical Analysis

We initially performed univariate analyses employing logistic regression and chi-square tests to investigate the correlation between maternal factors and the risk of neonatal PDA.

2.3. Machine Learning Models

A Random Forest model was initially created to assess the significance of maternal and medication variables in predicting PDA. The model was trained using 500 trees, employing a subset of features at each split. Feature importance scores were extracted from the RF model to determine the most significant predictors. Subsequent to the Random Forest model, XGBoost was employed to augment predictive precision and assess the impact of each predictor on PDA risk. The parameters of XGBoost, such as learning rate, maximum depth, and subsampling rate, were optimised through cross-validation to mitigate overfitting. The employed objective function was logistic regression for binary classification, utilising the area under the ROC curve (AUC) as the principal evaluation metric.

2.4. Model Training and Evaluation

The dataset was divided into training (70%) and testing (30%) subsets applying stratified sampling to preserve the ratio of PDA cases. Cross-validation was conducted within the training set to optimise model parameters and assess model stability. The model's performance was assessed on the test set utilising accuracy, sensitivity, specificity, and AUC. Confusion matrices were created to illustrate model performance regarding accurately and inaccurately classified instances. Hyperparameters for both RF and XGBoost were optimised through a grid search employing 5-fold cross-validation to enhance AUC while balancing sensitivity and specificity.

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2.5. Software and Tools

The study was conducted using R Studio (version 2023.09.1+494 for Mac) with packages caret, xgboost, and randomForest for machine learning modeling. Data preprocessing and visualization were performed using dplyr and ggplot2. The stats library was utilised for logistic regression (glm function) to compute odds ratios and p-values, whereas the MASS library was employed for determining confidence intervals for odds ratios. Furthermore, chi-square tests were conducted utilising the chisq.test function within the stats library to assess categorical associations between maternal variables and the presence of PDA. The dplyr and tidyverse libraries enabled data cleaning and preparation, ensuring precise and efficient data manipulation during the study.

3. Results

The study population consisted of 201 neonates admitted to the NICU during the specified period. Maternal conditions included urinary tract infections, chorioamnionitis, positive endocervical cultures, diabetes, pregnancy induced hypertension, anemia, prolonged rupture of membranes (>18 hours), thyroid disorders, viral infections, and other conditions. The principal pathologies are detailed in Table 1, along with their statistical significance. 89.1% of mothers exhibited at least one pathology during pregnancy, with 95.52% originating from supervised pregnancies (44.28% receiving basic care and 51.24% receiving comprehensive care), while a mere 4.48% were unmonitored pregnancies.

Table 1. Most important maternal pathologies and medication use from our studied lot and their significance in PDA risk.

Studied characteristic	n%	Odds ratio	p-value
Maternal pathology present	89.1%	1.88	0.226
Prolonged rupture of membranes	11.9%	13.03	0.00086
Diabetes	11.9%	1.5	0.491
GBS[1] – endocervical culture	1%	0.79	0.715
Anemia	5.5%	0.55	0.339
IVF[1]	11.4%	1.83	0.344
SARS-CoV-2 infection	3%	2.44	0.666
Cervical cerclage	8.5%	1.61	0.589
PIH[1]	16.9%	0.73	0.427
UTI[1]	10.9%	1.71	0.347
Autoimmune thyroiditis	2.5%	1.94	1
Comprehensive prenatal care	51.24%	1.31	0.429
Amoxicillin+clavulanic acid therapy	20.4%	1.20	0.711
Cefuroxime therapy	5.5%	0.83	0.749
Methyldopa	14.4%	1.07	1
Enoxaparin	9.5%	1.89	0.315
Aspirin	3.5%	0.34	0.216

[1] GBS – group B streptococcus, IVF – in vitro fertilization, PIH – pregnancy induced hypertension, UTI – urinary tract infection.

Maternal pathologies, notably prolonged rupture of membranes (PROM), show a strong correlation with increased PDA risk (Odds Ratio: 13.03, $p<0.001$). This suggests PROM may affect fetal circulatory dynamics, raising PDA risk. Hypertension and diabetes showed moderate, non-significant correlations with PDA; thyroid conditions had no impact. Anemia and IVF showed important odds but had non-significant associations. Medications like enoxaparin and amoxicillin with clavulanic acid slightly increased PDA odds without statistical significance. Methyldopa and

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cefuroxime didn't significantly affect PDA odds. Prenatal care didn't influence PDA risk significantly, although high-risk cases might increase its likelihood.

Our analysis confirmed that gestational age and low birthweight significantly predict patent ductus arteriosus (PDA) risk in neonates (Table 2). Each additional week of gestation reduced PDA probability, highlighting preterm infants' susceptibility due to underdeveloped circulatory systems. Lower birthweight was linked to higher PDA risk. The maternal ages in our cohort ranged from 19 to 42 years, while gestational ages ranged from 28 to 41 weeks. Birth weights varied from 1,200 to 4,200 grams.

Table 2. Maternal age and neonatal risk factors for PDA.

Studied characteristic	Mean/n%	Odds ratio	p-value
Maternal age	30.2 years	1.15	0.512
Gestational age	36.5 weeks	0.85	0.042
Birthweight	2.800grams	0.72	0.029
APGAR score	8.1	0.78	0.051
FGR[1]	14.4%	1.30	0.67

[1] FGR – fetal growth restriction.

3.1. Machine Learning Analysis for PDA Prediction

To improve our predictive modelling of PDA risk, we expanded our analysis utilising machine learning algorithms: Random Forest and XGBoost (Figure 1). These models were selected for their robustness in managing complex, nonlinear interactions and their effectiveness in identifying critical features associated with PDA risk.

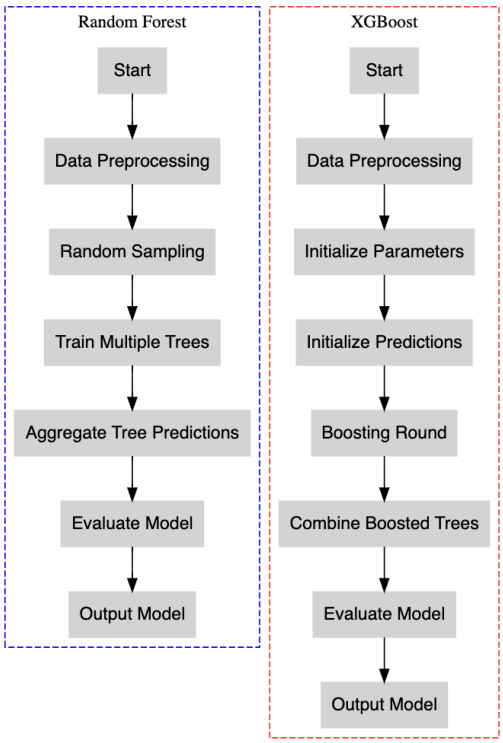

Figure 1. This flowchart encapsulates the procedures involved in both the Random Forest and XGBoost methodologies.

A Random Forest model was employed to forecast the risk of PDA in neonates, utilising maternal and neonatal variables. Our model achieved an accuracy of 76.3%, demonstrating moderate

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efficacy in distinguishing between neonates at high and low risk of PDA. However, the sensitivity was 47.4%, reflecting the model's ability to detected less than fifty percent of actual PDA cases, indicating limitations in recognizing all at-risk neonates, possibly due to the multifactorial nature of PDA and the variability of risk factors. Moreover, our model's specificity of 90%, reliably identifies neonates without PDA. This indicates that the model effectively minimizes false-positive results, making it valuable for excluding PDA in low-risk scenarios. The Kappa value of 0.41 indicates moderate agreement between predicted and actual classifications, accounting for random chance (Figures 2 and 3).

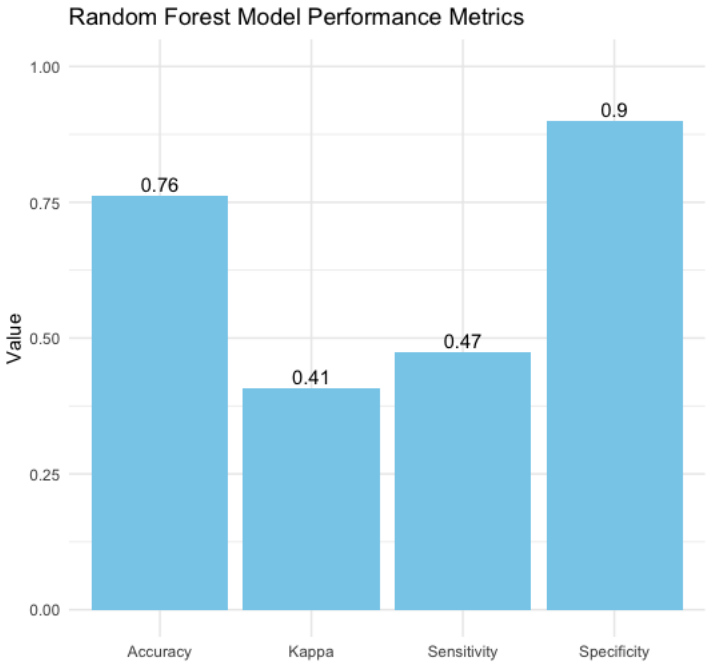

Figure 2. Our RF (Random Forest) performance model.

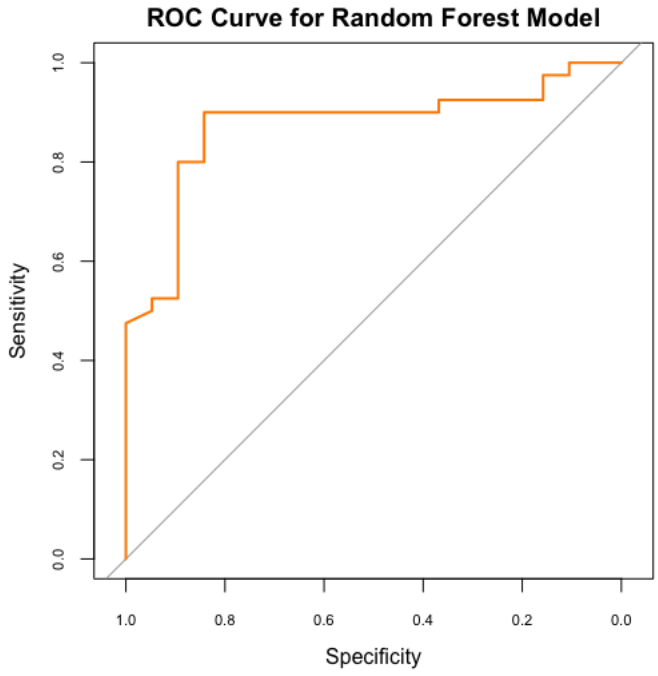

Figure 3. The ROC Curve for our RF performance model.

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Following the establishment of a baseline model with Random Forest, we implemented the XGBoost algorithm to enhance predictive performance and address the imbalance in sensitivity and specificity observed in the Random Forest model. In our study, we configured XGBoost with optimized hyperparameters, including the learning rate, maximum tree depth, and number of boosting rounds, to improve the model's accuracy in predicting the likelihood of PDA in neonates. We used cross-validation (Figure 4) to determine the optimal number of boosting rounds and mitigate overfitting, ensuring the model's effective generalization to new data.

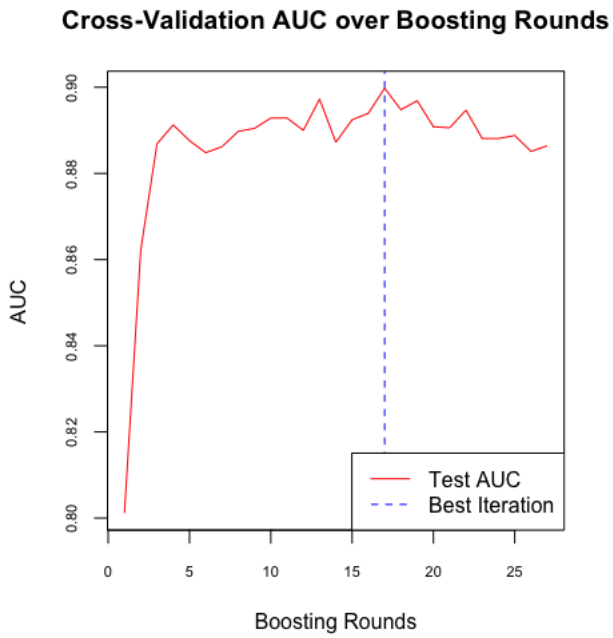

Figure 4. Cross-validation AUC for boosting rounds in our model.

The XGBoost model was used to improve predictive efficacy. Therefore, it achieved an accuracy of 81.4% and an AUC of 0.872 (Figure 5), indicating a strong ability to differentiate between PDA and non-PDA cases. Furthermore, the XGBoost showed a sensitivity of 92.5%, significantly enhancing the detection of true PDA cases, but with a specificity of 57.9%, indicating moderate precision in recognizing non-PDA cases, but a better result compared to the previous model. The Kappa statistic for XGBoost was 0.54, showing improved concordance between predictions and actual results. Our XGBoost model demonstrated superior sensitivity and overall accuracy compared to the Random Forest model, making it more effective for identifying at-risk neonates for PDA.

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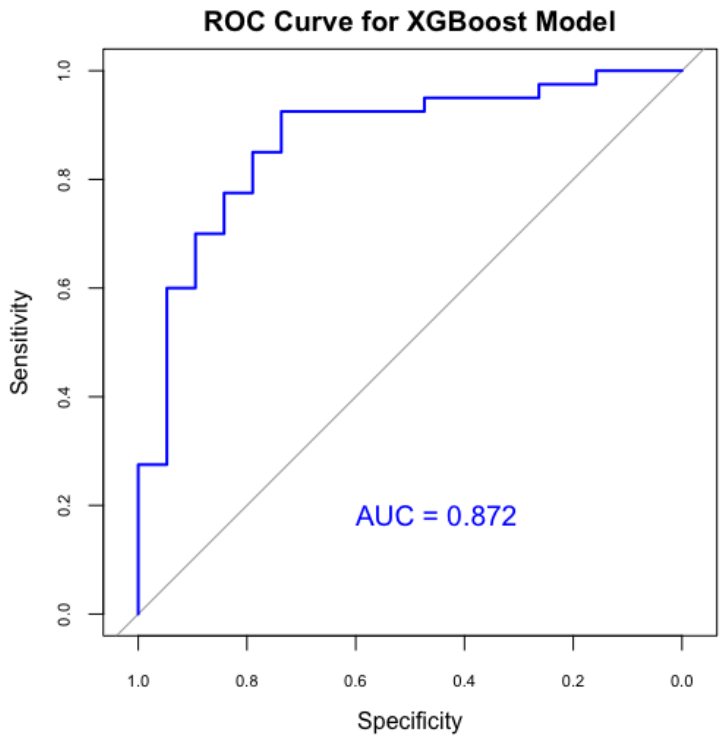

Figure 5. ROC curve for our XGBoost model.

Figure 6 provides a bar chart which illustrates the ten most significant features correlated with the probability of Patent Ductus Arteriosus (PDA) in neonates, as determined by the XGBoost model. The primary predictors provide a comprehensive view of the factors affecting PDA risk, emphasizing maternal health conditions, fetal development metrics, and prenatal care as essential components in PDA forecasting.

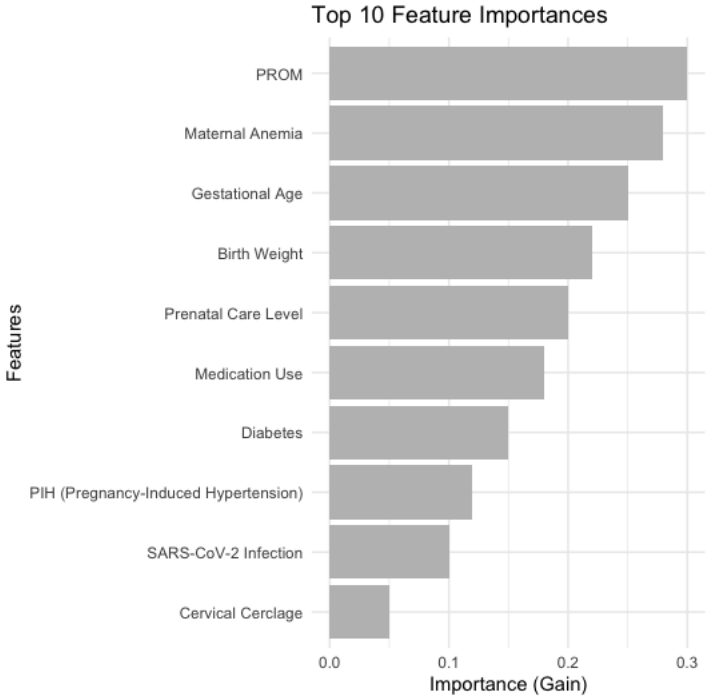

Figure 6. Top 10 predictors provided by our XGBoost model.

4. Discussion

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Our study identified multiple significant maternal and neonatal factors linked to an elevated risk of patent ductus arteriosus in neonates, including prolonged rupture of membranes (>18 hours), maternal anemia, gestational age, and birth weight. Lee et al. describes lower gestational age, female gender, and pregnancy induced hypertension a significant risk factor for symptomatic PDA [29]. PROM surfaced as the paramount predictor, exhibiting a substantial odds ratio and feature significance in both Random Forest and XGBoost models. This association may be attributed to the potential of PROM to precipitate infection or other complications that impact neonatal cardiovascular development. Kusuma et al. concluded that rupture of membranes >12 hours and thrombocytopenia in the first 24 hours were proven to increase the risk of PDA in preterm infants [30].

Another observation identified gestational age and birth weight as significant predictors, aligning with the existing literature. Low gestational age and low birth weight frequently indicate immature circulatory and pulmonary systems, thereby elevating the risk of PDA [31,32]. Bernati et al. noted that newborns <2000 grams at birth tended to have a 1.9 times higher risk for PDA [33].

Maternal anaemia demonstrated considerable feature importance, suggesting that inadequate maternal nutrition or oxygenation during gestation may impede foetal development, resulting in neonatal anaemia and potentially causing delayed ductal closure, demanding postnatal anaemia treatment, as suggested by literature [34,35]. Pregnancy-induced hypertension and diabetes were correlated with elevated odds of patent ductus arteriosus, albeit not consistently with statistical significance. These conditions may indirectly influence fetal cardiovascular development by modifying maternal blood flow and nutrient delivery, thereby affecting the neonate's capacity to regulate ductal closure [36,37]. Maternal infections, including SARS-CoV-2 and GBS, exhibited a potential association with PDA, although this was not statistically significant. However, infection-induced inflammation may elevate the risk of circulatory complications in neonates, indicating that infection control and maternal prevention could be significant in mitigating PDA risk [38,39].

Extensive prenatal care did not exhibit a significant correlation with the reduction of PDA risk, indicating that standard prenatal care alone may be insufficient to alleviate particular risks associated with PDA, with specialised prenatal interventions aimed at high-risk pregnancies yielding a more significant effect [40]. Medications, specifically enoxaparin and methyldopa, exhibited modest correlations with the risk of PDA. Hoeltzenbein et al describes a higher rate of major birth defects in methyldopa-exposed pregnancies (3.7%) compared to cohort (2.5%), but the difference was statistically not significant [41]. Similarly, Bar et al. observed 3 out of 46 neonates born from mothers with Enoxaparin treatment during pregnancy exhibited persistent ductus arteriosus [42].

Timely recognition of PDA risk factors, including PROM, reduced gestational age, and maternal anaemia, may facilitate targeted interventions, thereby enhancing neonatal outcomes. Healthcare providers may prioritise these factors in prenatal and postnatal care to mitigate the incidence of PDA. For preterm infants with recognised PDA risk factors, enhanced monitoring and management protocols may be instituted to reduce complications related to PDA. These findings may inform clinical decisions regarding antenatal and postnatal care, especially in NICUs that allocate resources to the management of high-risk neonates.

Our study was constrained by sample size and the omission or incompleteness of certain variables. Subsequent research should target larger cohorts to validate these associations and enhance the predictive accuracy of the models. Further research is required to elucidate the mechanisms connecting maternal health conditions and particular medications to PDA, in order to clarify potential causal relationships. Additional model optimisation and evaluation using alternative machine learning techniques, such as neural networks or ensemble methods, could improve predictive accuracy and provide greater understanding of the interactions among maternal, neonatal, and PDA risk factors. The incorporation of machine learning models such as Random Forest and XGBoost in clinical environments may enhance personalised medicine by enabling clinicians to more precisely stratify PDA risk according to specific maternal and neonatal variables.

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5. Conclusions

This study provides a comprehensive examination of maternal and neonatal factors influencing the risk of patent ductus arteriosus in neonates, combining conventional statistical methods with advanced machine learning techniques. Logistic regression and chi-square tests highlighted prolonged rupture of membranes (>18 hours) as a key predictor, while XGBoost identified a broader range of influential variables, including maternal anemia, gestational age, birth weight, and prenatal care level. The results underscore the crucial impact of maternal health and pregnancy-related factors on neonatal outcomes. Future research should confirm these findings in larger, diverse populations and explore using advanced predictive models in clinical decisions to improve neonatal care and outcomes.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of the Clinical Hospital of Obstetrics and Gynecology "Prof. Dr. Panait Sârbu" of Bucharest, no. 16516/11.12.2024 . The data was fully anonymized, with no identifiable personal information, ensuring compliance with privacy and confidentiality standards.

Informed Consent Statement: Patient consent was waived because it utilized **retrospective data** collected from existing medical records without directly involving human participants or interventions.

Data Availability Statement: All data is available in this paper.

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Conflicts of Interest: The authors declare no conflicts of interest.

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