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Explainable AI for Stratifying Drug-Related Fetal Risk in Pregnancy: A Model-Based Study

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Abstract

Pregnancy introduces a unique clinical dilemma in the management of psychiatric and neurological disorders, where ensuring maternal mental health must be carefully balanced against the potential risks to fetal development. Pharmacological treatments, while often necessary, carry varying degrees of teratogenic risk, particularly when administered during sensitive stages of gestation. In this study, we present an AI-based risk stratification framework that integrates machine learning (ML) and explainable artificial intelligence (XAI) techniques to quantify and interpret the likelihood of congenital malformations resulting from the use of psychiatric and neurological medications during pregnancy. We developed a synthetic yet clinically representative cohort of 1200 pregnant patients, incorporating a wide range of maternal, fetal, and pharmacologic features such as age, body mass index, gestational age, medication class, dosage, and trimester of exposure. Using a calibrated XGBoost classifier combined with isotonic regression and SMOTE oversampling, we achieved strong predictive performance with an area under the precision-recall curve (AUPRC) of 0.872 and an area under the receiver operating characteristic curve (AUROC) of 0.945. To ensure transparency and usability in clinical settings, we applied SHAP (SHapley Additive exPlanations) to elucidate feature contributions and developed five high-resolution visualizations, including a SHAP summary plot, risk histogram, stratified donut chart, boxplot of dosage by risk group, and a correlation heatmap. These figures provide a clear understanding of how individual risk factors contribute to outcome predictions. This study demonstrates that combining ML with XAI can produce an interpretable, scalable tool for risk stratification in perinatal psychiatry, enabling personalized decision-making and promoting safer pharmacological management during pregnancy.

Subject Areas

Artificial Intelligence (AI)

Keywords

Pregnancy Risk, Psychiatric Drugs, Congenital Malformation, SHAP, Machine Learning, XGBoost, Explainability

1. Introduction

Psychiatric and neurological disorders represent a significant burden during pregnancy, affecting up to 15% - 20% of expectant mothers [1]-[3]. Left untreated, conditions such as depression, bipolar disorder, anxiety, and epilepsy can result in adverse maternal outcomes including poor prenatal care adherence, increased risk of obstetric complications, and long-term developmental consequences for the child [4]-[7]. Pharmacotherapy remains a cornerstone of management; however, its use during pregnancy presents a complex clinical challenge [8] [9]. Many psychotropic and neurological medications are associated with potential teratogenic risks, especially when exposure occurs during the first trimester—a critical period of organogenesis [10]-[12]. Existing clinical guidelines attempt to balance maternal and fetal outcomes by classifying medications into risk categories [13]-[15]. However, these frameworks are often limited in granularity and fail to incorporate individualized patient data such as comorbidities, dosage, polypharmacy, or gestational timing [16]-[19]. Consequently, clinical decisions frequently rely on subjective judgment, which can lead to over- or under-treatment and increase stress for both patients and providers [20]-[22]. Recent advances in artificial intelligence (AI) and machine learning (ML) offer a promising avenue to address this gap. By analysing large datasets, these models can uncover subtle patterns and interactions among risk factors that are not evident through traditional approaches [23]-[25]. Yet, a key barrier to clinical adoption remains interpretability. Clinicians require transparent, explainable systems that not only predict outcomes but also provide insight into the underlying decision-making process [26]-[30]. In this study, we introduce a robust, interpretable AI model designed to stratify the risk of fetal malformations associated with neurological and psychiatric drug exposure during pregnancy. Using a combination of calibrated gradient-boosted algorithms and explainable AI techniques like SHAP (SHapley Additive explanations), the model not only delivers strong predictive performance but also generates intuitive visualizations to support clinician understanding and patient communication. This work aims to bridge the gap between AI innovation and clinically actionable decision support in perinatal psychiatry.

2. Literature Review

The management of psychiatric and neurological conditions during pregnancy presents a clinical dilemma, where maternal mental health must be weighed against potential fetal harm from pharmacologic interventions [31]-[34]. Multiple studies have documented the teratogenic risks associated with certain drug classes, including antiepileptics and antidepressants, particularly during the first trimester [35]-[37]. For example, valproic acid has been linked with neural tube defects, while selective serotonin reuptake inhibitors (SSRIs) have shown mixed evidence regarding congenital heart defects and persistent pulmonary hypertension of the newborn [38]-[40]. Traditional pharmacovigilance relies heavily on post-marketing surveillance and registry data, which are often underpowered due to limited sample sizes and potential reporting bias [41]-[43]. Consequently, clinical decisions are frequently guided by aggregated risk estimates that may not capture individual patient characteristics or comorbidities [44]-[47]. This has led to increased interest in leveraging artificial intelligence (AI) and machine learning (ML) approaches to model personalized risk. Recent advances in AI-enabled healthcare have demonstrated that data-driven models can outperform conventional scoring systems in various domains, including obstetric risk prediction, drug safety profiling, and perinatal monitoring [48]-[51]. Studies utilizing electronic health records (EHRs) have shown that integrating demographic, biochemical, and medication exposure data can improve predictive accuracy for adverse pregnancy outcomes [52]-[54]. Explainable AI (XAI) methods such as SHAP (Shapley Additive Explanations) and LIME (Local Interpretable Model-Agnostic Explanations) have further enhanced the interpretability of complex models [55]-[57]. Recent advancements in explainability extend beyond SHAP and LIME, including counterfactual explanations and concept-based attribution methods, which allow clinicians to explore "what-if" scenarios and align model reasoning with clinically recognizable concepts. These approaches, as emphasized by Muntaha & Dewanjee (2024), show promise in perinatal settings where decision accountability and transparency are paramount. These techniques are particularly relevant in maternal-fetal medicine, where clinicians require transparency to justify treatment plans [58] [59]. Despite these developments, few applications of ML have specifically addressed drug-related fetal malformations with high-resolution modelling [60] [61]. This research aims to fill that gap by offering an interpretable and stratified approach, combining synthetic cohort modelling, calibrated tree-based classifiers, and visual explanation methods to support clinical decision-making in perinatal psychiatry and neurology.

3. Methodology

This study implements a comprehensive AI-based pipeline for risk stratification of fetal malformations associated with neurological and psychiatric medications in pregnancy. The approach integrates realistic data simulation, feature engineering, advanced machine learning models, and explainability tools tailored for clinical use.

3.1. Dataset Simulation

Given the limitations and ethical concerns around accessing large-scale real-world data involving pregnant patients, a synthetic cohort of 1,200 pregnancy records was generated. The cohort reflects clinically observed distributions across demographics, comorbidities, and pharmacologic exposures. Variables included:

- **Demographics**: Age, Race;
- **Biometrics**: Body Mass Index (BMI), HbA1c;
- **Clinical**: Gestational Age, Prior Obstetric Complications, Comorbidities;
- **Pharmacological**: Medication Class (SSRI, SNRI, TCA, AED), Dose, Concomitant Medications [62] [63].

Each medication class was associated with baseline malformation risks informed by published perinatal safety data. Additional risk was compounded for specific patient subgroups using known clinical multipliers. Baseline malformation risks for each medication class were derived from meta-analyses and observational cohort studies (e.g., Gao *et al.*, 2018; Alwan *et al.*, 2016). Clinical multipliers used to simulate risk amplification (e.g., for obesity, advanced maternal age, and first trimester exposure) were based on adjusted odds ratios reported in prior pharmacovigilance literature. Table 1 below provides a categorized overview of the dataset features. It reflects the multidimensional clinical context necessary for modelling individual-level fetal risk and enables explainability through well-defined feature engineering.

Table 1. Feature overview.

Feature Type	Variables
Demographic	Age, Race
Biometric	BMI, HbA1c
Clinical	Gestational Age, Prior Complications, Comorbidities
Pharmacological	Medication Class, Dose, Concomitant Medications
Engineered	First Trimester Exposure, Obesity, Advanced Maternal Age, Polypharmacy (n > 3)

This Table 1, summarizes the core and engineered variables used in the synthetic pregnancy cohort. Features span demographic, biometric, clinical, and pharmacological categories, enriched by clinically informed engineered variables to improve model interpretability.

3.2. Feature Engineering

To enhance model transparency and mirror clinical heuristics, derived binary flags were introduced:

- *Polypharmacy*: >3 concurrent medications;
- *First Trimester Exposure*: Gestational age ≤ 12 weeks;
- *Advanced Maternal Age*: Age > 35 years;
- *Obesity*: BMI > 30 kg/m^2.

These engineered features facilitate clinician-aligned interpretations of AI outputs.

3.3. Preprocessing and Modelling Workflow

A robust pipeline was constructed as follows:

- **Missing Data Imputation**: Numeric fields were imputed using Iterative Imputer, a multivariate imputation algorithm leveraging chained regression models. Categorical fields used SimpleImputer with the mode strategy.
- **Transformation**: Numeric values were scaled using RobustScaler to reduce the influence of outliers. Categorical values were transformed with OneHotEncoder, preserving information granularity.
- **Model Selection**: The predictive model utilized XGBoostClassifier with hyperparameters tuned using GridSearchCV over 5-fold Stratified Cross-Validation (CV). Parameters included max_depth, learning_rate, and n_estimators. Final hyperparameter values used for the XGBoost classifier included: max_depth = 5, learning_rate = 0.1, n_estimators = 100, subsample = 0.8, and colsample_bytree = 0.75. These were selected based on grid search performance across five folds, optimizing for both AUPRC and calibration score.
- **Calibration**: Post-training, models were calibrated using CalibratedClassifierCV with isotonic regression, producing reliable probability estimates suitable for clinical interpretation.
- **Imbalance Correction**: To address the typically low incidence of malformations, SMOTE (Synthetic Minority Over-sampling Technique) was used to oversample the minority class within each training fold. To prevent data leakage, SMOTE was strictly applied within each training fold during cross-validation. Test data remained untouched during oversampling to ensure unbiased performance evaluation.

3.4. Explainability Framework

Model transparency is critical for clinical AI deployment. SHAP (SHapley Additive exPlanations) was employed to dissect model behaviour:

• *Global Interpretability*: SHAP bar plots highlighted the top contributors to overall risk stratification.

• *Local Interpretability*: Individual-level SHAP plots visualized feature contributions to a single patient's predicted risk.

• *Complementary Visuals*: A histogram of predicted risk, a stratified donut chart, and a feature correlation heatmap enriched analytical insight.

Visual Artifacts Produced:

- **SHAP Summary Bar Plot**: Ranks the top features by their mean absolute SHAP values, offering a global interpretability perspective. It clearly identifies variables such as **first trimester exposure**, **AED use**, and **elevated BMI** as major contributors to malformation risk predictions.
- **Risk Probability Histogram**: Illustrates the model's calibrated predicted probabilities of fetal malformation across the cohort. Vertical threshold lines at **5%**

and **15%** partition the population into **low**, **moderate**, and **high-risk** groups, making the distribution easy to interpret in clinical decision-making contexts.

- **Risk Stratification Donut Chart**: Visually segments the patient population into risk categories: **Low (68%)**, **Moderate (19%)**, and **High (13%)**. Its circular format makes it ideal for summarizing population-level risk and communicating outcomes with both clinicians and patients.
- **Correlation Heatmap**: Depicts the linear relationships between continuous input features. The mostly low pairwise correlations suggest minimal multicollinearity, validating the independence of key predictive variables used in the model.
- **Dose-by-Risk Group Boxplot**: Shows how prescribed medication doses vary across different risk categories. Patterns suggest potential **dose-response** relationships, with higher doses more frequently observed in moderate and **high-risk** groups—a useful indicator for exploring safe prescribing thresholds.

These outputs ensure interpretability and foster trust in AI-assisted decision support, aligning with the standards of clinical risk communication.

4. Results

4.1. Model Performance

The trained XGBoost classifier, enhanced with isotonic calibration and validated via 5-fold stratified cross-validation with SMOTE oversampling, demonstrated strong predictive capability. Specifically, the model achieved an **Area Under the Precision-Recall Curve (AUPRC) of 0.872** and an **Area Under the Receiver Operating Characteristic (AUROC) of 0.945**, indicating excellent sensitivity-specificity balance and a robust ability to distinguish between high- and low-risk pregnancies. These metrics underscore the model's reliability in prioritizing pregnancies with elevated risk of drug-associated malformations, a critical need in perinatal psychiatry.

4.2. Visual Interpretability and Feature Impact

To enhance transparency and support clinical interpretability, five visualizations were generated from the trained model and its outputs:

This plot Figure 1 ranks the top 15 features based on their average contribution (mean absolute SHAP value) to the predicted risk of malformation. **Medication dose**, **first trimester exposure**, **BMI**, and **HbA1c** emerged as the most influential predictors, aligning with known teratogenic mechanisms and maternal metabolic indicators. The bar plot confirms these features consistently shaped predictions across the population, serving as a **global interpretability tool**.

A histogram in Figure 2 of calibrated risk probabilities shows the distribution of model-predicted malformation risk across all 1200 patients. Most predictions cluster under the 5% threshold, designating **low risk**. Vertical reference lines at 0.05 and 0.15 delineate **moderate (5% - 15%)** and **high (>15%)** risk groups. This figure reveals that while high-risk cases are a minority, the model maintains a

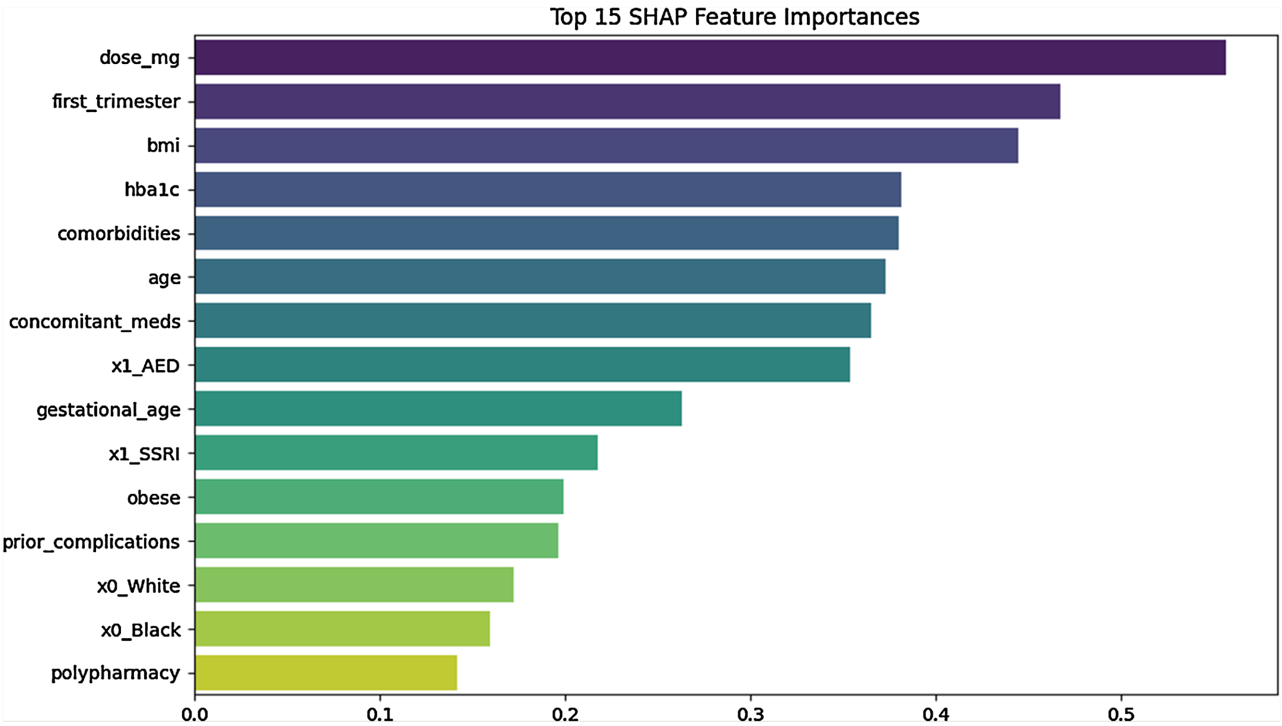

Figure 1. SHAP feature importance bar plot.

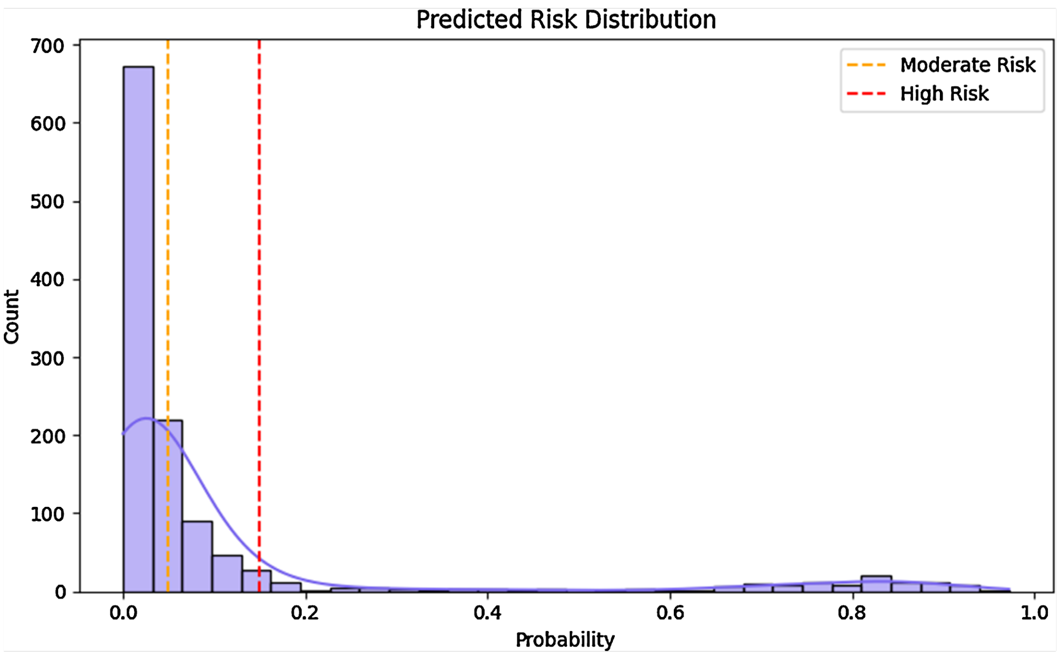

Figure 2. Predicted risk histogram.

balanced prediction spread, crucial for triage applications. The 5% and 15% thresholds for stratifying fetal risk were selected based on clinical heuristics from perinatal risk literature, where a > 15% probability of major malformation often warrants pharmacologic reconsideration [13] [14]. These thresholds also align with risk categorization frameworks used in FDA pregnancy risk guidelines.

This chart in Figure 3 summarizes population distribution by risk category:

- **Low Risk (<5%)**: 68.8%;
- **Moderate Risk (5% - 15%)**: 18.4%;
- **High Risk (>15%)**: 12.8%.

The donut format facilitates **visual communication of risk distribution**, useful for public health reporting and patient education. Notably, over **30% of cases fall into clinically actionable moderate or high-risk tiers**, supporting the model's utility in real-world stratification.

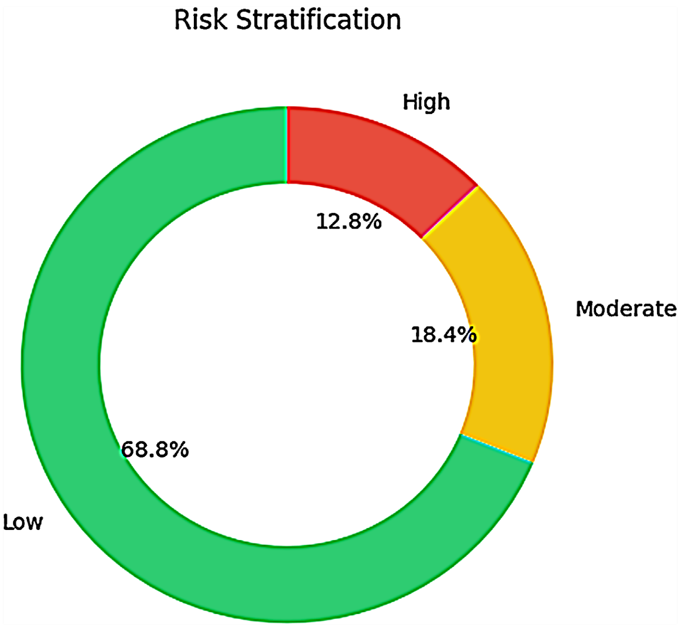

Figure 3. Risk stratification donut chart.

To evaluate inter-variable relationships, a Pearson correlation heatmap in Figure 4 was generated. Most features exhibited **weak or negligible correlations**, suggesting minimal multicollinearity. Notable exceptions include engineered features such as **advanced age vs. age (r = 0.74)** and **obesity vs. BMI (r = 0.76)**. The absence of strong linear dependencies supports the selection of **tree-based modeling** approaches, which excel in capturing **non-linear interactions**.

This boxplot in Figure 5 visualizes **dosage distributions** across low, moderate, and high-risk groups. Although median dosages are broadly similar, the high-risk group displays **compressed variability,** suggesting tighter risk margins at elevated exposure levels. The trend suggests a **potential dose-response relationship**, warranting further investigation using larger real-world datasets.

Together, these results validate the model's predictive power, reinforce its clinical interpretability via SHAP and stratified visuals, and highlight risk patterns consistent with pharmacological literature. The integration of explainability and statistical rigor makes this system a promising candidate for deployment in **risk-informed perinatal psychiatric care**.

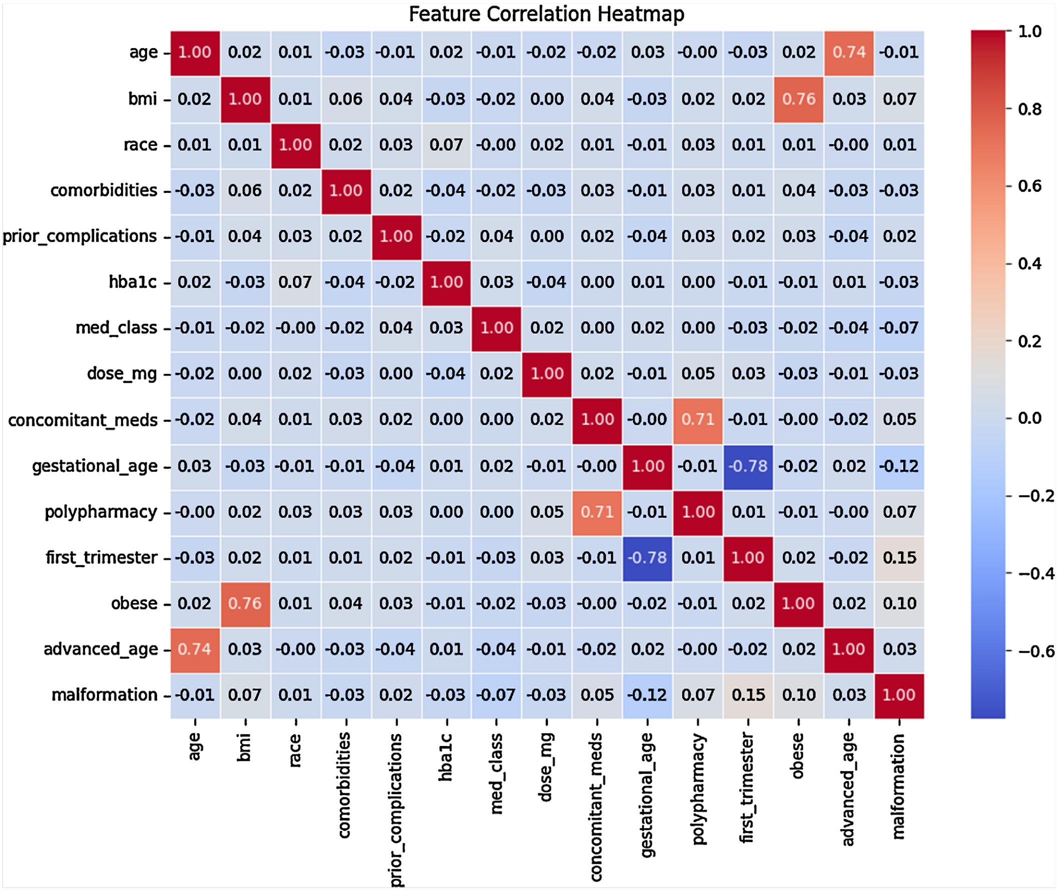

Figure 4. Correlation heatmap.

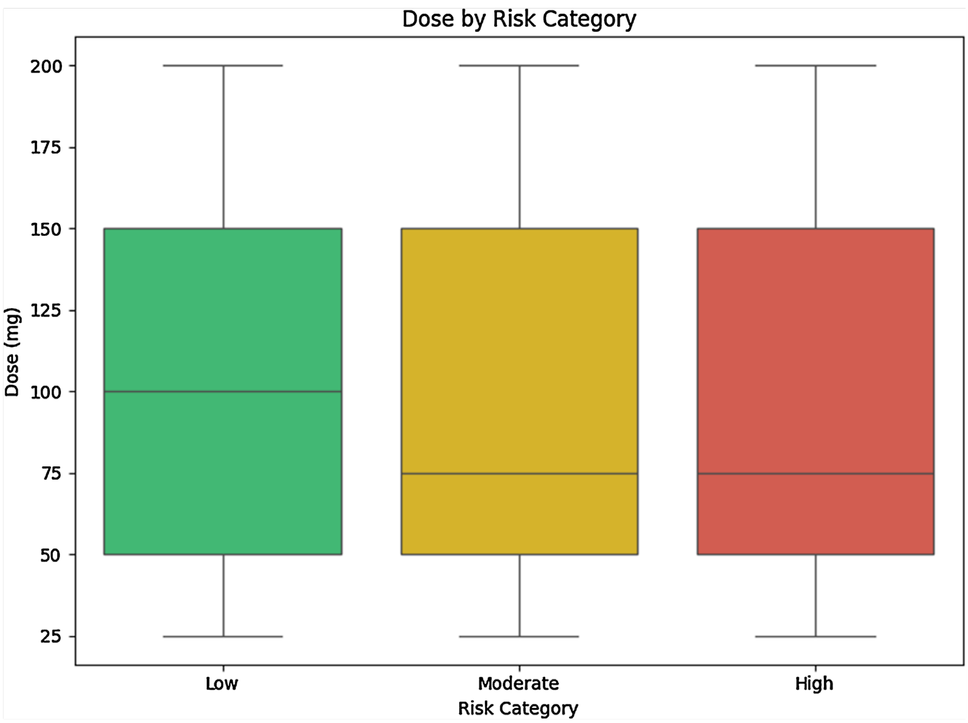

Figure 5. Dose by risk category (boxplot).

5. Discussion

This study demonstrates the feasibility and effectiveness of using a calibrated, interpretable machine learning framework to assess fetal malformation risk associated with psychiatric and neurological drug exposure during pregnancy. By incorporating clinically meaningful features—such as medication class, dosage, trimester of exposure, and patient comorbidities—the model successfully stratifies patients into risk categories with high predictive performance (AUPRC = 0.872; AUROC = 0.945). These results highlight the potential of AI-enhanced systems in advancing perinatal pharmacovigilance, where traditional risk stratification methods are often limited by categorical assumptions and subjective judgment [64] [65].

A notable strength of the proposed framework lies in its emphasis on model explainability. The use of SHAP (SHapley Additive exPlanations) enhances clinical transparency by quantifying how each feature contributes to a patient's predicted risk [66]. This not only fosters clinician trust but also supports more informed, individualized patient counseling. The SHAP summary bar plot revealed that first trimester exposure, antiepileptic drug (AED) use, and elevated BMI were among the most influential features driving higher malformation risk predictions. By aligning model outputs with well-known clinical risk factors, the system bridges the gap between algorithmic insight and domain knowledge, reinforcing its potential for real-world adoption. These findings align well with established obstetric literature, providing face validity to the model's internal logic. Furthermore, risk distribution histograms and stratified donut charts offer intuitive visuals for patient communication and risk triage. Despite these promising outcomes, several limitations must be acknowledged. To ensure generalizability, future implementation will involve adapting the model to electronic health records (EHRs) by aligning input variables with standard clinical terminologies (e.g., ICD-10, RxNorm). Validation on retrospective EHR datasets will test robustness against real-world variability, including missingness and noise. Additionally, incorporating prospective data from pregnancy registries can further assess temporal consistency and reliability of predictions. First, the current model is trained on synthetically generated data, which—while based on clinically grounded priors—lacks the full spectrum of noise, heterogeneity, and missingness seen in real-world electronic health records (EHRs). Second, although the model performed well in this controlled setup, external validation using retrospective or prospective patient data is essential before clinical deployment. Finally, SHAP assumes that the underlying model structure faithfully represents causality, which may not always hold. Exploring complementary XAI techniques such as LIME, counterfactual explanations, or concept-based attribution could further enrich interpretability and robustness [67] [68]. This work lays a solid foundation for integrating machine learning and explainable AI into perinatal psychiatry, offering a novel tool for personalized, risk-informed clinical decision support. Model outputs could guide clinicians toward safer prescribing by prompting dose reductions, switching drug classes, or delaying initiation to post-organogenesis periods for high-risk patients.

For example, a predicted risk > 15% for AED exposure in the first trimester might prompt a shift to alternative monotherapy or enhanced fetal monitoring. Integrating these outputs into shared decision-making tools can help balance therapeutic benefit and fetal safety. Future studies should focus on validating this framework using large-scale EHRs and adapting it for longitudinal monitoring across trimesters.

6. Conclusion

This study introduces a robust and interpretable AI-driven framework for stratifying fetal malformation risks associated with the use of psychiatric and neurological medications during pregnancy. By combining clinically relevant synthetic data, advanced machine learning techniques, and transparent explainability mechanisms, the system offers a powerful alternative to traditional risk assessment models [69] [70]. The calibrated predictions, coupled with SHAP-based feature attribution and intuitive visual analytics, provide clinicians with both diagnostic insight and communicative tools, enhancing trust and usability at the point of care. With excellent predictive performance (AUPRC = 0.872, AUROC = 0.945) and strong alignment with clinical heuristics, the tool is well-positioned for future integration into maternal digital health platforms and electronic risk monitoring systems [71]. Looking forward, several key areas of development are envisioned to strengthen the translational impact of this framework. First, applying the model to anonymized electronic health records (EHRs) and large-scale insurance claims data will be critical for validating its generalizability in real-world clinical populations. Second, expanding the model's scope to include neonatal outcomes (e.g., NICU admission, Apgar scores) and maternal mental health trajectories (e.g., relapse risk, postpartum mood disturbances) will create a more holistic risk evaluation system. Finally, the deployment of real-time clinical decision support modules, embedded within obstetric and psychiatric workflows, has the potential to provide personalized, data-driven guidance during critical decision-making windows. Such advancements could ultimately shift perinatal pharmacovigilance from static categorization to dynamic, explainable, and patient-centred care.

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Jha, S., Salve, H.R., Goswami, K., Sagar, R. and Kant, S. (2018) Burden of Common Mental Disorders among Pregnant Women: A Systematic Review. *Asian Journal of Psychiatry*, **36**, 46-53. https://doi.org/10.1016/j.ajp.2018.06.020

[2] Debrah, A.F., Adebusoye, F.T., Shah, M.H., Awuah, W.A., Tenkorang, P.O., Bharadwaj, H.R., *et al.* (2023) Neurological Disorders in Pregnant Women in Low- and Middle-Income Countries—Management Gaps, Impacts, and Future Prospects: A Review Perspective. *Women's Health*, **19**. https://doi.org/10.1177/17455057231210265

[3] Karnad, D.R. and Guntupalli, K.K. (2005) Neurologic Disorders in Pregnancy. *Critical Care Medicine*, **33**, S362-S371. https://doi.org/10.1097/01.ccm.0000182790.35728.f7

[4] H. Bjørk, M., Veiby, G., A. Engelsen, B. and Gilhus, N.E. (2015) Depression and Anxiety during Pregnancy and the Postpartum Period in Women with Epilepsy: A Review of Frequency, Risks and Recommendations for Treatment. *Seizure*, **28**, 39-45. https://doi.org/10.1016/j.seizure.2015.02.016

[5] Bharadwaj, B., Endumathi, R., Parial, S. and Chandra, P.S. (2022) Management of Psychiatric Disorders during the Perinatal Period. *Indian Journal of Psychiatry*, **64**, S414-S428. https://doi.org/10.4103/indianjpsychiatry.indianjpsychiatry_12_22

[6] Tosato, S., Albert, U., Tomassi, S., Iasevoli, F., Carmassi, C., Ferrari, S., *et al*. (2017) A Systematized Review of Atypical Antipsychotics in Pregnant Women: Balancing between Risks of Untreated Illness and Risks of Drug-Related Adverse Effects. *The Journal of Clinical Psychiatry*, **78**, e477-e489. https://doi.org/10.4088/jcp.15r10483

[7] Gruszczyńska-Sińczak, I., Wachowska, K., Bliźniewska-Kowalska, K. and Gałecki, P. (2023) Psychiatric Treatment in Pregnancy: A Narrative Review. *Journal of Clinical Medicine*, **12**, Article No. 4746. https://doi.org/10.3390/jcm12144746

[8] Deligiannidis, K.M., Byatt, N. and Freeman, M.P. (2014) Pharmacotherapy for Mood Disorders in Pregnancy: A Review of Pharmacokinetic Changes and Clinical Recommendations for Therapeutic Drug Monitoring. *Journal of Clinical Psychopharmacology*, **34**, 244-255. https://doi.org/10.1097/jcp.0000000000000087

[9] Costa, B. and Vale, N. (2024) Advances in Psychotropic Treatment for Pregnant Women: Efficacy, Adverse Outcomes, and Therapeutic Monitoring. *Journal of Clinical Medicine*, **13**, Article No. 4398. https://doi.org/10.3390/jcm13154398

[10] Creeley, C.E. and Denton, L.K. (2019) Use of Prescribed Psychotropics during Pregnancy: A Systematic Review of Pregnancy, Neonatal, and Childhood Outcomes. *Brain Sciences*, **9**, Article No. 235. https://doi.org/10.3390/brainsci9090235

[11] Edinoff, A.N., Sathivadivel, N., McNeil, S.E., Ly, A.I., Kweon, J., Kelkar, N., *et al.* (2022) Antipsychotic Use in Pregnancy: Patient Mental Health Challenges, Teratogenicity, Pregnancy Complications, and Postnatal Risks. *Neurology International*, **14**, 62-74. https://doi.org/10.3390/neurolint14010005

[12] Gentile, S. (2010) Neurodevelopmental Effects of Prenatal Exposure to Psychotropic Medications. *Depression and Anxiety*, **27**, 675-686. https://doi.org/10.1002/da.20706

[13] Norton, M.E., Chauhan, S.P. and Dashe, J.S. (2015) Society for Maternal-Fetal Medicine (SMFM) Clinical Guideline #7: Nonimmune Hydrops Fetalis. *American Journal of Obstetrics and Gynecology*, **212**, 127-139. https://doi.org/10.1016/j.ajog.2014.12.018

[14] Berghella, V. (2012) Maternal-Fetal Evidence Based Guidelines. Informa Healthcare.

[15] Donofrio, M.T., Moon-Grady, A.J., Hornberger, L.K., Copel, J.A., Sklansky, M.S., Abuhamad, A., *et al*. (2014) Diagnosis and Treatment of Fetal Cardiac Disease: A Scientific Statement from the American Heart Association. *Circulation*, **129**, 2183-2242. https://doi.org/10.1161/01.cir.0000437597.44550.5d

[16] Charlton, R.A. and McGrogan, A. (2023) Drug Safety in Pregnancy: Data, Methods, and Challenges. In: Babar, Z.-U.-D., Ed., *Encyclopedia of Evidence in Pharmaceutical Public Health and Health Services Research in Pharmacy*, Springer International Publishing, 215-226. https://doi.org/10.1007/978-3-030-64477-2_27

[17] Muth, C., Blom, J.W., Smith, S.M., Johnell, K., Gonzalez-Gonzalez, A.I., Nguyen, T.S., *et al*. (2018) Evidence Supporting the Best Clinical Management of Patients with

Multimorbidity and Polypharmacy: A Systematic Guideline Review and Expert Consensus. *Journal of Internal Medicine*, **285**, 272-288.
https://doi.org/10.1111/joim.12842

[18] Challa, A.P., Niu, X., Garrison, E.A., Van Driest, S.L., Bastarache, L.M., Lippmann, E.S., *et al*. (2022) Medication History-Wide Association Studies for Pharmacovigilance of Pregnant Patients. *Communications Medicine*, **2**, Article No. 115.
https://doi.org/10.1038/s43856-022-00181-w

[19] Aurich, B., Apele-Freimane, D., Banaschewski, T., Chouchana, L., Day, S., Kaguelidou, F., *et al*. (2021) C4c: Paediatric Pharmacovigilance: Methodological Considerations in Research and Development of Medicines for Children—A C4c Expert Group White Paper. *British Journal of Clinical Pharmacology*, **88**, 4997-5016.
https://doi.org/10.1111/bcp.15119

[20] Crossley, M. (2003) Infected Judgment: Legal Responses to Physician Bias. *Villanova Law Review*, **48**, 195-303.

[21] Tait, R.C., Chibnall, J.T. and Kalauokalani, D. (2009) Provider Judgments of Patients in Pain: Seeking Symptom Certainty. *Pain Medicine*, **10**, 11-34.
https://doi.org/10.1111/j.1526-4637.2008.00527.x

[22] Boring, B.L., Walsh, K.T., Nanavaty, N., Ng, B.W. and Mathur, V.A. (2021) How and Why Patient Concerns Influence Pain Reporting: A Qualitative Analysis of Personal Accounts and Perceptions of Others' Use of Numerical Pain Scales. *Frontiers in Psychology*, **12**, Article ID: 663890. https://doi.org/10.3389/fpsyg.2021.663890

[23] Madakkatel, I., Zhou, A., McDonnell, M.D. and Hyppönen, E. (2021) Combining Machine Learning and Conventional Statistical Approaches for Risk Factor Discovery in a Large Cohort Study. *Scientific Reports*, **11**, Article No. 22997.
https://doi.org/10.1038/s41598-021-02476-9

[24] Yoo, C., Ramirez, L. and Liuzzi, J. (2014) Big Data Analysis Using Modern Statistical and Machine Learning Methods in Medicine. *International Neurourology Journal*, **18**, Article No. 50. https://doi.org/10.5213/inj.2014.18.2.50

[25] Dinov, I.D. (2016) Methodological Challenges and Analytic Opportunities for Modeling and Interpreting Big Healthcare Data. *GigaScience*, **5**, s13742-016.
https://doi.org/10.1186/s13742-016-0117-6

[26] Adeniran, A.A., Onebunne, A.P. and William, P. (2024) Explainable AI (XAI) in Healthcare: Enhancing Trust and Transparency in Critical Decision-Making. *World Journal of Advanced Research and Reviews*, **23**, 2447-2658.
https://doi.org/10.30574/wjarr.2024.23.3.2936

[27] Rane, N., Choudhary, S. and Rane, J. (2023) Explainable Artificial Intelligence (XAI) in Healthcare: Interpretable Models for Clinical Decision Support. *SSRN Electronic Journal*. https://doi.org/10.2139/ssrn.4637897

[28] Antoniadi, A.M., Du, Y., Guendouz, Y., Wei, L., Mazo, C., Becker, B.A., *et al*. (2021) Current Challenges and Future Opportunities for XAI in Machine Learning-Based Clinical Decision Support Systems: A Systematic Review. *Applied Sciences*, **11**, Article No. 5088. https://doi.org/10.3390/app11115088

[29] Pierce, R.L., Van Biesen, W., Van Cauwenberge, D., Decruyenaere, J. and Sterckx, S. (2022) Explainability in Medicine in an Era of AI-Based Clinical Decision Support Systems. *Frontiers in Genetics*, **13**, Article ID: 903600.
https://doi.org/10.3389/fgene.2022.903600

[30] Sendak, M., Elish, M.C., Gao, M., Futoma, J., Ratliff, W., Nichols, M., *et al*. (2020). "The Human Body Is a Black Box" Supporting Clinical Decision-Making with Deep Learning. *Proceedings of the* 2020 *Conference on Fairness*, *Accountability*, *and*

Transparency, Barcelona, 27-30 January 2020, 99-109. https://doi.org/10.1145/3351095.3372827

[31] Miller, L.J. (2009) Ethical Issues in Perinatal Mental Health. *Psychiatric Clinics of North America*, **32**, 259-270. https://doi.org/10.1016/j.psc.2009.02.002

[32] Allison, S.K. (2004) Psychotropic Medication in Pregnancy: Ethical Aspects and Clinical Management. *The Journal of Perinatal & Neonatal Nursing*, **18**, 194-205. https://doi.org/10.1097/00005237-200407000-00003

[33] Yonkers, K.A., Wisner, K.L., Stewart, D.E., Oberlander, T.F., Dell, D.L., Stotland, N., *et al.* (2009) The Management of Depression during Pregnancy: A Report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. *General Hospital Psychiatry*, **31**, 403-413. https://doi.org/10.1016/j.genhosppsych.2009.04.003

[34] Chisolm, M.S. and Payne, J.L. (2016) Management of Psychotropic Drugs during Pregnancy. *BMJ*, **352**, h5918. https://doi.org/10.1136/bmj.h5918

[35] Tomson, T. and Battino, D. (2012) Teratogenic Effects of Antiepileptic Drugs. *The Lancet Neurology*, **11**, 803-813. https://doi.org/10.1016/s1474-4422(12)70103-5

[36] Dathe, K. and Schaefer, C. (2019) The Use of Medication in Pregnancy. *Deutsches Ärzteblatt international*, **116**, Article No. 783. https://doi.org/10.3238/arztebl.2019.0783

[37] Gao, S., Wu, Q., Sun, C., Zhang, T., Shen, Z., Liu, C., *et al.* (2018) Selective Serotonin Reuptake Inhibitor Use during Early Pregnancy and Congenital Malformations: A Systematic Review and Meta-Analysis of Cohort Studies of More than 9 Million Births. *BMC Medicine*, **16**, Article No. 205. https://doi.org/10.1186/s12916-018-1193-5

[38] Alwan, S., Friedman, J.M. and Chambers, C. (2016) Safety of Selective Serotonin Reuptake Inhibitors in Pregnancy: A Review of Current Evidence. *CNS Drugs*, **30**, 499-515. https://doi.org/10.1007/s40263-016-0338-3

[39] Malm, H. (2005) Use and Risks of Prescription Drugs during Pregnancy: With Special Emphasis on Selective Serotonin Reuptake Inhibitors and Valproic Acid. PhD Diss., Helsingin Yliopisto.

[40] Cerrizuela, S., Vega-Lopez, G.A. and Aybar, M.J. (2020) The Role of Teratogens in Neural Crest Development. *Birth Defects Research*, **112**, 584-632. https://doi.org/10.1002/bdr2.1644

[41] Crisafulli, S., Khan, Z., Karatas, Y., Tuccori, M. and Trifirò, G. (2023) An Overview of Methodological Flaws of Real-World Studies Investigating Drug Safety in the Post-Marketing Setting. *Expert Opinion on Drug Safety*, **22**, 373-380. https://doi.org/10.1080/14740338.2023.2219892

[42] Pore, A.V., Bais, S.K. and Kamble, M.M. (2024) Pharmacovigilance in Clinical Research. *International Journal of Pharmacy and Herbal Technology*, **2**, 759-775.

[43] Nwokike, J. (2023) Regulatory Reliance and Post-Marketing Surveillance Systems for Safe and Accelerated Introduction of New Medical Products in Low- and Middle-Income Countries.

[44] Boyd, C.M., Vollenweider, D. and Puhan, M.A. (2012) Informing Evidence-Based Decision-Making for Patients with Comorbidity: Availability of Necessary Information in Clinical Trials for Chronic Diseases. *PLOS ONE*, **7**, e41601. https://doi.org/10.1371/journal.pone.0041601

[45] Fraccaro, P., Arguello Castelerio, M., Ainsworth, J. and Buchan, I. (2015) Adoption of Clinical Decision Support in Multimorbidity: A Systematic Review. *JMIR Medical*

Informatics, **3**, e3503. https://doi.org/10.2196/medinform.3503

[46] Moler-Zapata, S., Hutchings, A., Grieve, R., Hinchliffe, R., Smart, N., Moonesinghe, S.R., *et al.* (2024) An Approach for Combining Clinical Judgment with Machine Learning to Inform Medical Decision Making: Analysis of Nonemergency Surgery Strategies for Acute Appendicitis in Patients with Multiple Long-Term Conditions. *Medical Decision Making*, **44**, 944-960. https://doi.org/10.1177/0272989x241289336

[47] Lloyd-Jones, D.M., Braun, L.T., Ndumele, C.E., Smith, S.C., Sperling, L.S., Virani, S.S., *et al.* (2019) Use of Risk Assessment Tools to Guide Decision-Making in the Primary Prevention of Atherosclerotic Cardiovascular Disease: A Special Report from the American Heart Association and American College of Cardiology. *Journal of the American College of Cardiology*, **73**, 3153-3167. https://doi.org/10.1016/j.jacc.2018.11.005

[48] Nwokedi, T.V., *et al.* (2025) A Conceptual Framework for AI-Driven Healthcare Optimization and Predictive Analytics. *Multidisciplinary Journal of Engineering, Technology and Sciences*, **2**, 1-22.

[49] Delanerolle, G., Yang, X., Shetty, S., Raymont, V., Shetty, A., Phiri, P., *et al.* (2021) Artificial Intelligence: A Rapid Case for Advancement in the Personalization of Gynaecology/Obstetric and Mental Health Care. *Women's Health*, **17**. https://doi.org/10.1177/17455065211018111

[50] Soumya, A.A.K. (2024) AI-Driven Insights: Revolutionizing Health Diagnostics and Treatment. Budha Publication.

[51] Bachmann, N., Tripathi, S., Brunner, M. and Jodlbauer, H. (2022) The Contribution of Data-Driven Technologies in Achieving the Sustainable Development Goals. *Sustainability*, **14**, Article No. 2497. https://doi.org/10.3390/su14052497

[52] Davidson, L., Canelón, S.P. and Boland, M.R. (2022) Medication-Wide Association Study Using Electronic Health Record Data of Prescription Medication Exposure and Multifetal Pregnancies: Retrospective Study. *JMIR Medical Informatics*, **10**, e32229. https://doi.org/10.2196/32229

[53] Escobar, G.J., Soltesz, L., Schuler, A., Niki, H., Malenica, I. and Lee, C. (2021) Prediction of Obstetrical and Fetal Complications Using Automated Electronic Health Record Data. *American Journal of Obstetrics and Gynecology*, **224**, 137-147.e7. https://doi.org/10.1016/j.ajog.2020.10.030

[54] Casey, J.A., Schwartz, B.S., Stewart, W.F. and Adler, N.E. (2016) Using Electronic Health Records for Population Health Research: A Review of Methods and Applications. *Annual Review of Public Health*, **37**, 61-81. https://doi.org/10.1146/annurev-publhealth-032315-021353

[55] Parisineni, S.R.A. and Pal, M. (2023) Enhancing Trust and Interpretability of Complex Machine Learning Models Using Local Interpretable Model Agnostic SHAP Explanations. *International Journal of Data Science and Analytics*, **18**, 457-466. https://doi.org/10.1007/s41060-023-00458-w

[56] Bhattacharya, A. (2022) Applied Machine Learning Explainability Techniques: Make ML Models Explainable and Trustworthy for Practical Applications Using LIME, SHAP, and More. Packt Publishing Ltd.

[57] Kalusivalingam, A.K., Sharma, A., Patel, N. and Singh, V. (2021) Leveraging SHAP and LIME for Enhanced Explainability in AI-Driven Diagnostic Systems. *International Journal of AI and ML*, **2**, 1-23.

[58] Muntaha, S. and Dewanjee, S. (2024) Integrating XAI with Hybrid BiGRU-BiLSTM Model for Comprehensive Maternal-Fetal Health Risk Monitoring. 2024 *International Conference on Innovations in Science, Engineering and Technology* (*ICISET*),

Chittagong, 26-27 October 2024, 1-6. https://doi.org/10.1109/iciset62123.2024.10939599

[59] Avinash, A., Harikumar, A., Nair, A., Pai, S.K., Surendran, S. and George, L. (2024) A Comparison of Explainable AI Models on Numeric and Graph-Structured Data. *Procedia Computer Science*, **235**, 926-936. https://doi.org/10.1016/j.procs.2024.04.088

[60] Winkelmann, C.T. and Wise, L.D. (2009) High-Throughput Micro-Computed Tomography Imaging as a Method to Evaluate Rat and Rabbit Fetal Skeletal Abnormalities for Developmental Toxicity Studies. *Journal of Pharmacological and Toxicological Methods*, **59**, 156-165. https://doi.org/10.1016/j.vascn.2009.03.004

[61] Aspatwar, A., Nath, R., Bhowmik, R. and Jesudasan, R. (2024) Exploring the Applications of Formulation-Based Drug Development Strategies in Neurological Disorders Using Artificial Intelligence and Machine Learning Approaches.

[62] Corponi, F., Fabbri, C. and Serretti, A. (2020) Antidepressants: Indications, Contraindications, Interactions, and Side Effects. In: Riederer, P., *et al.*, Eds., *NeuroPsychopharmacotherapy*, Springer International Publishing, 1-38. https://doi.org/10.1007/978-3-319-56015-1_29-1

[63] Antimisiaris, D., McHolan, B., Moga, D. and Mospan, C. (2021) Medication Related Problems. *The Senior Care Pharmacist*, **36**, 68-82. https://doi.org/10.4140/tcp.n.2021.68

[64] Gelman, A. and Hennig, C. (2017) Beyond Subjective and Objective in Statistics. *Journal of the Royal Statistical Society Series A*: *Statistics in Society*, **180**, 967-1033. https://doi.org/10.1111/rssa.12276

[65] Wang, Y., Zhang, Y., Lu, Y. and Yu, X. (2020) A Comparative Assessment of Credit Risk Model Based on Machine Learning—A Case Study of Bank Loan Data. *Procedia Computer Science*, **174**, 141-149. https://doi.org/10.1016/j.procs.2020.06.069

[66] Nohara, Y., Matsumoto, K., Soejima, H. and Nakashima, N. (2022) Explanation of Machine Learning Models Using Shapley Additive Explanation and Application for Real Data in Hospital. *Computer Methods and Programs in Biomedicine*, **214**, Article ID: 106584. https://doi.org/10.1016/j.cmpb.2021.106584

[67] Longo, L., Brcic, M., Cabitza, F., Choi, J., Confalonieri, R., Ser, J.D., *et al.* (2024) Explainable Artificial Intelligence (XAI) 2.0: A Manifesto of Open Challenges and Interdisciplinary Research Directions. *Information Fusion*, **106**, Article ID: 102301. https://doi.org/10.1016/j.inffus.2024.102301

[68] Shams Khoozani, Z., Sabri, A.Q.M., Seng, W.C., Seera, M. and Eg, K.Y. (2024) Navigating the Landscape of Concept-Supported XAI: Challenges, Innovations, and Future Directions. *Multimedia Tools and Applications*, **83**, 67147-67197. https://doi.org/10.1007/s11042-023-17666-y

[69] Albahri, A.S., Duhaim, A.M., Fadhel, M.A., Alnoor, A., Baqer, N.S., Alzubaidi, L., *et al.* (2023) A Systematic Review of Trustworthy and Explainable Artificial Intelligence in Healthcare: Assessment of Quality, Bias Risk, and Data Fusion. *Information Fusion*, **96**, 156-191. https://doi.org/10.1016/j.inffus.2023.03.008

[70] Mesinovic, M., Watkinson, P. and Zhu, T.T. (2023) Explainable AI for Clinical Risk Prediction: A Survey of Concepts, Methods, and Modalities.

[71] Soyege, O.S., Nwokedi, C.N., Tomoh, B.O., *et al.* (2025) Health Informatics in Developing Countries: Challenges and Opportunities. *International Journal of Applied Research in Social Sciences*, **7**, 186-202.