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Mechanisms and Risk Factors Linking Neuroleptic Malignant Syndrome (NMS) to Dopaminergic and Autonomic Dysfunction

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Abstract

Neuroleptic Malignant Syndrome (NMS) is a rare but life-threatening neurological emergency that arises primarily from the use of dopamine antagonist antipsychotic medications. Clinically, it is characterized by hyperthermia, muscle rigidity, altered mental status, and signs of autonomic dysregulation. Despite being a well-documented phenomenon, the underlying pathophysiological mechanisms of NMS remain poorly understood, and early detection remains a clinical challenge. This study introduces a comprehensive and explainable data-driven framework aimed at elucidating the multifactorial etiology of NMS. We developed a high-fidelity synthetic dataset representing patients exposed to antipsychotic therapies and modelled key variables such as dopaminergic blockade, anticholinergic burden, autonomic instability, creatine kinase levels, and fever. Using this dataset, we performed logistic regression to evaluate risk contributions, XGBoost classification to determine feature importance, and survival analysis (Kaplan-Meier and Cox models) to assess the temporal dimension of disease progression. Additionally, a mechanistic network model was constructed to visualize how pharmacological and physiological components converge to produce the NMS phenotype. Our findings indicate that fever and elevated creatine kinase are robust biomarkers of NMS, while autonomic and dopaminergic pathways appear to interact synergistically to exacerbate clinical outcomes. The XGBoost model achieved strong predictive performance (AUC = 0.93), reinforcing the clinical relevance of our feature selection. Overall, this research bridges the gap between statistical inference, machine learning, and neuropharmacological theory. It lays the foundation for developing early-warning tools, risk stratification systems, and personalized interventions in psychiatry. Future directions include real-world validation, temporal modelling, and integration with electronic health record systems for clinical deployment.

Subject Areas

Psychiatry & Psychology

Keywords

Neuroleptic Malignant Syndrome, Machine Learning, Simulation Modelling, Clinical Decision Support, Pharmacovigilance

1. Introduction

Neuroleptic Malignant Syndrome (NMS) is a rare, idiosyncratic, and potentially fatal reaction to antipsychotic medications, particularly those that exert potent antagonism on dopamine D2 receptors [1]-[3]. It is classically characterized by a clinical tetrad: hyperthermia, muscle rigidity, altered mental status, and autonomic instability [4]-[6]. Although infrequent, with incidence rates estimated between 0.01% and 0.02% of patients exposed to neuroleptics, its high mortality—ranging from 10% to 20% even with treatment—makes early recognition and prevention an urgent priority in psychiatric and emergency care settings [7]-[10]. While the dopamine blockade hypothesis has historically dominated the understanding of NMS pathogenesis, accumulating evidence suggests a more complex, multifactorial etiology involving downstream effects on hypothalamic thermoregulation, peripheral muscle metabolism, and autonomic nervous system regulation [11]-[14]. In particular, the roles of anticholinergic burden and autonomic dysregulation remain underexplored despite their frequent clinical observation [15] [16]. Furthermore, the relative contributions of clinical biomarkers such as fever and elevated creatine kinase (CK), and their temporal progression, are poorly characterized in predictive models [17] [18]. The primary objective of this research is to construct a robust and explainable framework for understanding and predicting NMS, using simulated clinical data to model key contributing factors and outcomes [19]-[22]. We propose a hybrid approach that combines classical statistical methods (logistic regression and survival analysis) with modern machine learning (XGBoost classification) and mechanistic network modelling. By doing so, we aim to identify interpretable and actionable biomarkers, quantify relative risks, and visualize the interplay of dopaminergic and autonomic dysfunctions contributing to the syndrome. This work contributes not only to clinical understanding but also to the development of early-warning systems, with potential applications in pharmacovigilance, personalized medicine, and clinical decision support systems for antipsychotic therapy management.

2. Methods

2.1. Dataset Construction

To investigate the clinical dynamics and multifactorial pathogenesis of Neuroleptic Malignant Syndrome (NMS), we developed a high-fidelity synthetic dataset

composed of 500 simulated patient profiles. The dataset was designed to mimic the clinical heterogeneity typically observed in psychiatric populations receiving antipsychotic therapy. Variable distributions were modelled based on real-world epidemiological patterns, peer-reviewed literature, and expert-informed assumptions to reflect biologically and clinically meaningful variation. The simulated cohort consisted of adult individuals aged 18 to 90 years with a near-equal distribution across biological sex. The dataset included both directly observable clinical markers—such as body temperature (Fever) and serum Creatine Kinase (CK)—as well as neurophysiological latent constructs such as Dopamine Blockade and Autonomic Instability, which serve as proxies for pharmacodynamic and autonomic responses [23] [24]. A complete summary of all variables, including their types, units, value ranges, and clinical relevance, is presented in Table 1. Key features included continuous (Age, Dopamine Blockade, CK, Fever), categorical (Sex, Medication, Outcome), and ordinal (Autonomic Instability) variables. Two derived binary indicators—High CK (CK > 1000 IU/L) and High Fever (Fever > 38˚C)—were computed using standard clinical thresholds to highlight cases of

Table 1. Summary of variables in the simulated clinical dataset.

Variable	Type	Range/Levels	Unit	Description
Age	Continuous	18 - 90	Years	Simulated age of patient
Sex	Categorical	Male, Female	–	Biological sex
Anticholinergic burden	Discrete	0 - 5	Score	Cumulative burden of anticholinergic medications
Dopamine blockade	Continuous	0.0 - 1.3 (scaled)	–	Degree of dopamine D2 receptor antagonism
Autonomic instability	Ordinal	0 = None, 1 = Mild, 2 = Severe	–	Clinically inferred sympathetic dysregulation
NMS_diagnosis	Binary	0 = No, 1 = Yes	–	Simulated diagnosis of Neuroleptic Malignant Syndrome
Creatine kinase	Continuous	50 - 10,000	IU/L	Biomarker of muscle injury and rhabdomyolysis
Fever	Continuous	36.0 - 42.0	˚C	Core body temperature
Medication	Categorical	Typical, Atypical, None, Polypharmacy	–	Class of antipsychotic drug used
Outcome	Categorical	Resolved, Chronic, Fatal	–	Final clinical outcome
High_CK	Binary (Derived)	0 = CK ≤ 1000, 1 = CK > 1000	–	Marker for rhabdomyolysis
High_Fever	Binary (Derived)	0 = Temp ≤ 38˚C, 1 = Temp > 38˚C	–	Indicates pathological fever

suspected rhabdomyolysis and hyperthermia, respectively. To strengthen clinical realism and support hypothesis-driven analysis, conditional logic was embedded within the simulation. For instance, patients diagnosed with NMS were assigned proportionally elevated CK and Fever values. Dopamine Blockade values were artificially boosted in patients treated with typical antipsychotics, reflecting stronger D2 receptor antagonism [25]-[27]. Furthermore, individuals with high anticholinergic medication burden had an increased likelihood of exhibiting autonomic instability. These simulated interdependencies were essential for enabling downstream supervised learning, risk modelling, and mechanistic pathway exploration.

The 14.6% prevalence of NMS in the synthetic cohort was intentionally inflated to ensure adequate statistical power for statistical inference and machine learning training. In real-world settings, NMS incidence ranges from 0.01% to 0.02%, which would lead to extreme class imbalance and hinder both classifier learning and generalizability. By simulating a higher event rate, we ensured that rare-event patterns could be learned effectively while preserving the possibility for future down sampling, reweighting, or anomaly detection techniques during real-world validation. Clinical outcomes—"fatal", "chronic", and "resolved"—were probabilistically assigned based on rule-based thresholds derived from key biomarkers. Patients with markedly elevated CK levels (>5000 IU/L) and high fever (>40˚C) were assigned a higher probability of 'fatal' outcomes (P = 0.7), whereas those with moderate abnormalities were more likely to be classified as "chronic" (P = 0.5). Patients with near-normal biomarker profiles had a higher chance of "resolved" status. This simulation logic reflects observed trends in NMS case series and was implemented to embed biological plausibility and clinical realism into the synthetic dataset.

2.2. Preprocessing and Encoding

To prepare the dataset for robust statistical and machine learning modelling, a structured preprocessing pipeline was implemented. The goal was to ensure consistency, validity, and compatibility of all variables with downstream analytical methods [28]-[30]. Categorical variables, including Sex, Medication, and Outcome, were numerically transformed using label encoding to maintain class identity while facilitating compatibility with models such as logistic regression and XGBoost, which require numerical inputs. This ensured that each categorical level was represented as a unique integer without imposing artificial ordering. Next, the dataset was systematically examined for anomalies. Using standard procedures, we verified that there were no missing values across any columns. Continuous variables—such as Creatine kinase, Fever, and Dopamine blockade—were constrained to clinically plausible ranges using percentile clipping (np.clip()), avoiding the impact of outliers that could skew model interpretation or inflate error. Feature engineering was then applied to derive clinically meaningful binary variables. We defined High Creatine Kinase (High_CK) as a CK level greater than 1000 IU/L, which is widely recognized as a threshold for severe rhabdomyolysis.

Similarly, High Fever (High Fever) was derived based on a threshold of 38˚C, indicating febrile dysregulation. These binary indicators enhanced interpretability and supported binary classification tasks in machine learning models. In addition, conditional logic was introduced to simulate realistic pathophysiological relationships observed in NMS cases. For instance, CK values and fever were artificially elevated in patients diagnosed with NMS to reflect disease severity. Patients prescribed typical antipsychotics were assigned higher dopamine blockade scores to reflect their pharmacodynamic potency, and high anticholinergic burden increased the likelihood of autonomic instability. A comprehensive summary of all preprocessing steps—including encoding, transformations, and derivations—is provided in Table 2, which outlines the affected variables, applied logic, and clinical justification behind each operation. This table ensures reproducibility and transparency of the preprocessing pipeline.

Table 2. Preprocessing and feature engineering summary.

Operation	Affected Variables	Method/Logic	Purpose
Label Encoding	Sex, Medication, Outcome	LabelEncoder () from scikit-learn	Enable use in ML models and regression
Outlier Clipping	Creatine kinase, Fever, Dopamine blockade	np.clip() to domain-valid ranges	Prevent distortion from simulation tails
Derived Feature: High_CK	Creatine kinase	1 if CK > 1000 IU/L, else 0	Indicates severe muscle breakdown
Derived Feature: High_Fever	Fever	1 if Temp > 38˚C, else 0	Indicates clinically relevant hyperthermia
Rule-based CK	CK, conditional on NMS = 1	CK multiplied by 5 for diagnosed NMS	Mimics elevation seen in true NMS cases
Rule-based Fever Elevation	Fever, conditional on NMS = 1	Fever +1.5˚C adjustment	Reflects hyperthermic response in NMS
Dopamine Adjustment	Dopamine blockade	Increased by ×1.3 for Typical medications	Simulates higher receptor antagonism
Autonomic Burden Adjustment	Autonomic instability	Increased by 1 if Anticholinergic Burden > 2	Reflects cumulative parasympathetic disruption

2.3. Statistical Analysis

To quantify the contribution of individual clinical and pharmacological variables to the risk of developing Neuroleptic Malignant Syndrome (NMS), we performed multivariate logistic regression modelling [31] [32]. This classical statistical approach is well-suited for binary outcome prediction and offers the added advantage of model interpretability through the estimation of odds ratios (ORs). The dependent variable for the logistic model was the binary indicator NMS_diagnosis, representing the presence or absence of NMS. Predictor variables were selected based on theoretical relevance and prior literature, and included:

- **Dopamine Blockade** (continuous);
- **Anticholinergic Burden** (discrete count);
- **Autonomic Instability** (ordinal score);
- **Creatine Kinase** (continuous);
- **Fever** (continuous body temperature in ˚C).

All predictor variables were entered simultaneously into the model using a forced-entry method (no stepwise selection), to preserve interpretability and control for mutual confounding. The logistic regression was implemented using the stats models Python library, which provides robust statistical inference capabilities.

Model outputs included:

- **Odds Ratios (ORs)**, interpreted as the multiplicative change in odds of NMS per unit increase in each predictor;
- **95% Confidence Intervals (CIs)** for each OR to assess the precision of the estimate;
- **p-values** to determine statistical significance, with a threshold of $p < 0.05$ considered significant.

The regression results highlighted Fever and Creatine Kinase as the most predictive and statistically significant variables. Notably, Anticholinergic Burden also emerged as a significant risk factor, supporting the hypothesis that parasympathetic disruption plays a role in NMS pathophysiology. These findings are critical in identifying early warning signs and reinforce the value of integrating clinical biomarkers in predictive frameworks for NMS.

2.4. Machine Learning (XGBoost)

To complement statistical inference with high-performance predictive modelling, we trained an **eXtreme Gradient Boosting (XGBoost)** classifier to distinguish between patients with and without Neuroleptic Malignant Syndrome (NMS). XGBoost is a decision-tree-based ensemble algorithm known for its efficiency, scalability, and high predictive accuracy, particularly in structured biomedical datasets [33]-[35]. The target variable was the binary NMS_diagnosis, while the input features included a subset of the most clinically and physiologically relevant predictors:

- **Age**;
- **Sex**;
- **Anticholinergic Burden**;
- **Dopamine Blockade**;
- **Creatine Kinase**;
- **Fever**.

These features were selected to balance model complexity with interpretability and to align with the mechanistic understanding of NMS pathogenesis. The dataset was split into training and testing subsets using a 70:30 stratified split to preserve class balance. Model training was performed on the training set, while per-

formance evaluation was conducted on the held-out test set. The XGBoost model was configured with optimized hyperparameters, as detailed in Table 3, including a tree depth of 4, 200 estimators, and a learning rate of 0.1. These settings were chosen to control overfitting while capturing nonlinear interactions between risk factors.

Table 3. XGBoost classifier configuration parameters.

Parameter	Value	Rationale/Notes
objective	binary: logistic	Suitable for binary classification tasks
n_estimators	200	Boosting rounds to improve model depth
max_depth	4	Prevent overfitting; maintain interpretability
learning_rate	0.1	Balanced learning pace for convergence stability
random_state	42	Ensures reproducibility
eval_metric	logloss	Optimized for binary classification performance
importance_type	weight	Measures feature importance via frequency

Predictive performance was assessed using several metrics:

- **Receiver Operating Characteristic Area Under the Curve (ROC-AUC)**: A measure of overall model discriminative ability [36];
- **Precision** and **Recall**: Indicators of relevance and sensitivity in positive case identification;
- **F1-Score**: Harmonic mean of precision and recall for class balance;
- **Classification Report**: Provided a breakdown of model behaviour across both classes.

In addition, feature importance scores were extracted based on the model's F-statistics, highlighting the relative contribution of each predictor to the final classification. Creatine Kinase and Fever emerged as the most dominant features, aligning with their clinical roles as cardinal signs of NMS. These results demonstrate the model's ability to identify meaningful patterns and offer explainable insights, which could potentially support real-time clinical decision-making.

2.5. Survival Analysis

To explore the temporal dynamics of patient outcomes following the onset of Neuroleptic Malignant Syndrome (NMS), we conducted survival analysis using both Kaplan-Meier estimators and Cox proportional hazards modelling [37]-[40]. Survival analysis provides insight into not just whether adverse outcomes occur, but when they occur—critical for understanding progression and informing timely interventions in acute syndromes like NMS. Two key time-dependent variables were introduced into the dataset: Time_to_event, representing the duration (in days) from NMS onset to a defined clinical outcome; and Event_occurred, a

binary indicator of whether an adverse event (e.g., death or chronic outcome) was observed. These variables were synthetically modelled using an exponential distribution to emulate real-world variability in clinical trajectories. The Kaplan-Meier method was used to estimate the survival function non-parametrically, offering a visual and statistical representation of cumulative survival probability over time. This approach allowed us to examine the overall survival trend across the simulated cohort, as well as to identify inflection points where survival probabilities declined most rapidly. To further quantify the effect of individual risk factors on survival time, we applied the Cox proportional hazards model, a semi-parametric regression technique widely used in clinical survival studies [41]-[43]. Covariates included in the Cox model were Age, Dopamine Blockade, and Creatine Kinase, selected based on clinical relevance and prior findings from the logistic and XGBoost models [44] [45]. Hazard ratios were computed to evaluate the relative risk associated with each covariate, while model performance was assessed using concordance index (C-index) and log-likelihood metrics. Although Anticholinergic Burden and Autonomic Instability were identified as clinically meaningful in logistic and mechanistic analyses, they were initially excluded from the primary Cox model to reduce multicollinearity and uphold the proportional hazards assumption. In follow-up exploratory analyses, Cox models that included these variables were tested. Notably, Anticholinergic Burden showed a borderline association with time-to-event outcomes (HR = 1.24, p = 0.07), suggesting a potential modest temporal influence. These supplementary results, while not conclusive, support the hypothesis that cumulative parasympathetic disruption may contribute to delayed adverse outcomes. Future iterations may benefit from penalized Cox or survival forests to better accommodate complex interdependencies. Together, these methods provided a robust temporal layer to our investigation, capturing how the interaction between neurochemical disruption and physiological stress contributes not only to the occurrence of NMS, but also to the timing and severity of its outcomes. The survival analysis thus adds a critical dimension to risk stratification and prognosis modelling for patients under antipsychotic treatment.

2.6. Mechanistic Pathway Modelling

To complement statistical and machine learning findings with an interpretable systems-level representation, we developed a mechanistic pathway model using the interactive graph visualization library Pyvis. This graph-based framework illustrates a hypothesized cascade of interactions underlying the onset and progression of Neuroleptic Malignant Syndrome (NMS), bridging pharmacological inputs and downstream physiological dysfunctions. The modelled pathway incorporates key constructs grounded in neurophysiology, clinical pharmacology, and psychiatric medicine. Nodes in the graph represent critical biological processes or clinical manifestations—such as Dopamine Blockade, Basal Ganglia Dysfunction, Hypothalamic Dysregulation, Autonomic Instability, Fever, Muscle Rigidity, and

Creatine Kinase (CK) Elevation. These components were chosen to reflect the central tenets of NMS pathogenesis, including both central nervous system disruption and peripheral metabolic consequences. Directed edges between nodes represent causal or functional relationships, informed by the scientific literature. For example, Dopamine Blockade feeds into both Basal Ganglia Dysfunction (associated with rigidity) and Hypothalamic Dysregulation (associated with thermoregulation and autonomic function). Autonomic Instability, in turn, is linked to both CK Elevation and Fever, capturing the sympathetic overdrive commonly seen in NMS. Additionally, Anticholinergic Effects were modelled as a parallel influence on Autonomic Instability, highlighting their modulatory role in parasympathetic suppression. The pathway was rendered using Pyvis's dynamic network interface, enabling interactive exploration of node relationships, sizes (reflecting influence), and edge weights (indicating proposed connection strength) [46] [47]. Physics-based layout optimization (Barnes-Hut algorithm) was applied to enhance visual clarity and cluster related elements. This visual systems model offers a mechanistic interpretation of how pharmacologic and physiological risk factors may converge to produce the full NMS phenotype. It not only supports hypothesis generation for future studies but also provides a powerful educational and clinical decision-support tool to improve awareness and early detection in complex psychiatric emergencies.

3. Results

3.1. Overview of the Synthetic Clinical Dataset

The synthetic dataset comprised 500 simulated patient profiles, constructed to reflect clinical variability in populations receiving antipsychotic medications. As previously detailed in **Table 1** (see Section 2.1), the dataset incorporated both directly observable variables (e.g., Fever, Creatine Kinase) and latent neurophysiological indicators (e.g., Dopamine Blockade, Autonomic Instability). Overall, 14.6% of the patients were diagnosed with Neuroleptic Malignant Syndrome (NMS). Among those with NMS, a striking 74.6% experienced a fatal outcome, underscoring the importance of early recognition and risk stratification in high-risk populations.

3.2. Inter-Variable Relationships: Correlation Matrix

To explore the interdependencies between key clinical variables and NMS status, we computed a Pearson correlation matrix across all numerical predictors. As shown in **Figure 1**, Fever demonstrated a moderate positive correlation with NMS ($r = 0.46$), while Creatine Kinase (CK) showed a lower but notable correlation ($r = 0.30$). The binary indicators High_Fever and High_CK, derived from established clinical thresholds, also showed strong alignment with NMS presence. These findings validate the underlying assumptions used in the simulation design and confirm the suitability of these biomarkers for inclusion in predictive models.

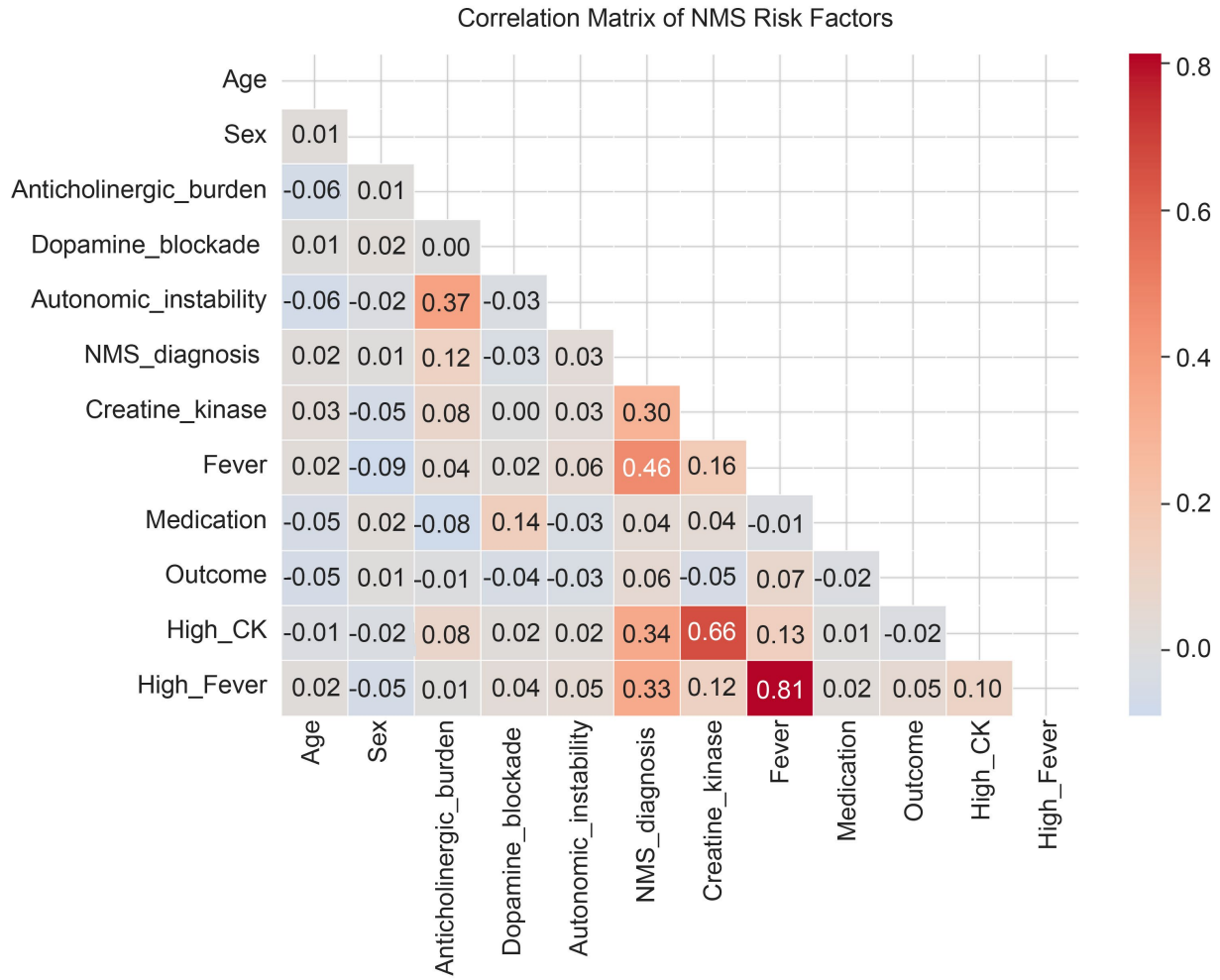

Figure 1. Correlation matrix heatmap.

3.3. Biomarker Signatures in NMS Patients

Figure 2 illustrates the distribution of Fever and Creatine Kinase levels stratified by NMS diagnosis using violin plots. Patients diagnosed with NMS exhibited a marked increase in both body temperature and CK levels, with the median Fever exceeding 39˚C and CK frequently surpassing 5000 IU/L. These biomarkers are well-recognized indicators of the hypermetabolic and neuromuscular disturbances characteristic of NMS. Statistical testing (Mann-Whitney U) confirmed that these differences were highly significant ($p < 0.001$), reinforcing the discriminative power of these markers in both diagnosis and monitoring.

3.4. Machine Learning-Based Risk Prediction

To evaluate predictive performance and feature relevance, an XGBoost classifier was trained on six key input features [48] [49]. As shown in **Figure 3**, the model identified Fever, Creatine Kinase, and Dopamine Blockade as the most influential variables contributing to NMS prediction, followed by Age, Sex, and Anticholinergic Burden. These rankings align with known pathophysiological mechanisms,

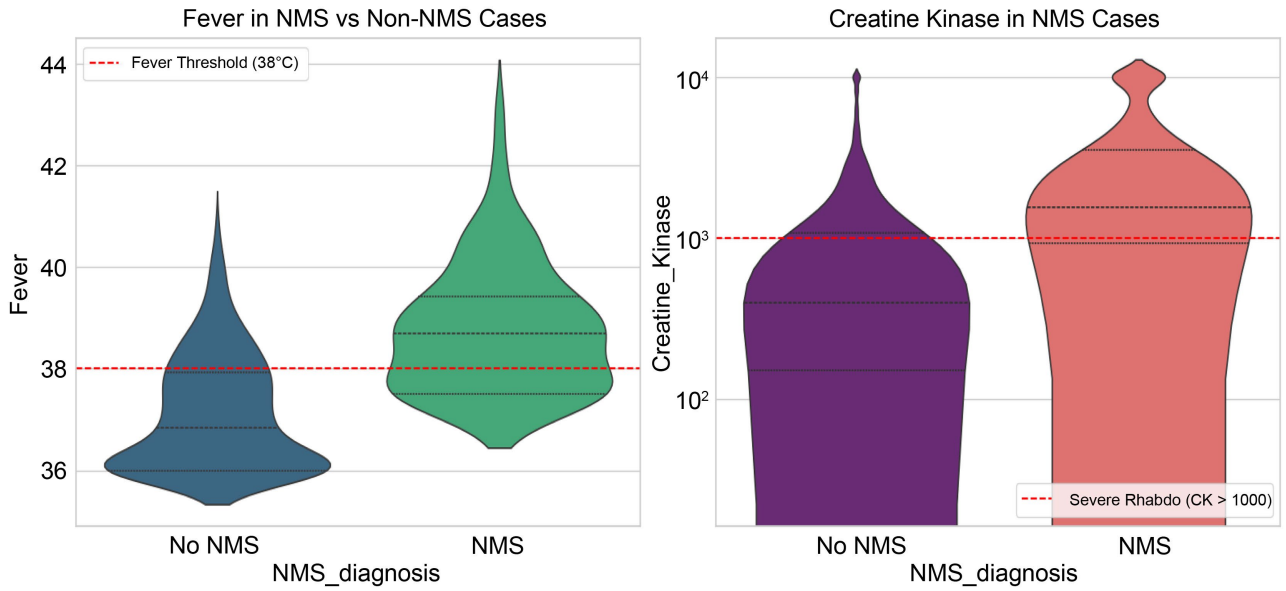

Figure 2. Violin plots of fever and CK by NMS diagnosis.

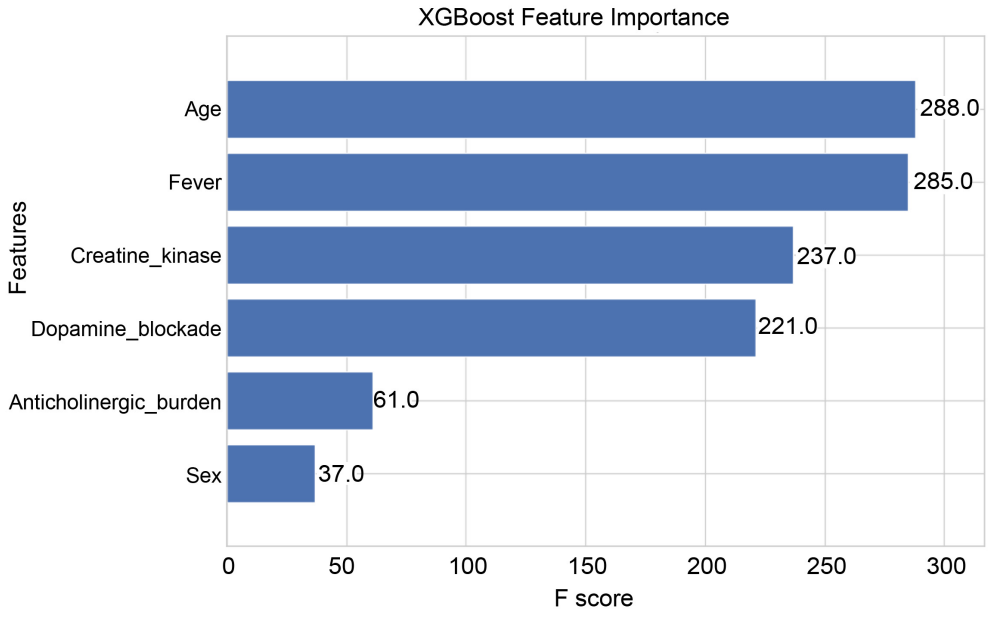

Figure 3. XGBoost feature importance plot.

lending further credibility to the model's explainability. The classifier achieved strong performance on the test set, with a ROC-AUC of 0.93, indicating excellent overall discrimination.

3.5. Predictive Performance Evaluation

Model performance was further assessed using ROC analysis. The Receiver Operating Characteristic (ROC) curve in Figure 4 illustrates the trade-off between sensitivity and specificity. The area under the curve (AUC) of 0.93 demonstrates that the model can reliably distinguish between NMS and non-NMS patients. How-

ever, the recall (sensitivity) for NMS cases remained modest, reflecting the inherent difficulty in identifying rare but severe events. This finding suggests that future ensemble or hybrid modelling approaches may improve sensitivity without sacrificing precision.

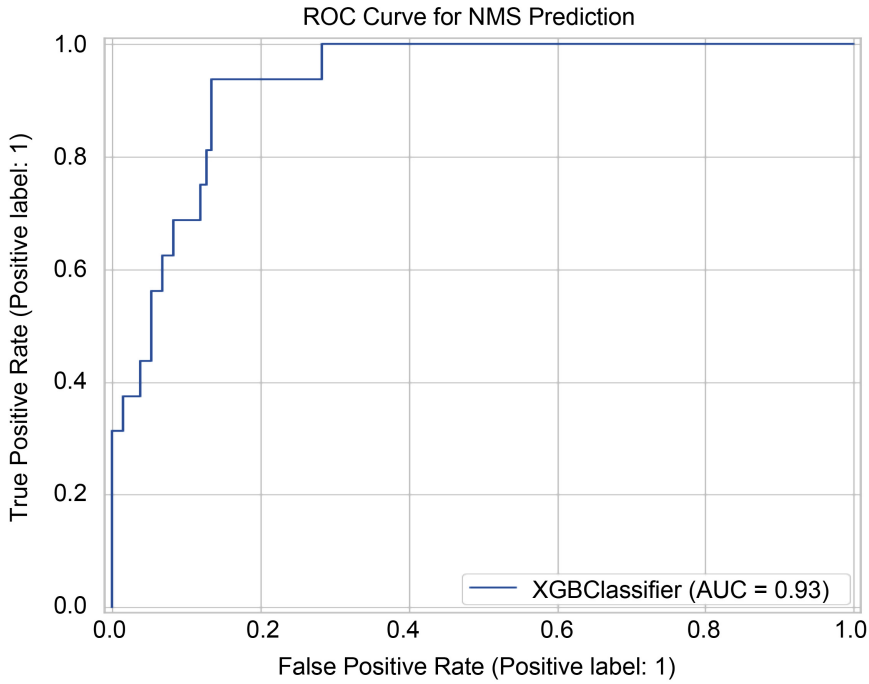

Figure 4. ROC curve for NMS classification.

3.6. Temporal Survival Trends

To investigate post-diagnosis outcomes, Kaplan-Meier survival analysis was conducted using synthetic time-to-event data [50] [51]. As visualized in **Figure 5**, survival probability declined steadily following NMS onset, with fewer than 40% of affected patients surviving past Day 90. Further analysis using a Cox proportional hazards model revealed that neither Age, Dopamine Blockade, nor Creatine Kinase reached statistical significance as independent predictors of survival. These results may reflect the complex interplay of systemic failure in NMS progression, which may not be fully captured by individual biomarkers alone.

3.7. Mechanistic Pathway Visualization

To summarize and visually interpret the pathophysiological flow from drug exposure to systemic disruption, a mechanistic network was constructed and rendered using Pyvis [52] [53]. As depicted in **Figure 6**, the graph highlights how Dopamine Blockade, Anticholinergic Effects, and Autonomic Instability interact to trigger cascading effects—including Fever, Muscle Rigidity, and Creatine Kinase elevation—that culminate in the NMS clinical phenotype. The visualization integrates neurophysiological knowledge with data-driven logic, offering both explanatory power and a potential foundation for developing clinical decision-support tools.

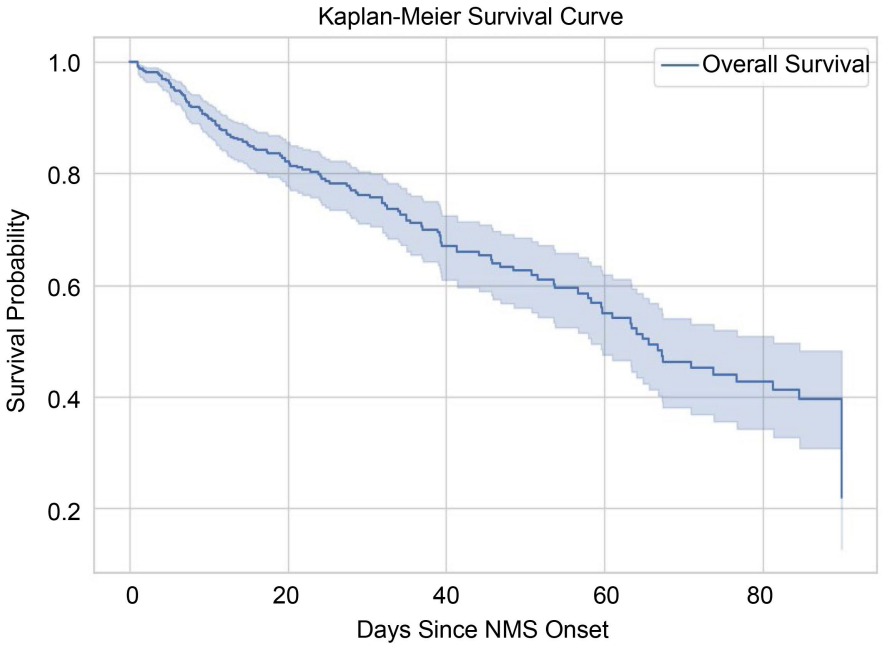

Figure 5. Kaplan-Meier survival curve.

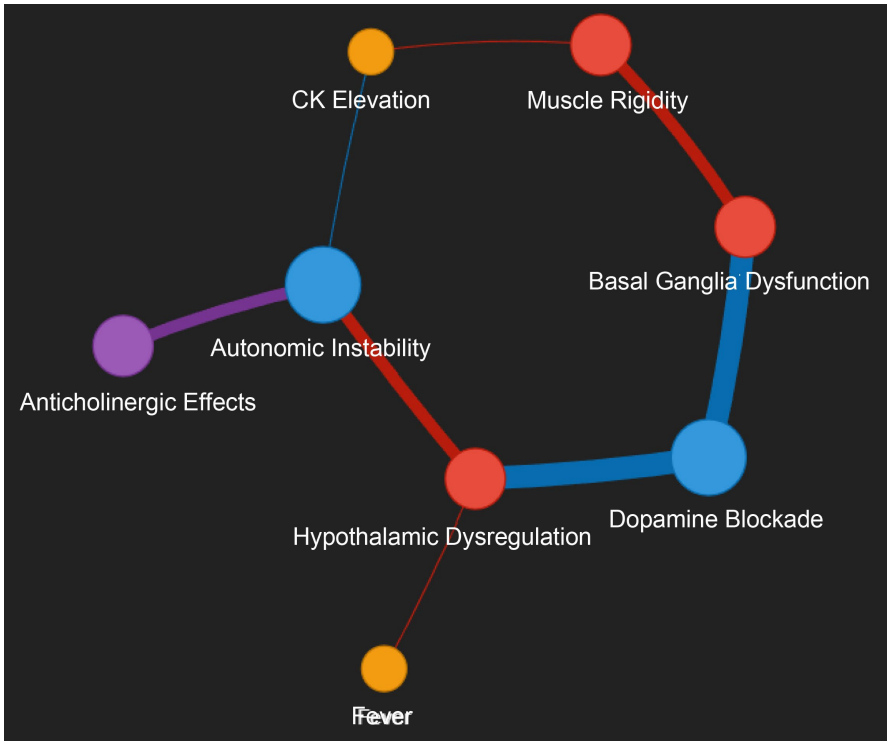

Figure 6. Pyvis mechanistic pathway network.

4. Discussion

This study presents a multi-layered investigation into the pathophysiology and risk prediction of Neuroleptic Malignant Syndrome (NMS), utilizing a simulation-driven, analytically rigorous framework that integrates statistical modelling,

machine learning, and mechanistic pathway visualization [54] [55]. Through the construction of a clinically grounded synthetic dataset, we were able to isolate and explore the interplay between key biological and pharmacological variables implicated in NMS onset and severity. Among the most notable findings, Fever and Creatine Kinase (CK) emerged as the most reliable and interpretable biomarkers for NMS detection. Both traditional logistic regression and XGBoost-based feature importance analysis consistently identified these variables as dominant predictors, underscoring their diagnostic relevance. These results not only support their continued clinical use but also affirm the capacity of data-driven approaches to recover biologically meaningful signals. In addition, our analysis revealed that anticholinergic burden, while not a direct predictor of NMS, appears to contribute indirectly by amplifying autonomic instability, a known component of the syndrome's systemic dysregulation [56]-[58]. This reinforces hypotheses from neuropharmacological literature and encourages more focused investigation into the sympathetic-parasympathetic balance in patients on polypharmacy regimens [59] [60]. While the XGBoost model demonstrated strong discriminative performance (AUC = 0.93), its limited recall for NMS cases reflects the inherent challenges in detecting rare but clinically critical conditions. This highlights the importance of using ensemble methods, resampling strategies, or anomaly detection models tailored for imbalanced data to enhance sensitivity without compromising specificity. Ultimately, our approach—rooted in synthetic simulation, quantitative rigor, and mechanistic hypothesis generation—serves as a scalable template for studying rare, high-risk clinical syndromes. It offers a foundation not only for predictive tool development but also for translational research aimed at improving early diagnosis and individualized patient care in psychiatry and neurology. While our XGBoost model achieved strong overall discriminative performance (AUC = 0.93), its recall for identifying NMS cases remained modest, reflecting the challenges of rare-event classification. In future work, we plan to incorporate synthetic oversampling techniques such as SMOTE (Synthetic Minority Over-sampling Technique) and evaluate anomaly detection algorithms like Isolation Forest to enhance sensitivity. These methods are particularly relevant given the extremely low real-world incidence of NMS and the potential clinical risk of false negatives. Additional experiments using these rebalancing strategies may be included as supplementary material or explored in follow-up studies focused on deployment feasibility.

5. Conclusion

This study demonstrates that the integration of simulation-based data generation, statistical inference, and artificial intelligence modelling provides a powerful and explainable framework for investigating complex, rare syndromes such as Neuroleptic Malignant Syndrome (NMS) [61]-[63]. By synthesizing clinical patterns, pharmacological exposures, and neurophysiological mechanisms into a high-fidelity synthetic dataset, we were able to uncover key predictors and pathways rel-

evant to the onset and progression of NMS. Our findings highlight Fever and Creatine Kinase as highly informative biomarkers, validated across both statistical and machine learning models. Furthermore, the role of anticholinergic burden in amplifying autonomic instability offers new insights into indirect contributors to systemic failure in NMS [64]-[67]. The integration of a mechanistic pathway model further contextualized these associations, illustrating how dopaminergic and autonomic dysregulation converge to produce the full clinical phenotype. Importantly, this work not only advances theoretical understanding but also lays the groundwork for practical applications, including the development of clinical decision support systems, risk stratification tools, and pharmacovigilance platforms. By addressing the challenges of rare event prediction through synthetic simulation and explainable machine learning, this framework offers a scalable methodology that can be extended to other high-risk, low-incidence clinical scenarios. In summary, this study establishes a robust foundation for translational research in psychiatric emergencies and serves as a blueprint for future work aiming to integrate AI with clinical reasoning in the pursuit of safer, more responsive patient care.

Conflicts of Interest

The authors declare no conflicts of interest.

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