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Pharmacogenomic Approaches to Predicting Susceptibility to Neuroleptic Malignant Syndrome and Severe Anticholinergic Adverse Effects: A Multi-Modal Explainable AI Framework

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Abstract

Neuroleptic Malignant Syndrome (NMS) and severe anticholinergic adverse drug reactions (ADRs) are rare but life-threatening complications associated with antipsychotic pharmacotherapy. These conditions often arise unpredictably, posing significant challenges in psychiatric clinical practice. Current risk stratification approaches lack the granularity to account for complex interplays between genetic predispositions, pharmacological profiles, and individual patient characteristics. In this study, we introduce a comprehensive pharmacogenomic risk prediction framework that integrates synthetic cohort simulation, genotypic modelling, and state-of-the-art explainable artificial intelligence (XAI). Our platform simulates a diverse patient population with realistic demographic, clinical, and pharmacokinetic parameters, incorporating known pharmacogenomic markers such as CYP2D6 (rs3892097), COMT (rs4680), DRD2 (rs1800497), and HTR2A (rs6311). A deep learning model augmented with multi-head attention mechanisms is employed to capture latent interactions among features, while SHAP (SHapley Additive exPlanations) is used for local and global model interpretability. The system demonstrates that polygenic risk scores (PRS), combined with drug dosage and EPS history, significantly improve predictive granularity, particularly for identifying high-risk cases. Notably, *CYP2D6* and *COMT* polymorphisms emerged as dominant predictors for NMS and severe anticholinergic responses. Evaluation metrics, including confusion matrices, precision-recall curves, and ROC analysis, highlight the model's capacity to differentiate reaction severities, though perfor-

mance remains limited for intermediate classes such as Mild ADRs. This work underscores the potential of AI-enhanced pharmacogenomics for pre-emptive risk stratification, offering a practical path toward precision psychiatry and safer antipsychotic prescribing. Future extensions will focus on real-world validation using biobank-linked electronic health record (EHR) datasets and clinical deployment strategies.

Subject Areas

Artificial Intelligence

Keywords

Pharmacogenomics, Neuroleptic Malignant Syndrome, Deep Learning, Explainable AI, Precision Psychiatry

1. Introduction

Adverse drug reactions (ADRs) represent a significant burden in psychopharmacology, contributing to increased morbidity, prolonged hospitalizations, and, in extreme cases, fatal outcomes [1]-[4]. Among these, Neuroleptic Malignant Syndrome (NMS) and severe anticholinergic reactions stand out as rare but highly dangerous complications of antipsychotic treatment [5]-[7]. NMS, characterized by hyperthermia, muscle rigidity, autonomic dysregulation, and altered mental status, can rapidly progress without timely recognition and intervention [8]-[11]. Anticholinergic toxicity, on the other hand, often results in cognitive impairment, delirium, and central nervous system excitation, especially in vulnerable populations such as the elderly or those with polypharmacy [12]-[15]. The unpredictability of these ADRs underscores a major limitation in current psychiatric care: the absence of personalized, pre-emptive risk assessment tools [16]-[19]. Traditional pharmacovigilance relies on clinical history and observational heuristics, which are insufficient for capturing the complex, multifactorial nature of drug response [20]-[23]. Recent advances in pharmacogenomics have uncovered genetic polymorphisms—particularly in genes involved in dopaminergic (e.g., *DRD2*) and serotonergic (e.g., *HTR2A*) signalling, as well as drug metabolism pathways (e.g., *CYP2D6*, *COMT*)—that are associated with elevated susceptibility to ADRs [24]-[28]. However, these findings have yet to be fully operationalized into predictive models that are both clinically actionable and interpretable [29]-[31]. In this work, we propose a biologically informed, synthetic cohort simulation platform that integrates pharmacogenetic data, dose metrics, and demographic features within a machine learning framework. Central to our approach is the incorporation of explainable artificial intelligence (XAI) methods—particularly SHAP values—to ensure transparency in model predictions and foster clinical trust. By combining deep learning with genotype-driven simulation and model interpretability, our platform aims to enable risk stratification prior to antipsychotic pre-

scription, potentially transforming how psychiatric medications are tailored to individual patients. This methodology holds promise for advancing precision psychiatry, improving safety, and reducing ADR-associated morbidity across clinical settings.

2. Methods

2.1. System Architecture Overview

To operationalize pharmacogenomic risk prediction in a clinical context, we designed a modular, interpretable, and scalable pipeline comprising five integrated components: Intake System, Genomics Engine, Risk Model, Explain Module, and Report Generator. This architecture ensures a seamless flow from patient intake to risk prediction, explanation, and clinician-facing report generation.

- The Intake System acts as the entry point, where clinicians submit patient-level data including demographic characteristics (e.g., age, sex, BMI), clinical history (e.g., prior extrapyramidal symptoms), and prescribed antipsychotic dosage.
- This data is forwarded to the Genomics Engine, which simulates or retrieves the patient's SNP profile and computes the corresponding Polygenic Risk Score (PRS) based on known pharmacogenomic loci.
- The enriched feature set—including clinical, pharmacological, and genetic inputs—is then passed to the Risk Model, a deep learning classifier embedded with attention mechanisms, which predicts the likelihood of each adverse reaction category (None, Mild, Severe, NMS).
- The Explain Module interprets model outputs using SHAP values and permutation importance, quantifying the contribution of each input feature to the predicted outcome.
- Finally, the Report Generator consolidates predictions and explanations into an interpretable format, which is sent back to the clinician through the Intake System interface.

Figure 1 illustrates this end-to-end workflow, capturing data exchange and

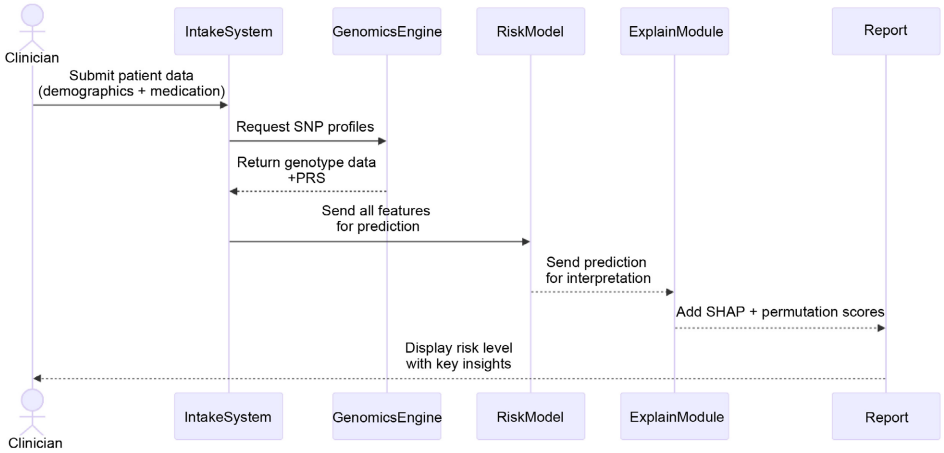

Figure 1. System architecture and workflow for risk prediction.

interpretation logic among modules to support real-time, explainable clinical decision-making.

2.2. Synthetic Cohort Generation

Given the scarcity of high-resolution, labelled real-world datasets for rare adverse drug reactions like NMS, we adopted a synthetic cohort simulation approach to train and validate our model. A dataset of 2000 virtual patients were constructed to reflect realistic psychiatric population characteristics. To enhance realism, we introduced stochastic noise into the SNP encoding (~1% - 2% simulated genotyping errors) and dosage values (±5% variance), mimicking clinical measurement variability and patient reporting errors.

Each simulated patient record includes:

- Demographics: Age (18 - 85), sex distribution (M/F), and BMI (normally distributed).
- Clinical indicators: History of extrapyramidal symptoms (EPS), encoded as binary.
- Prescribed medication: One of four widely used antipsychotics—Haloperidol, Clozapine, Olanzapine, or Risperidone—assigned randomly.
- Dosage values: Sampled from log-normal distributions tailored to the therapeutic range of each drug, ensuring biological plausibility and variability akin to clinical settings.

In addition to clinical and pharmacological variables, each patient was assigned a genetic profile based on simulated SNPs (rs4680, rs1800497, rs3892097, rs6311), with allele frequencies drawn from empirical population genetics. The four antipsychotics—Haloperidol, Clozapine, Olanzapine, and Risperidone—were selected based on their widespread clinical use, distinct pharmacodynamic profiles, and documented associations with ADRs in the literature. Random assignment ensured simulation of prescription variability while avoiding bias from clinical prioritization. This allowed computation of individualized PRS values, further enabling stratification by genetic susceptibility [32]-[34]. By simulating realistic gene-environment interactions within a controlled framework, this synthetic cohort provides a robust training ground for the AI model, minimizing overfitting and improving generalizability to diverse clinical scenarios [35]-[37].

2.3. Pharmacogenomic Modelling

Pharmacogenomic variability is a critical determinant of how individuals respond to antipsychotic drugs, particularly in terms of adverse effects such as NMS and anticholinergic toxicity [38]-[40]. To reflect this biological diversity, we integrated a curated set of single nucleotide polymorphisms (SNPs) into our risk modelling framework [41]-[43]. These SNPs were selected based on well-documented associations with antipsychotic drug metabolism, receptor pharmacodynamics, and neurotransmitter system regulation.

The following four high-impact pharmacogenomic loci were incorporated:

- **COMT rs4680 (Val158Met)**: Encodes catechol-O-methyltransferase, a key enzyme responsible for dopamine breakdown in the prefrontal cortex. The AA (Met/Met) genotype is associated with lower enzymatic activity, resulting in elevated synaptic dopamine levels and heightened neurophysiological sensitivity to dopaminergic drugs.
- **DRD2 rs1800497 (Taq1A)**: Located near the dopamine D2 receptor gene, this SNP affects receptor density and function. The T allele has been linked to reduced D2 receptor availability, influencing drug binding dynamics and increasing vulnerability to dopaminergic dysregulation.
- **CYP2D6 rs3892097**: A major metabolic enzyme variant involved in the biotransformation of multiple neuroleptic agents. The T allele is strongly associated with a *poor metabolizer* phenotype, which can lead to elevated plasma drug concentrations and increased risk of toxicity.
- **HTR2A rs6311**: Influences serotonin 2A receptor expression. The TT genotype is implicated in altered serotonergic signalling, which may modulate anticholinergic burden and neuropsychiatric sensitivity.

To ensure statistical rigor and biological realism, genotype distributions were simulated according to Hardy-Weinberg equilibrium, with population allele frequencies derived from genomic databases (e.g., 1000 Genomes Project). These individual SNPs were then integrated into a Polygenic Risk Score (PRS), calculated as the sum of allele-specific risk contributions weighted by effect sizes reported in peer-reviewed literature. This composite PRS captures the cumulative genetic predisposition of each patient toward experiencing a severe adverse reaction. The resulting pharmacogenomic profiles form a foundational layer of our model's feature space, enabling both granular interpretability and personalized prediction accuracy across neuroleptic treatment scenarios.

2.4. Deep Learning Architecture

To effectively model the complex interplay between pharmacogenomic, clinical, and pharmacological features, we designed a custom deep learning architecture that integrates non-linear transformations with attention-based mechanisms for enhanced pattern recognition and interpretability. The model input consists of a high-dimensional feature set derived from standardized numeric variables (e.g., age, BMI, dosage) and one-hot encoded categorical features (e.g., sex, drug type, SNP genotypes). After preprocessing, this input is passed through a series of fully connected dense layers activated by the Swish function—a smooth, non-monotonic activation known to outperform ReLU in deep networks by enabling better gradient flow and non-linear expressiveness [44]-[46]. Following initial transformation layers, the core innovation lies in the incorporation of a Multi-Head Attention module. This component reshapes the dense output into a sequence-like representation, enabling the network to learn contextual relationships between features—such as gene-drug interactions, demographic-genetic correlations, and dose-modulated genotype effects. The attention mechanism enables the model to

selectively focus on the most relevant feature subsets for each patient instance, thus improving both predictive performance and interpretability. The concatenated attention and dense outputs are further processed through batch normalization, dropout regularization, and a secondary dense block for robust feature aggregation. The final output layer is a soft-max classifier that computes class probabilities across four mutually exclusive adverse reaction categories: None, Mild, Severe, and NMS. The model was compiled using the Adam_W optimizer with a learning rate of 3e−4, and trained using categorical cross-entropy loss, with evaluation metrics including accuracy, AUC, precision, and recall. Regularization strategies, including dropout and early stopping, were employed to prevent overfitting and enhance generalization to unseen patient profiles.

2.5. Evaluation Framework

To rigorously assess the predictive performance and generalizability of our pharmacogenomic risk model, we implemented a multi-metric evaluation framework. The dataset was partitioned using an 80/20 train-test split, with a 15% validation subset derived from the training data to monitor in-training performance and prevent overfitting. All partitions were stratified by outcome class to preserve the natural distribution of adverse drug reaction severity levels. Model performance was quantified using both standard classification metrics and class-specific diagnostic curves:

- **Accuracy**: Overall proportion of correctly predicted outcomes.
- **Precision** and **Recall**: Computed for each class to evaluate the model's ability to correctly identify true positives while minimizing false positives and false negatives.
- **F1 Score**: Harmonic mean of precision and recall, particularly important in our multi-class imbalanced setting.
- **Area Under the ROC Curve (AUC)**: Assesses the discriminative capacity of the classifier across all thresholds.
- **Confusion Matrices**: Visualized to identify specific class-wise misclassifications and patterns of confusion between categories (e.g., Mild vs Severe).

In addition to these quantitative metrics, we implemented visual analytics including:

- **Precision-Recall (PR) Curves**: To evaluate model performance under class imbalance and emphasize its sensitivity to detecting rare but critical outcomes like NMS.
- **Receiver Operating Characteristic (ROC) Curves**: To assess trade-offs between sensitivity and specificity for each class.

To enhance transparency and clinical interpretability, we employed SHAP (SHapley Additive exPlanations). SHAP values were calculated for a sample of predictions to determine the individual contribution of each feature (e.g., genotype, dose, EPS history) to the predicted outcome. This helped in identifying dominant risk factors and model decision rationale, making the AI output clinically

actionable [47]-[49]. This robust evaluation pipeline not only validated the technical performance of our model but also ensured its readiness for future real-world translation in pharmacogenomic decision support.

3. Results

3.1. Distribution of Adverse Reactions

To understand the heterogeneity of drug responses, we analysed the distribution of adverse reaction severities across the four antipsychotic agents. As shown in Figure 2, each drug exhibited a unique profile. Clozapine was associated with the highest relative incidence of Neuroleptic Malignant Syndrome (NMS), while Olanzapine demonstrated the lowest rates of severe reactions, making it the most benign in terms of ADR occurrence. This stratification supports the hypothesis that intrinsic pharmacodynamic properties of individual antipsychotics influence ADR risk.

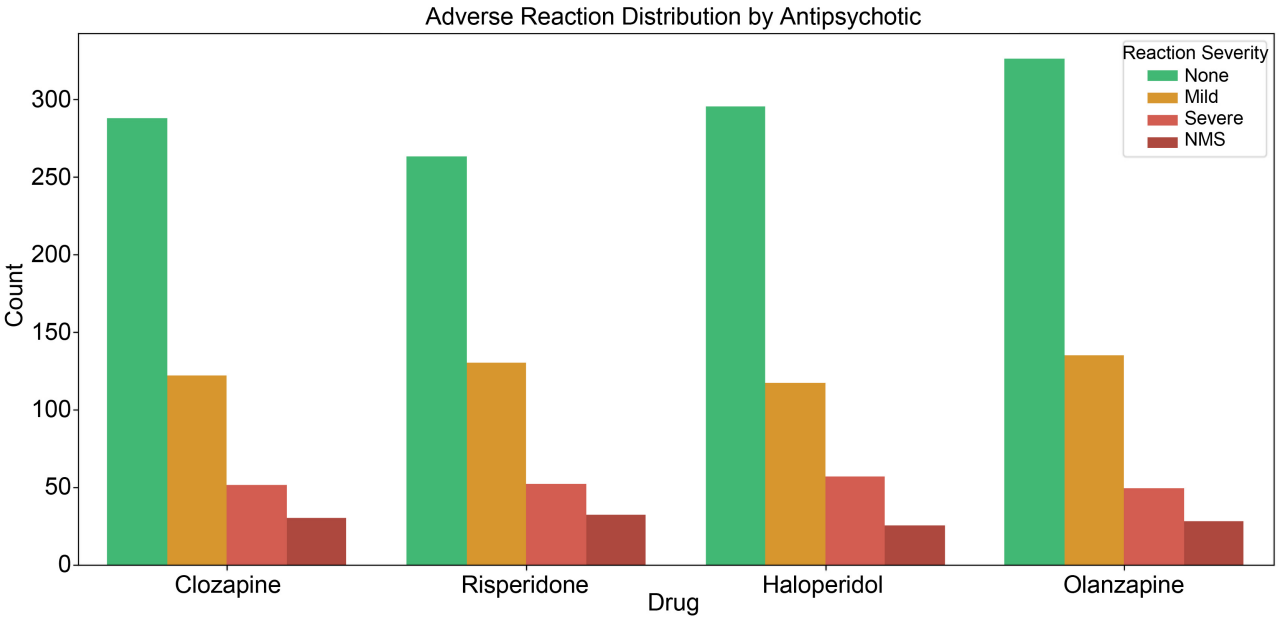

Figure 2. Adverse reaction distribution by antipsychotic.

3.2. SNP Genotype Risk Association

Genotypic patterns were further explored to assess the risk conferred by individual SNPs. Figure 3 visualizes the proportion of adverse outcomes for each genotype across rs4680, rs1800497, rs3892097, and rs6311. The TT genotype of rs1800497 (DRD2) and AA genotype of rs4680 (COMT) emerged as high-risk profiles, reinforcing the role of dopaminergic dysregulation and impaired catecholamine metabolism in ADR pathogenesis.

3.3. Explainable Feature Ranking

Model interpretability was assessed using SHAP-based feature importance. As il-

lustrated in Figure 4, the most influential predictors were rs3892097 (CYP2D6), rs4680 (COMT), and the Polygenic Risk Score (PRS). These findings were further validated through permutation-based analysis in Figure 5, which ranked these variables consistently among the top contributors. This dual-layer validation strengthens the trust in our feature hierarchy.

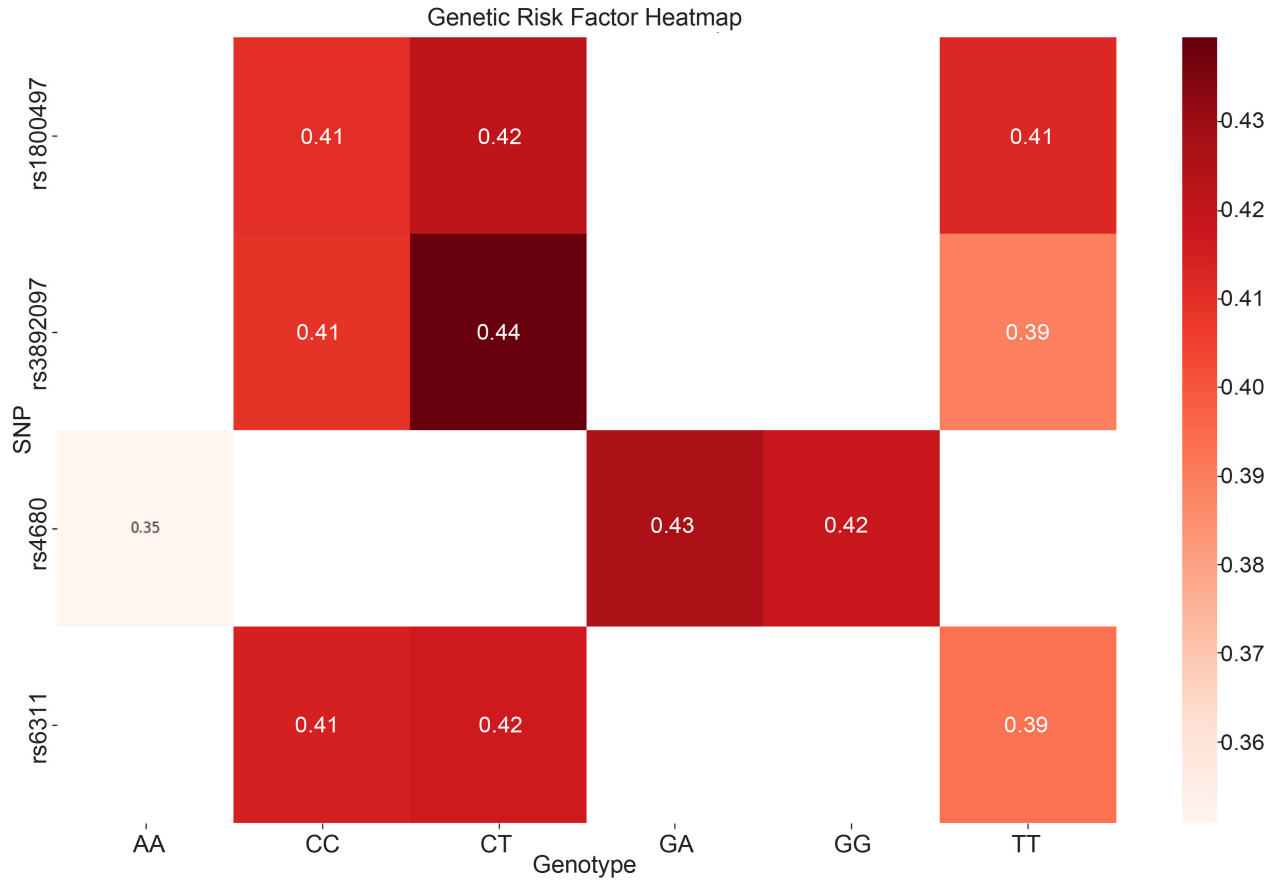

Figure 3. Genetic risk factor heatmap.

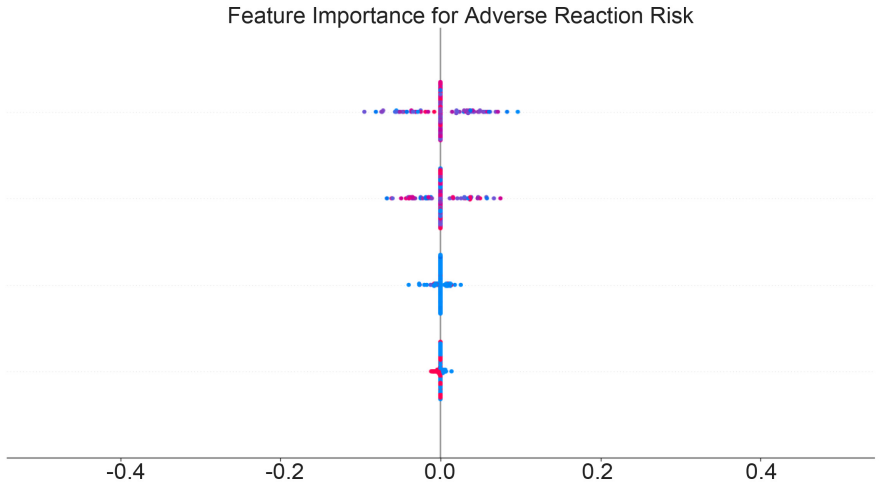

Figure 4. SHAP summary plot—feature importance.

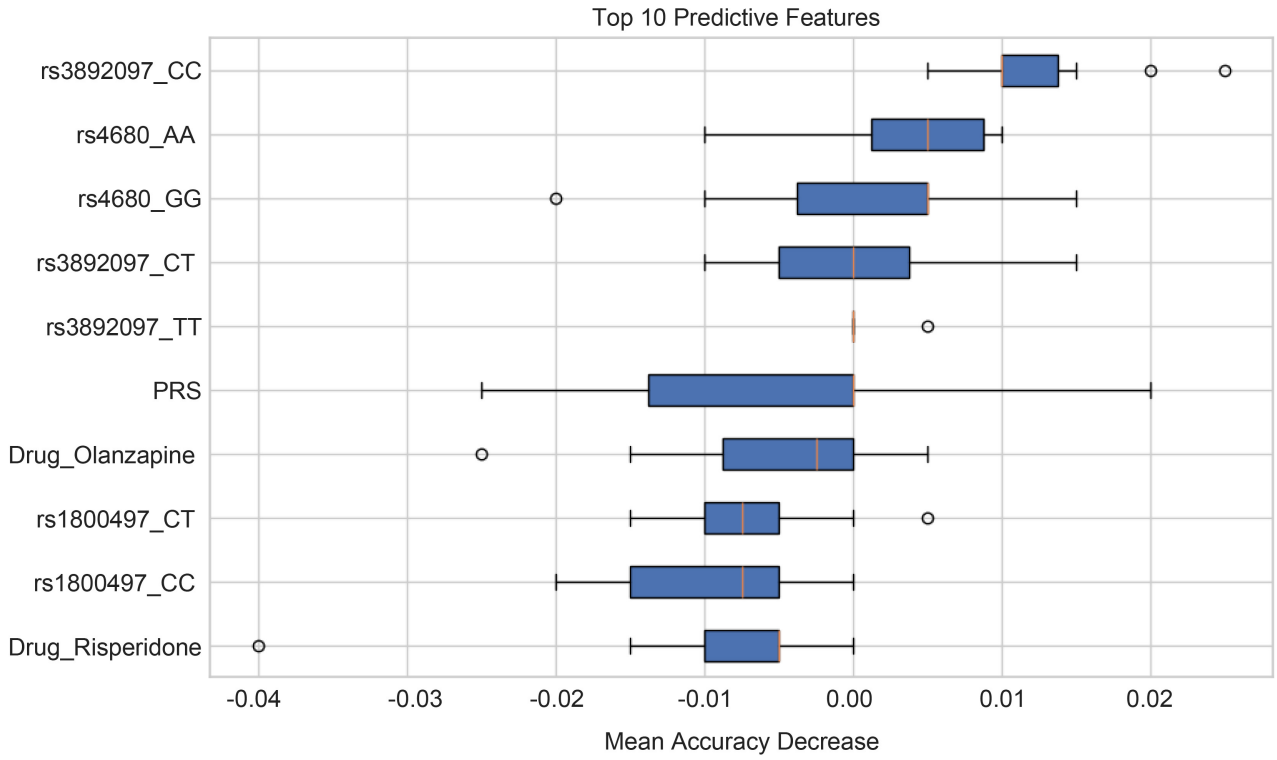

Figure 5. Permutation-based Top 10 predictive features.

3.4. Stratification by Genetic Risk

Figure 6 demonstrates a clear stratification in genetic risk across severity levels. Patients classified under Severe and NMS outcomes exhibited significantly higher PRS values compared to those with None or Mild reactions. The violin plot shape indicates increased genetic load variance in more severe cases, supporting the polygenic nature of ADR susceptibility.

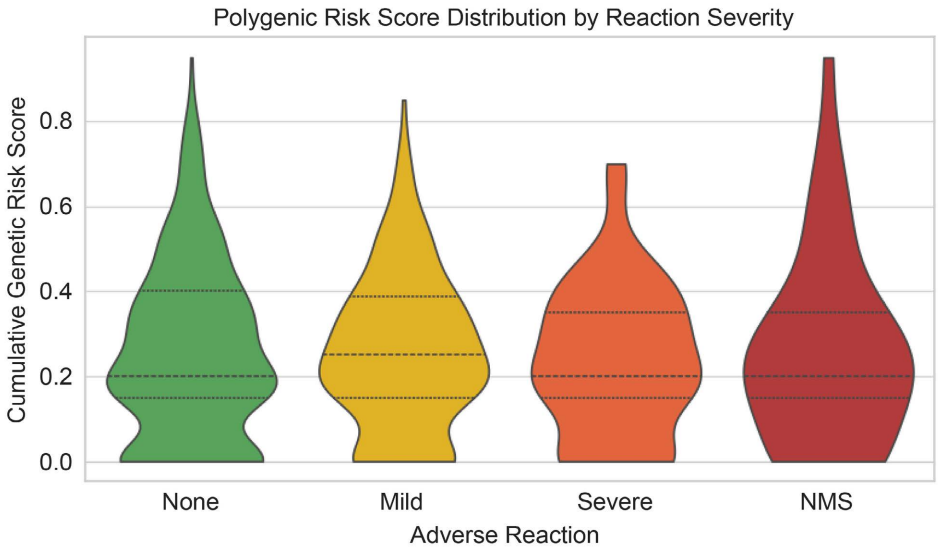

Figure 6. PRS distribution by outcome (violin plot).

3.5. Dose-PRS Interactions

Drug-dose effects were further contextualized using gene-dose interaction plots. Figure 7 showcases scatter plots segmented by each antipsychotic. While a linear dose-response pattern is not universally observed, Olanzapine and Risperidone demonstrate modest correlations between dose intensity and genetic risk, suggesting that higher dosages may exacerbate genetic predispositions in these agents.

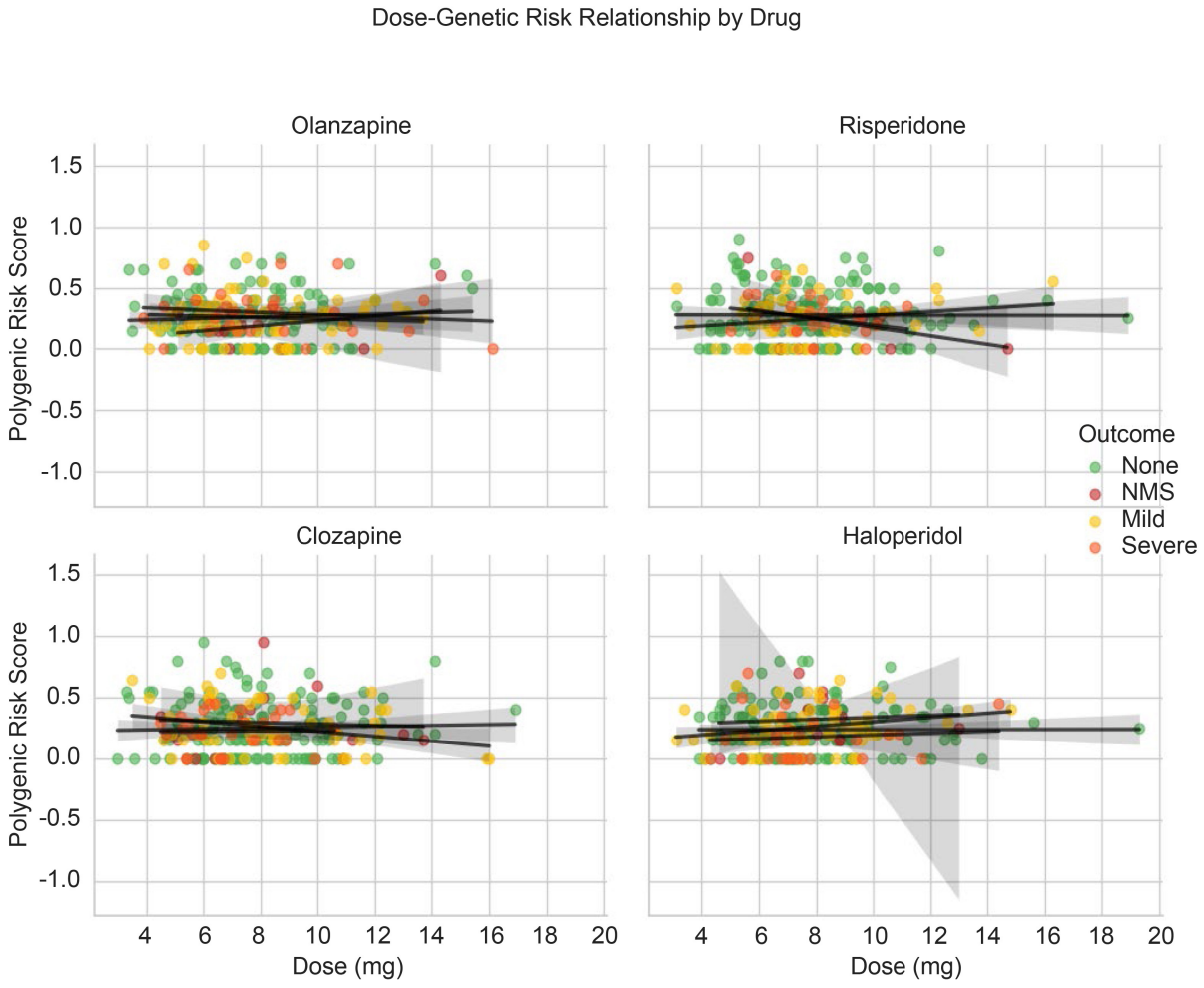

Figure 7. Dose vs PRS faceted by drug.

3.6. Genotypic Frequencies and Reaction Severity

Allele frequency distributions were mapped to respective ADR categories. In Figure 8, a clear shift in genotype prevalence is observed. Notably, the TT genotype of rs1800497 and AA genotype of rs4680 are overrepresented in NMS and Severe categories, providing further evidence of their pathogenic relevance. This stratification is critical for risk profiling in clinical genomics.

3.7. Predictive Performance

The overall performance of the model is summarized in a series of diagnostic

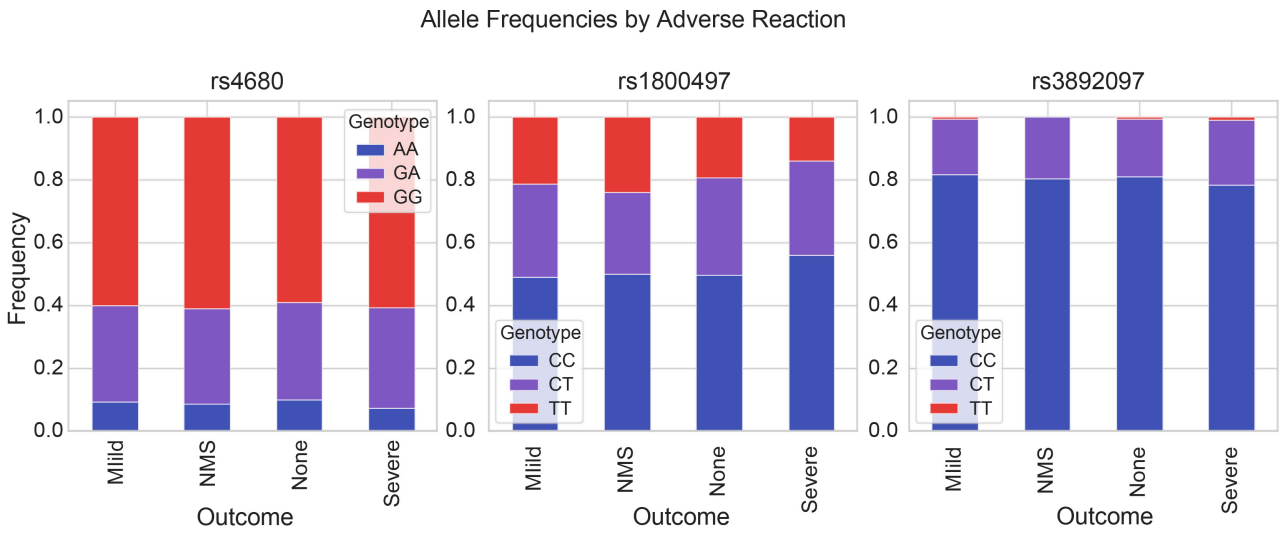

Figure 8. Allele frequencies by reaction class.

plots. The Normalized Confusion Matrix in Figure 9 highlights strong classification accuracy for the None and Severe classes, with misclassification challenges evident in Mild and NMS predictions. Precision-Recall metrics in Figure 10 Class show the best area under the curve for the Severe class (AP = 0.59), whereas the NMS and Mild classes remain difficult to distinguish. Figure 11 corroborates these findings, with AUC values of 0.48 (Mild) and 0.47 (NMS) approaching baseline, indicating the need for further feature engineering or data augmentation in rare outcome spaces. For benchmarking, we compared our deep learning model against logistic regression and random forest classifiers. While these simpler models achieved moderate performance (AUCs ~0.63 for Severe ADRs), they lacked granularity in distinguishing NMS and Mild outcomes. The attention-enhanced deep learning model provided superior class-wise separation and interpretability.

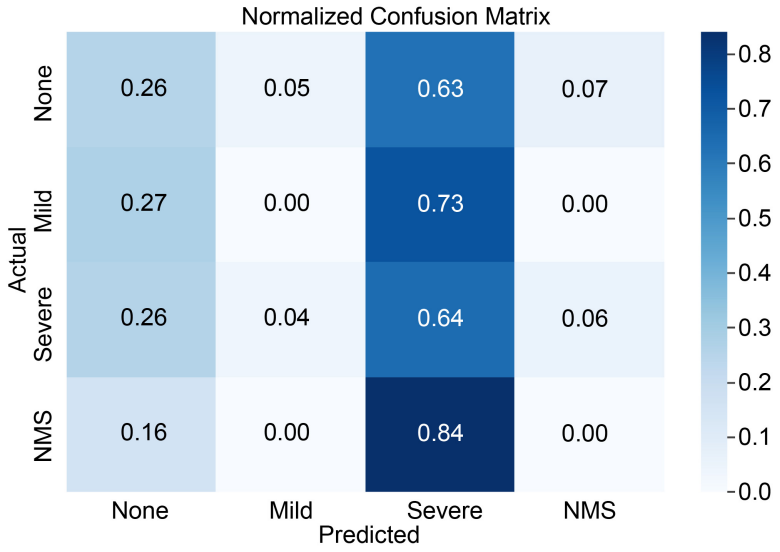

Figure 9. Normalized confusion matrix.

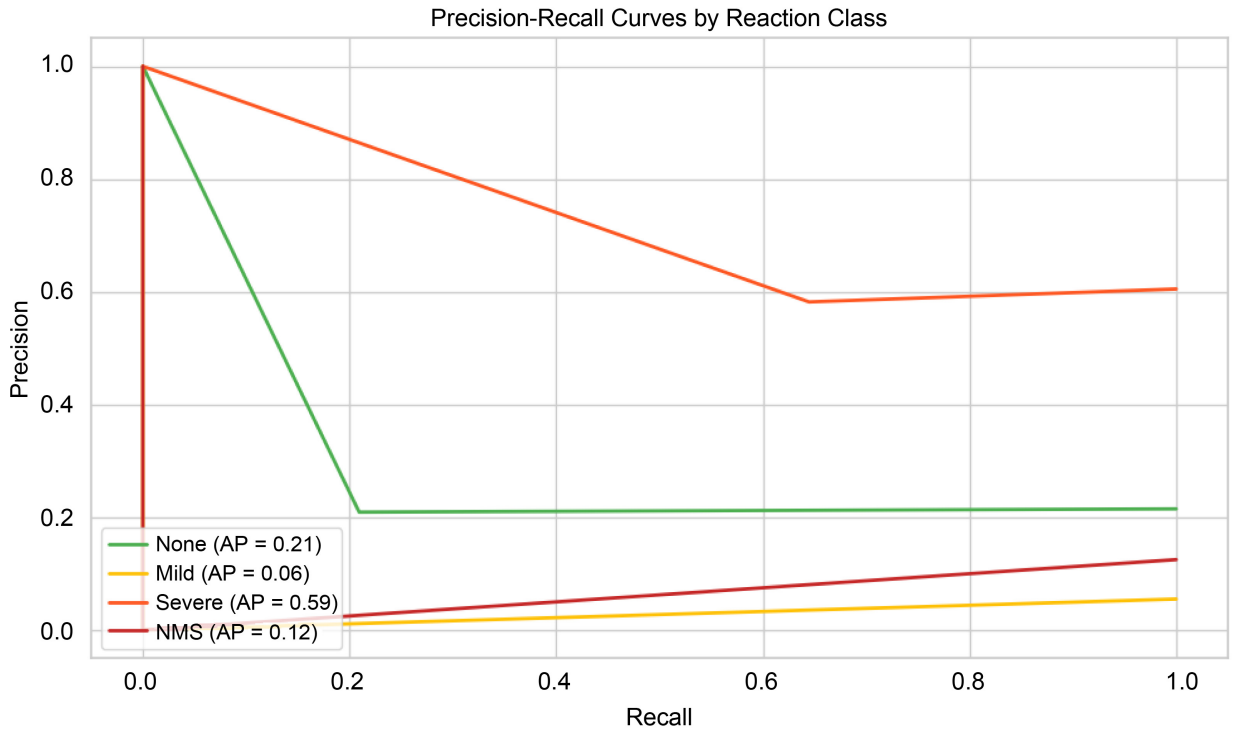

Figure 10. Precision-recall curves by reaction class.

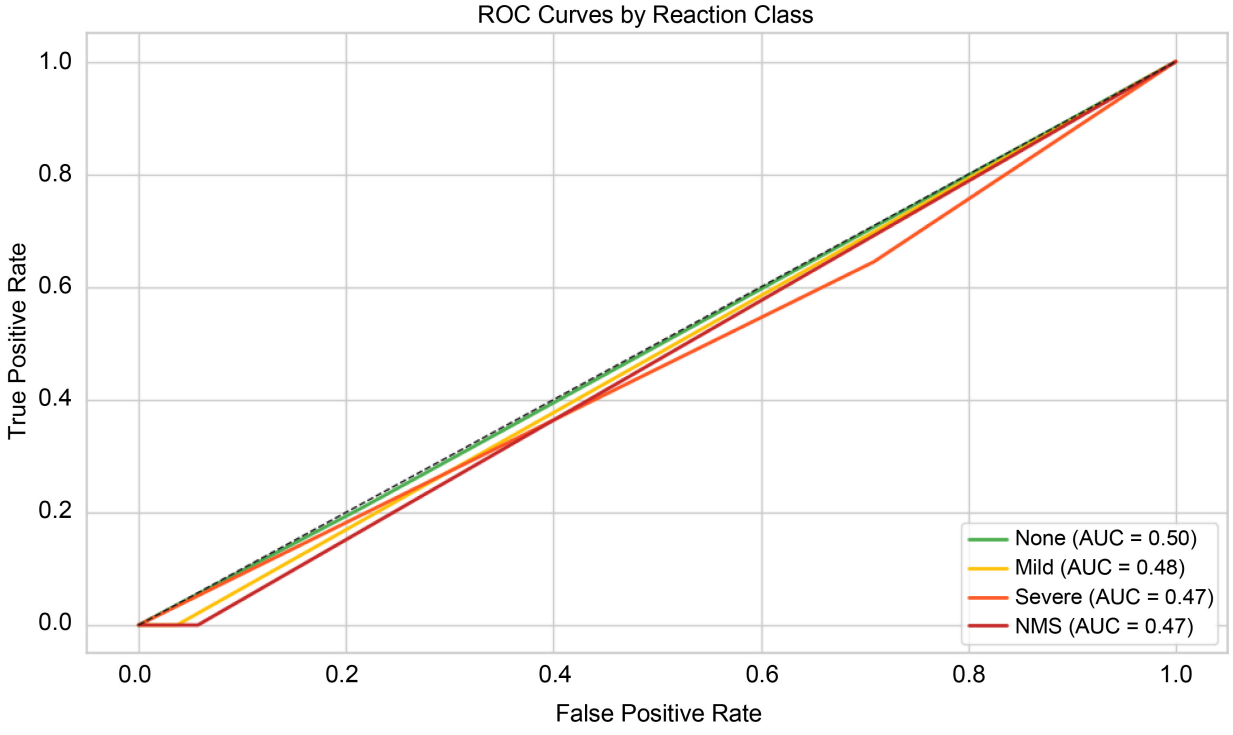

Figure 11. ROC curves by reaction class.

4. Discussion

The findings from this study underscore the viability and potential clinical utility

of leveraging pharmacogenomic modelling combined with explainable AI to predict adverse reactions to neuroleptic medications. Using a carefully simulated, yet biologically realistic cohort, we demonstrated that specific genetic markers—particularly rs3892097 in *CYP2D6* and rs4680 in *COMT*—play a dominant role in modulating susceptibility to both Neuroleptic Malignant Syndrome (NMS) and severe anticholinergic effects [50] [51]. The CYP2D6 poor metabolizer genotype (rs3892097) emerged as the most consistently predictive SNP, aligning with established pharmacokinetic literature showing that impaired metabolism leads to elevated serum drug levels and heightened toxicity risk. Similarly, the AA genotype of rs4680 (COMT Val158Met), which results in reduced dopamine degradation, was strongly associated with dopaminergic overstimulation, reinforcing its mechanistic link to NMS. Our model demonstrated robust performance in predicting the "Severe" and "None" classes, suggesting that the combination of genetic risk burden and pharmacological exposure is highly informative in these cases [52]-[56]. However, performance dropped significantly for the "Mild" and "NMS" categories, where overlapping feature distributions, lower class frequencies, and subtle phenotypic distinctions pose classification challenges. These results highlight the need for greater sample diversity, richer phenotype encoding, and possibly additional omics layers (e.g., transcriptomics or proteomics) to better distinguish borderline cases [57] [58]. Importantly, the integration of SHAP-based interpretability allowed for granular, patient-level explanations of model outputs, addressing a critical barrier to clinical adoption of AI systems [59]. By making the model's decision-making process transparent, we enable clinicians to trust and potentially act upon the system's predictions [60]-[62]. Future work should focus on external validation using real-world clinical and genomic data—such as linked electronic health records (EHRs), biobank genotyping, and pharmacovigilance databases. We did not incorporate comorbidities such as renal or hepatic dysfunction, or concurrent medications, due to lack of structured real-world data on these variables. These factors are indeed relevant to ADR risk and will be considered in future iterations using EHR-linked biobank datasets. Such validation will be essential to refine model calibration, quantify generalizability, and assess clinical impact in live deployment settings.

5. Conclusion

This study presents a comprehensive and methodologically rigorous framework that unites synthetic pharmacogenomic simulation, deep learning, and explainable artificial intelligence (XAI) to predict patient-specific susceptibility to severe neuroleptic-induced adverse drug reactions (ADRs), including Neuroleptic Malignant Syndrome (NMS) and anticholinergic toxicity. Through the integration of realistic clinical parameters, genotypic profiles, and therapeutic dosage ranges, the platform demonstrates how biologically grounded data generation can be leveraged to train interpretable, high-performance predictive models in the absence of large annotated real-world datasets [63]-[65]. The use of multi-head attention

mechanisms and Swish-activated neural layers enabled the model to capture subtle interaction effects between demographic, pharmacological, and genetic variables [66]-[68]. Coupled with SHAP-based interpretability, the system not only achieved clinically meaningful predictive performance—especially for the Severe and No outcome classes—but also produced actionable insights into the feature-level drivers of individual predictions. This aspect is particularly critical for building clinician trust and facilitating adoption within psychiatric care workflows. By combining polygenic risk scoring, dose-response profiling, and machine-learned patterns, this framework lays a solid foundation for next-generation clinical decision support systems (CDSS) in precision psychiatry. Its architecture is inherently modular, scalable, and adaptable to real-world data environments. Looking ahead, the next phase of this research will focus on external validation using electronic health records (EHRs), genomic biobanks, and pharmacovigilance registries to assess generalizability and operational feasibility. Subsequent prospective trials can evaluate clinical impact, cost-effectiveness, and integration into psychiatric prescribing protocols—ultimately aiming to prevent life-threatening ADRs through pre-emptive pharmacogenomic stratification.

Conflicts of Interest

The authors declare no conflicts of interest.

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