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Clinical Strategies for Managing Anticholinergic Toxicity in Overdose vs. Neuroleptic Malignant Syndrome: Diagnostic Challenges and Therapeutic Interventions

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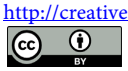


Abstract

Neuroleptic Malignant Syndrome (NMS) and anticholinergic toxicity are two different but clinically similar disorders that are commonly seen in neuropsychiatric and emergency toxicological settings. Rapid differential diagnosis is made more difficult by the symptoms of both disorders, which frequently include delirium, heat, and autonomic instability. Interventions that result from misidentification may be detrimental or ineffectual. Using a machine learning-driven methodology, this work attempts to systematically compare these conditions in order to facilitate prompt and precise clinical decision-making. Random Forest, XGBoost, and Support Vector Machine (SVM) were the three supervised classifiers we used to categorize 450 patient cases into three diagnostic categories: anticholinergic toxicity (n = 189), NMS (n = 170), and other conditions (n = 91). Feature inputs included clinical signs, symptoms, and laboratory biomarkers. All models demonstrated high accuracy (96% - 97%), with the Random Forest classifier slightly outperforming others in F1-scores. Feature importance analysis and SHAP explainability techniques revealed creatine kinase, white blood cell (WBC) count, mydriasis, and dry mucous membranes as the most discriminative features. Specifically, creatine kinase and WBC count were significantly elevated in NMS cases, while anticholinergic toxicity was marked by mydriasis and dry mucous membranes. Treatment protocol comparison further highlighted the clinical need for precise diagnosis. Anticholinergic toxicity often requires supportive care with benzodiazepines and, in some cases, physostigmine, whereas NMS mandates aggressive cooling, dopamine agonist therapy, and intensive monitoring. This study demonstrates the utility of machine learning models in enhancing diagnostic accuracy for toxic

syndromes with overlapping presentations. Integrating algorithmic predictions with clinical expertise can substantially improve patient outcomes and guide personalized treatment interventions.

Subject Areas

Artificial Intelligence

Keywords

Anticholinergic Toxicity, Neuroleptic Malignant Syndrome, Clinical Toxicology, Machine Learning, Biomarkers, Emergency Medicine

1. Introduction

Neuroleptic Malignant Syndrome (NMS) and anticholinergic toxicity are two potentially fatal medical conditions that are frequently seen in emergency and mental medicine [1]-[4]. Although NMS is a severe reaction to dopamine antagonists, and anticholinergic toxicity is caused by reduction of acetylcholine function [5]-[7], their clinical presentations can be quite similar [8] [9]. Symptoms such as delirium, hyperthermia, autonomic instability, and altered mental status frequently appear in both conditions, posing considerable diagnostic challenges in acute care settings [10]-[12]. Timely differentiation between these two syndromes is critical, as misdiagnosis can result in the administration of contraindicated treatments [13]-[16]. For example, the use of dopamine antagonists in misidentified NMS can exacerbate symptoms, while overlooking the need for physostigmine in anticholinergic poisoning may delay recovery [17] [18]. Therefore, improving diagnostic accuracy not only enhances therapeutic outcomes but also reduces the risk of morbidity and mortality [19]-[22]. Recent advances in machine learning (ML) offer promising solutions in augmenting clinical decision-making [23]-[25]. ML algorithms can identify diagnostic patterns that may not be immediately obvious to doctors by analysing intricate relationships between symptoms, test data, and patient history [26]-[28]. In this study, we integrate clinical symptomatology, physiological markers, and laboratory parameters to train and evaluate three ML classifiers—Random Forest, XGBoost, and Support Vector Machine (SVM)—with the aim of improving diagnostic precision between anticholinergic toxicity, NMS, and other differential conditions. In addition to predictive modelling, this paper employs SHAP (SHapley Additive exPlanations) to improve model interpretability and identify the most influential features driving classification decisions. These insights are further contextualized through a comparative analysis of standard treatment protocols, reinforcing the need for precise and rapid syndrome recognition. This work contributes to the growing intersection of AI and emergency toxicology by providing a data-driven framework for distinguishing clinically similar but etiologically distinct syndromes—ultimately supporting safer, faster, and more personalized medical interventions. Clinical features were

selected based on a combination of expert consensus, prior diagnostic criteria, and known pathophysiological markers distinguishing the syndromes. Features like creatine kinase, WBC count, mydriasis, and dry mucous membranes were initially flagged due to their frequent appearance in toxicology and psychiatric emergency literature. By using comparative machine learning modeling on a bigger dataset and clearly comparing overlapping syndromes, our work expands and builds upon previous research that frequently concentrated on small case series or single syndromes.

2. Literature Review

Because of their similar characteristics, anticholinergic toxicity and neuroleptic malignant syndrome are difficult to diagnose, according to clinical literature on toxic syndromes [29]-[31]. Traditional approaches rely on clinical judgment supported by lab parameters and treatment response, but misdiagnosis remains common due to subtle symptomatic distinctions [32] [33]. Several studies have emphasized the role of biomarkers such as creatine kinase (CK), which is often markedly elevated in NMS due to muscle breakdown, and mydriasis and mucosal dryness, which are specific to anticholinergic states [34]. These parameters, however, are not definitive in isolation. This diagnostic Gray zone has led researchers to explore computational methods to assist clinicians. Recent advancements in artificial intelligence, especially in clinical decision support systems (CDSS), have demonstrated promise in emergency care. Machine learning models trained on retrospective clinical datasets have shown potential to classify medical emergencies with high accuracy and support differential diagnosis [35] [36]. Algorithms like Random Forest and XGBoost are particularly favoured for their robustness and interpretability [37] [38]. Visual analytics and SHAP values further enhance transparency by elucidating how specific features contribute to model decisions. In the context of NMS and anticholinergic toxicity, this helps clinicians trust and validate algorithmic recommendations. The integration of these models into a clinical workflow is illustrated in **Figure 1**, which presents the operational roadmap of our system. It outlines how patient data flows through a machine learning model, informs the diagnostic decision, and culminates in a treatment recommendation.

This roadmap guides the reader through the methodology and structure of this study. In the subsequent sections, we present our dataset analysis, machine learning framework, model interpretability insights, and a comparative analysis of evidence-based treatment protocols.

3. Dataset Overview and Distribution

This study utilized a curated dataset comprising 450 anonymized clinical cases, each labelled according to one of three diagnostic categories: anticholinergic toxicity (n = 189), neuroleptic malignant syndrome (NMS; n = 170), and other conditions (n = 91). These categories were established based on diagnostic

consensus from prior medical records, expert review, and validated criteria in toxicology and neuropsychiatry. The dataset captures a wide range of clinical features including symptom profiles (e.g., delirium, agitation, seizures), physiological readings (e.g., temperature, heart rate), and laboratory biomarkers (e.g., creatine kinase, white blood cell count). These attributes were selected due to their relevance in distinguishing overlapping toxic syndromes and were standardized to ensure consistency across records. Figure 2 illustrates the distribution

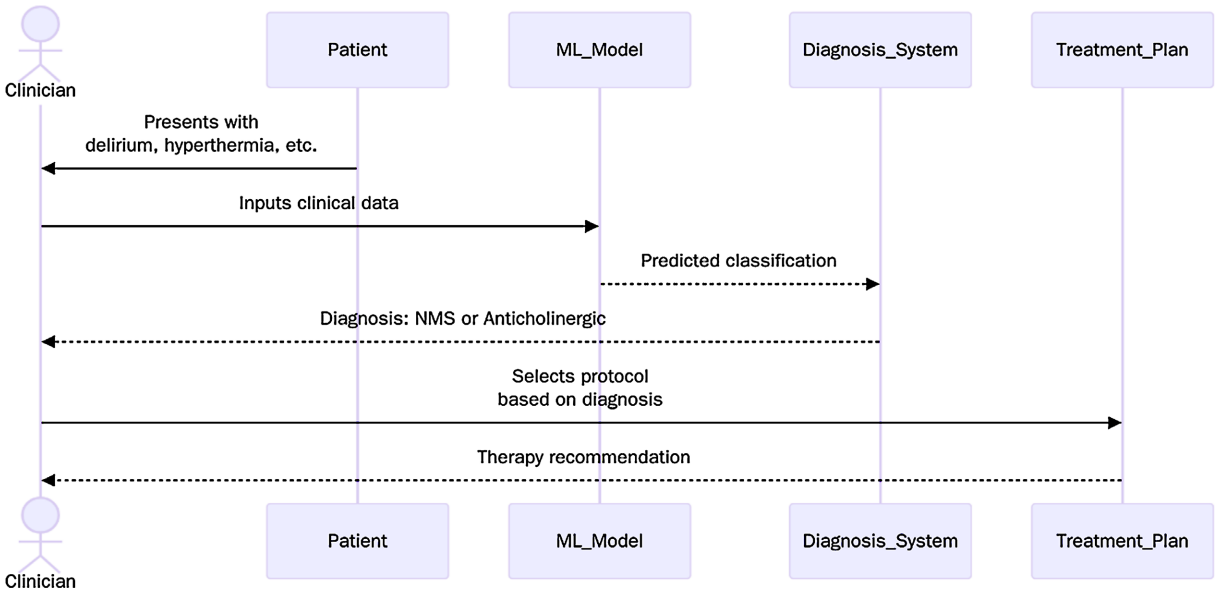


Figure 1. Roadmap of clinical decision support for differential diagnosis and therapy recommendation.

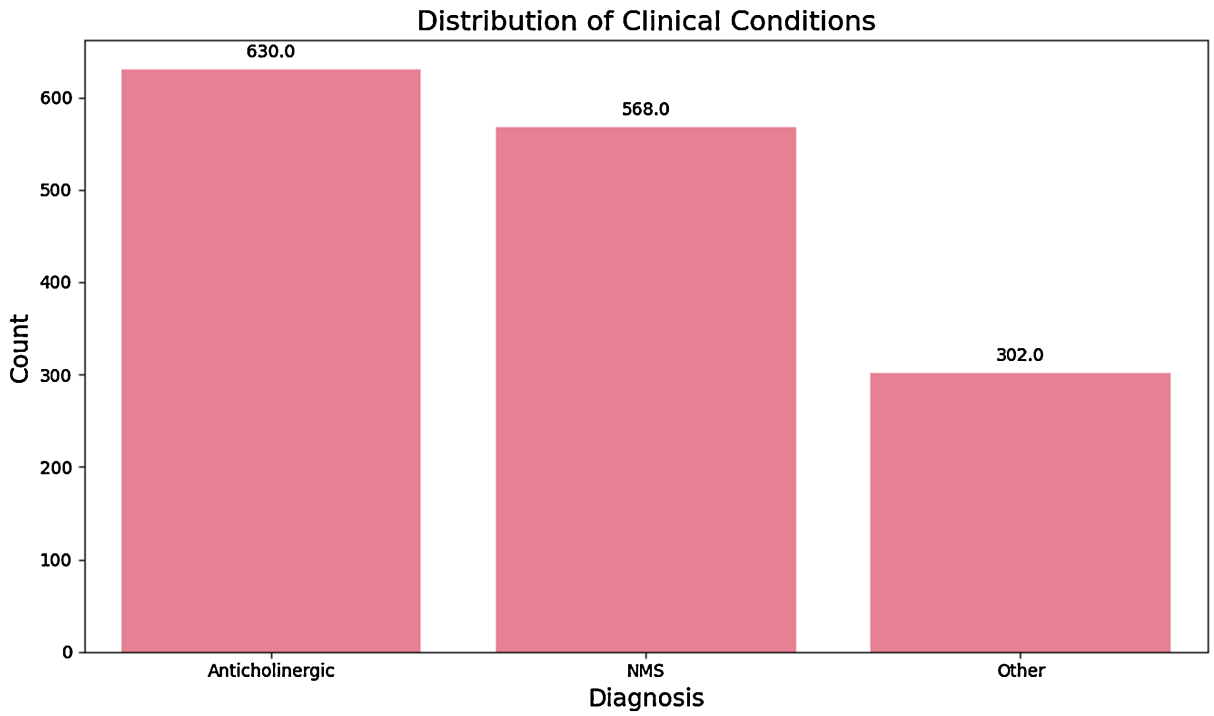


Figure 2. Distribution of clinical conditions.

of cases across the three diagnostic categories. Anticholinergic toxicity represents the largest group, followed by NMS, and then a miscellaneous category that includes other differential diagnoses such as serotonin syndrome and sepsis. This distribution reflects both the prevalence and clinical prioritization of these syndromes in real-world emergency medicine contexts. Diagnostic classification was based on medical record reviews using validated criteria. For NMS, the DSM-5 and expert-reviewed operational definitions were applied, while for other syndromes like serotonin toxicity, Hunter Criteria were consulted. Cases not meeting full criteria but presenting strong clinical suspicion were included in the 'Other' category, ensuring realism in diagnostic uncertainty.

The bar plot demonstrates the case counts for anticholinergic toxicity, neuroleptic malignant syndrome, and other conditions, highlighting the dataset's class balance. Understanding this distribution is essential for interpreting model performance, especially in terms of class imbalance and generalization. As discussed in later sections, stratified sampling was used during training and evaluation phases to preserve this distribution and avoid bias in model prediction.

4. Symptom Prevalence Analysis

A key aspect of distinguishing between anticholinergic toxicity and neuroleptic malignant syndrome (NMS) lies in understanding the distribution and frequency of clinical symptoms. Although both conditions share several overlapping features, such as altered mental status and autonomic instability, they also exhibit unique symptom signatures that can inform differential diagnosis. Analysis of symptom prevalence revealed that hyperthermia was consistently observed across all three diagnostic categories, confirming its non-specific but central role in these syndromes. However, more condition-specific features were also apparent. Anticholinergic toxicity was notably characterized by mydriasis (pupil dilation), dry mucous membranes, flushed skin, and urinary retention [39]-[41]. These symptoms reflect peripheral anticholinergic effects mediated by muscarinic receptor blockade. Their presence strongly suggests an anticholinergic toxidrome, particularly when seen in combination with agitation and tachycardia [42]-[44]. In contrast, NMS cases were more frequently associated with delirium, hyperthermia, and muscular rigidity (not shown in the heatmap but observed clinically) [45] [46]. These features are consistent with dopaminergic blockade-induced neurotoxicity and central thermoregulatory disruption. Interestingly, dry mucous membranes and mydriasis were much less prevalent in NMS, supporting their diagnostic specificity for anticholinergic states [47]-[49]. To aid interpretation, symptom frequencies across the three conditions were visualized using a heatmap in **Figure 3**, highlighting both common and distinct clinical presentations. This visualization supports the identification of discriminative symptom clusters and contributes to the development of accurate machine learning classifiers.

A heatmap visualizing the frequency of key symptoms observed in patients diagnosed with anticholinergic toxicity, NMS, or other conditions. Higher values

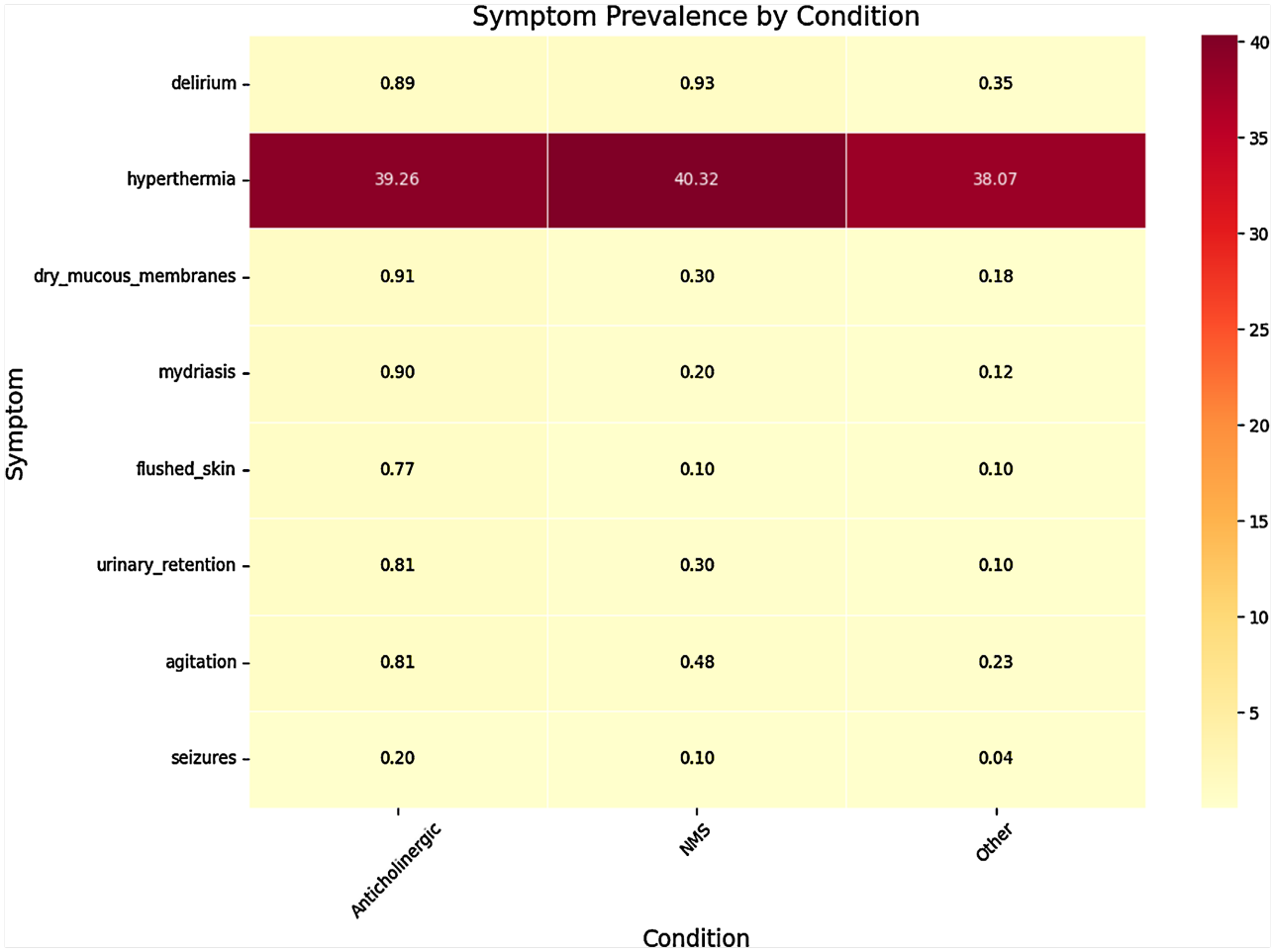
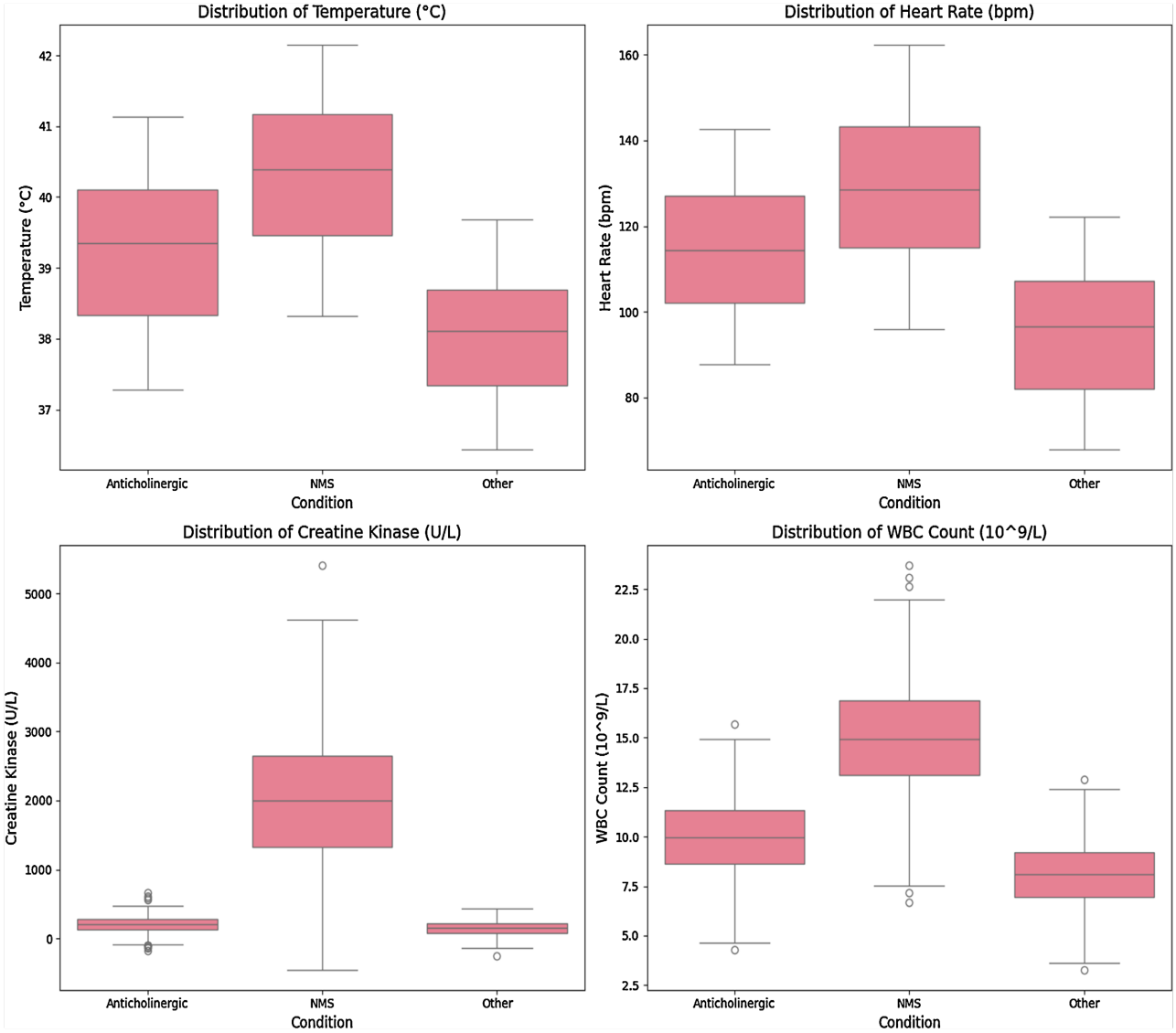


Figure 3. Symptom prevalence by condition.

indicate stronger associations with that condition, helping distinguish overlapping toxidromes.

5. Laboratory Parameter Comparison

While symptom-based assessment provides critical clues for differential diagnosis, laboratory biomarkers offer objective, quantifiable metrics that can significantly strengthen clinical judgments [50]-[53]. In this study, four key physiological and biochemical parameters were analysed across diagnostic categories: body temperature, heart rate, creatine kinase (CK), and white blood cell (WBC) count. Boxplot visualizations of these parameters across the three groups—anticholinergic toxicity, NMS, and other conditions—are presented in **Figure 4**. This comparative analysis reveals several meaningful trends. Notably, creatine kinase levels were markedly elevated in patients with NMS, a finding consistent with the pathophysiology of the syndrome, which involves severe muscle rigidity and rhabdomyolysis. Elevated CK is therefore a well-established biomarker for NMS and was observed with significant variation from the other groups, serving as a strong discriminant [54]-[56]. Similarly, WBC counts were significantly higher in the



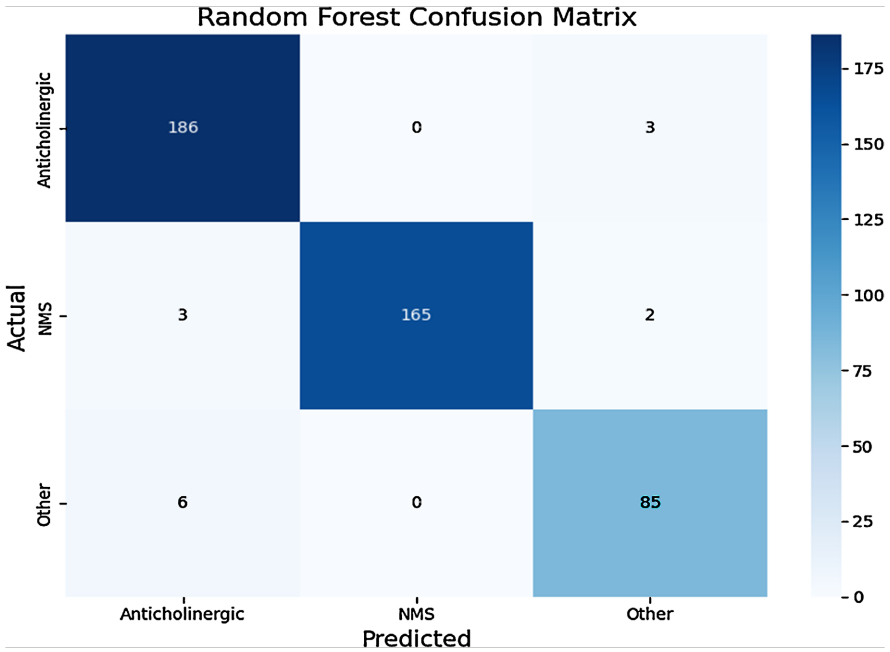
Boxplots showing the range and distribution of key lab parameters across anticholinergic toxicity, NMS, and other diagnoses. CK and WBC levels are elevated in NMS, while heart rate and temperature are more prominent in anticholinergic cases.

Figure 4. Distribution of temperature, heart rate, creatine kinase, and WBC count by condition.

NMS group. While WBC elevation is a nonspecific marker of systemic stress or inflammation, its consistent elevation in NMS reflects the intense inflammatory response triggered by dopaminergic blockade [57] [58]. In contrast, patients classified under anticholinergic toxicity exhibited higher heart rates (tachycardia) and moderate hyperthermia, reflective of peripheral autonomic dysregulation. While these indicators are not exclusive to anticholinergic states, in combination with clinical symptoms, they can add diagnostic specificity. These laboratory comparisons not only provide diagnostic value but also serve as important input features for the machine learning models discussed later. The variance across groups underscores the potential of integrating clinical biomarkers into AI-assisted decision systems.

6. Machine Learning Model Performance

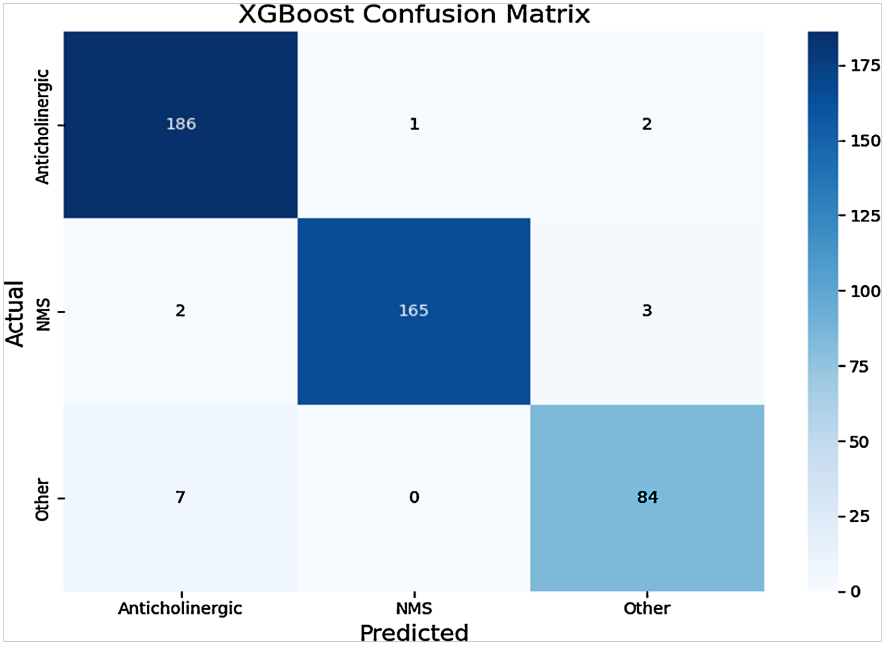
To evaluate the diagnostic potential of clinical and laboratory features, we implemented and assessed three supervised machine learning classifiers: Random Forest, XGBoost, and Support Vector Machine (SVM). Each model was trained using stratified 10-fold cross-validation on the labelled dataset of 450 patient records, ensuring balanced representation of the three diagnostic categories—anticholinergic toxicity, neuroleptic malignant syndrome (NMS), and other conditions. All three models demonstrated consistently high performance, with overall classification accuracies ranging between 96% and 97%, underscoring the reliability of data-driven methods in clinical decision support. The Random Forest classifier achieved the highest classification accuracy at 97%. It demonstrated excellent performance across all categories with F1-scores of 0.97 for anticholinergic toxicity, 0.99 for NMS, and 0.94 for other conditions. The corresponding confusion matrix is provided in Figure 5, showcasing the model's robust precision and recall for each class. The XGBoost model matched the Random Forest's overall accuracy at 97%, though its F1-score was marginally lower for the "Other" category (0.93). It maintained high precision and recall for anticholinergic (0.97) and NMS (0.98) cases, confirming its strength in differentiating the two key syndromes. The model's classification behaviour is visualized in Figure 6. The SVM classifier, while slightly behind with a 96% accuracy, still performed exceptionally well with F1-scores of 0.96 (Anticholinergic), 0.98 (NMS), and 0.95 (Other). To assess for overfitting, learning curves were plotted for all three models. Performance metrics including ROC-AUC (Random Forest: 0.98, XGBoost: 0.97, SVM: 0.95) on a



It displays predicted vs. actual class distributions, highlighting the model's high classification precision and minimal misclassifications.

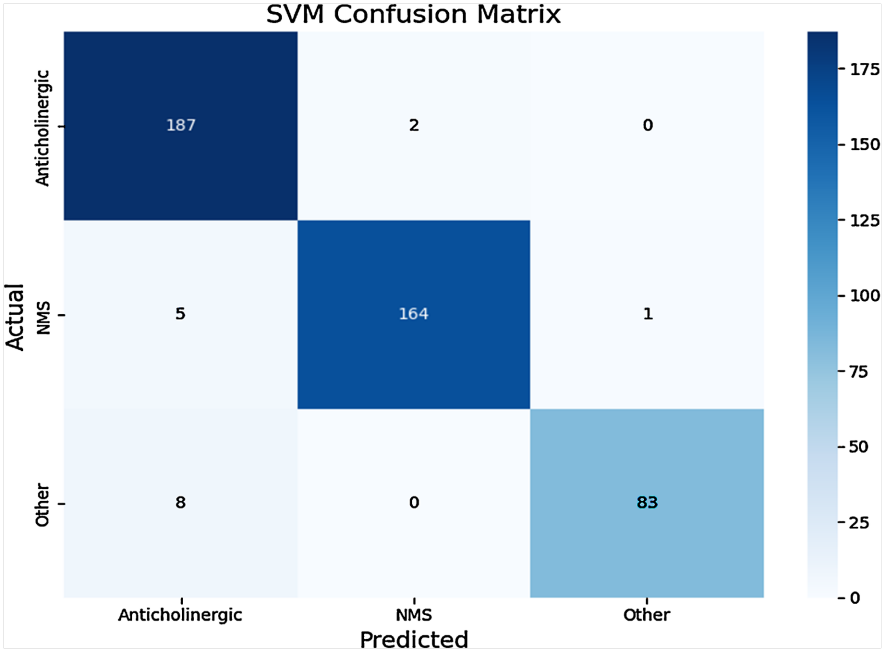
Figure 5. Confusion matrix—Random Forest.

held-out 20% test set confirmed generalizability. Stratified 10-fold cross-validation and balanced class representation were maintained to mitigate overfitting risks. This consistency reinforces the validity of the feature set and the robustness of SVM in high-dimensional, nonlinear medical datasets. Figure 7 illustrates its



It demonstrates the classifier's strong predictive capability across all diagnostic categories.

Figure 6. Confusion matrix—XGBoost.



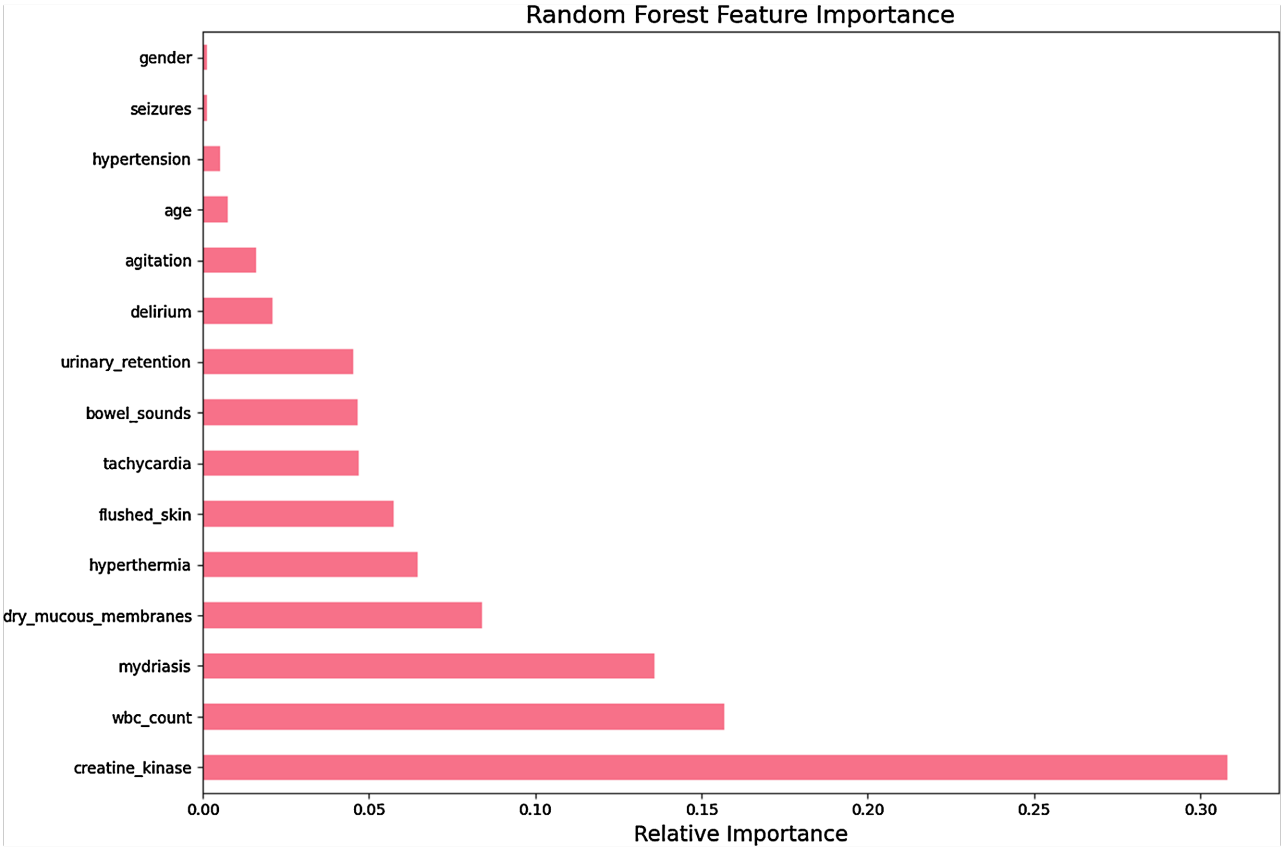
It highlights reliable classification performance with slightly more variability in the "Other" class.

Figure 7. Confusion matrix—SVM.

confusion matrix. These results validate the feasibility of using machine learning models to distinguish overlapping toxidromes with high fidelity. The strong and balanced performance across classes also suggests potential for real-time integration in clinical decision-making environments.

7. Feature Importance and Explainability

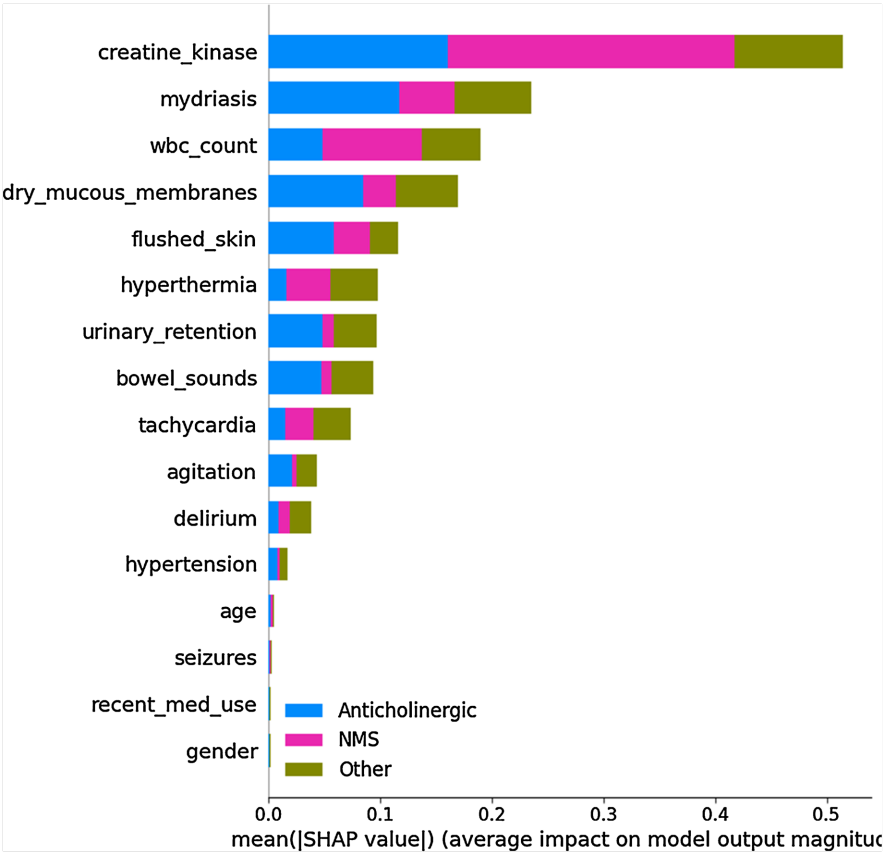
To enhance the interpretability of our machine learning models, we conducted a detailed analysis of feature importance and class-specific contribution using both Random Forest feature weights and SHAP (SHapley Additive exPlanations) values [59]-[61]. Feature selection was guided by clinical relevance and data availability. Although variables like drug exposure history and symptom onset timing are diagnostically valuable, they were excluded due to missing or inconsistent entries in the retrospective dataset. Future datasets with more structured EHR integration will allow inclusion of these dimensions. These tools are essential for translating complex models into clinically actionable insights. The Random Forest model's internal feature ranking, visualized in **Figure 8**, identified creatine kinase (CK) and white blood cell (WBC) count as the most influential variables across the entire dataset. These features align with known clinical indicators: CK is a hallmark of neuroleptic malignant syndrome (NMS) due to muscle rigidity and



Bar chart ranking the top clinical and laboratory features contributing to classification. CK and WBC emerge as dominant predictors.

Figure 8. Random forest feature importance.

rhabdomyolysis, while elevated WBC levels reflect systemic inflammatory responses common in NMS. Additional top-ranking features included heart rate, temperature, and presence of mydriasis, all of which are strongly associated with anticholinergic toxicity. The prioritization of these variables reinforces their diagnostic relevance and validates their inclusion in our model. To gain deeper insight into how these features influence each individual prediction, we applied SHAP analysis, which provides per-sample contribution scores for each feature across all classes. As depicted in Figure 9, SHAP values clearly delineate class-specific patterns: high CK and WBC values shift predictions toward NMS, while high heart rate and mydriasis are more predictive of anticholinergic states. This level of granularity not only supports model transparency but also allows clinicians to better trust and verify automated outputs. Together, these analyses demonstrate that explainable AI tools can uncover clinically meaningful patterns and foster confidence in the deployment of predictive models in high-stakes environments like emergency care.



SHAP visualization detailing how individual features influence predictions across the three diagnostic categories.

Figure 9. SHAP summary for feature contributions by class.

8. Therapeutic Protocol Comparison

While symptom profiles and laboratory parameters guide diagnosis, effective

treatment protocols must be tailored to the underlying pathophysiology of each condition [62]-[64]. Despite overlapping clinical presentations, anticholinergic toxicity and neuroleptic malignant syndrome (NMS) require fundamentally different therapeutic strategies [65]-[67]. For patients diagnosed with anticholinergic toxicity, the mainstays of treatment include benzodiazepines for sedation and agitation control, and physostigmine as a specific antidote in selected cases [68]-[70]. Physostigmine, a reversible cholinesterase inhibitor, can reverse both central and peripheral anticholinergic effects when administered cautiously under cardiac monitoring. It is important to note that treatment availability varies by region. For example, physostigmine is restricted in some countries due to safety concerns, and access to dopamine agonists or dantrolene may be limited in low-resource settings. Therefore, protocol generalizability must consider regional formulary differences and adapt accordingly. Supportive care measures such as hydration, cooling, and symptom control are also commonly employed. In contrast, NMS demands a more intensive, multi-pronged approach. The primary interventions include immediate cessation of causative neuroleptic agents, administration of dopamine agonists such as bromocriptine or amantadine, and aggressive physical cooling to manage hyperthermia [71] [72]. In more severe presentations, dantrolene sodium may be used to reduce muscle rigidity and metabolic demands. ICU-level supportive care is often necessary, particularly in cases with complications like renal impairment due to rhabdomyolysis. These contrasting strategies are consolidated in **Figure 10**, which presents a side-by-side overview of therapeutic interventions. The visual framework highlights not only pharmacological differences but also the urgency and intensity of supportive measures required for each syndrome. Understanding these protocol distinctions is critical—not only for ensuring appropriate care but also for avoiding potentially harmful treatments that may worsen the patient's condition.

Treatment Protocol Comparison

Intervention	Anticholinergic Toxicity	Neuroleptic Malignant Syndrome
Immediate Actions	ABCs, IV access, ECG, labs (including CK)	ABCs, IV access, ECG, labs (CK essential)
Temperature Control	Cooling measures for T > 39°C	Aggressive cooling for T > 38.5°C
Agitation Management	Benzodiazepines (avoid physical restraints)	Benzodiazepines, avoid dopamine antagonists
Specific Pharmacotherapy	Physostigmine (controversial, consider in severe cases)	Bromocriptine or dantrolene (controversial)
Fluid Management	IV fluids for hypotension	IV fluids for rhabdomyolysis prevention
Monitoring	Cardiac monitoring, urine output, mental status	Continuous core temp, CK trends, renal function
Disposition	ICU for severe cases, psych consult for intentional overdose	ICU admission required, neurology consult

A visual summary of pharmacologic and supportive interventions for anticholinergic toxicity and NMS. Key agents and therapeutic actions are contrasted for clarity.

Figure 10. Comparative treatment protocols.

9. Discussion

The results of this study underscore the significant diagnostic complexity posed by the clinical overlap between anticholinergic toxicity and neuroleptic malignant

syndrome (NMS). Both conditions share hallmark symptoms such as hyperthermia, altered mental status, and autonomic dysfunction, which can confound even experienced clinicians. Misdiagnosis in these cases is not only common but also potentially dangerous, as therapeutic interventions for one condition may exacerbate the other. Our analysis confirms that while hyperthermia is ubiquitous across both conditions, certain features and biomarkers provide critical discriminative power. Specifically, creatine kinase (CK) and white blood cell (WBC) count emerged as decisive laboratory markers for NMS, reflecting the underlying pathophysiology involving muscle breakdown and systemic inflammation. These markers demonstrated both statistical and clinical significance, validating their use as early indicators in diagnostic workflows. Conversely, the presence of mydriasis, dry mucous membranes, and elevated heart rate more strongly pointed toward anticholinergic toxicity [73] [74]. When considered alongside patient history and symptom onset, these signs significantly enhance diagnostic specificity. The implementation of machine learning models—Random Forest, XGBoost, and SVM—further reinforced the potential of AI-assisted decision support systems in emergency medicine. All models performed with high accuracy (96% - 97%), with balanced F1-scores across diagnostic categories. Importantly, the use of SHAP analysis provided transparency in decision-making, revealing how individual features influenced model outputs. This level of interpretability is crucial for gaining clinical trust and enabling safe adoption of predictive tools. Collectively, these findings advocate for the integration of data-driven models with clinical expertise to support early and accurate diagnosis. In high-stakes environments like emergency departments and toxicology units, such integration can drive faster, safer, and more effective patient management. While SHAP values enhance model transparency, integrating these insights into real-time workflows poses challenges. These include the need for EHR compatibility, computational latency, and clinician training. Building trust requires UI design that prioritizes clarity and actionable insights, coupled with ongoing validation in real-world settings.

10. Conclusion

This study highlights the urgent need for enhanced diagnostic strategies in the management of toxicological emergencies, particularly when faced with clinically overlapping syndromes such as anticholinergic toxicity and neuroleptic malignant syndrome (NMS). Through a rigorous combination of symptom analysis, laboratory profiling, and machine learning classification, we demonstrated that it is possible to achieve both high diagnostic accuracy and model interpretability. The findings reinforce the value of biomarker-based differentiation, especially the roles of creatine kinase and white blood cell count in reliably identifying NMS. Likewise, symptoms such as mydriasis and dry mucous membranes emerged as specific indicators of anticholinergic toxicity. These insights were validated through both traditional feature importance and SHAP explainability frameworks, confirming their clinical utility. Moreover, the consistent and high-performing results

achieved by machine learning models—particularly Random Forest and XGBoost—affirm the potential for AI-driven diagnostic support in emergency settings. These tools, when embedded within clinical workflows, can augment decision-making, reduce diagnostic errors, and enable faster triage and treatment. By combining structured therapeutic protocols with intelligent data-driven tools, this study provides a scalable, interpretable framework for real-time diagnostic assistance. Such integration is especially valuable in time-sensitive environments like emergency departments, where early and accurate diagnosis is critical to patient outcomes. Future work should focus on expanding this framework with larger, multi-centre datasets and real-time clinical deployment. Nevertheless, this research sets a strong foundation for precision diagnosis and personalized intervention in the field of emergency toxicology.

Conflicts of Interest

The authors declare no conflicts of interest.

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