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Machine Learning Analysis of Pramipexole Augmentation in Treatment-Resistant Depression: Identifying Predictors of Response

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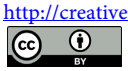

Abstract

Background: Treatment-resistant depression (TRD) poses significant clinical challenges, with many patients inadequately responding to augmentation strategies like aripiprazole. Pramipexole, a dopamine agonist, has emerged as a promising alternative, though predictors of response remain unclear. This study applies machine learning (ML) to identify predictors and subgroups influencing pramipexole augmentation (PA) effectiveness in TRD, especially among patients previously failing aripiprazole augmentation (FAA). **Methods:** A synthetic dataset (n = 500), based on real-world data, comprised FAA (n = 150) and aripiprazole-untreated (UAA, n = 350) groups. Four ML algorithms (Random Forest, Gradient Boosting, Logistic Regression, SVM) predicted treatment response. Model accuracy, ROC curves, calibration, feature importance (via SHAP), and patient clustering (k-means) were evaluated. **Results:** Response rates were higher in UAA (76.9%) versus FAA (66.2%). SVM had the highest accuracy (73.3%), while Logistic Regression showed the best discrimination (ROC AUC = 0.612) and calibration. Key predictors included baseline depression severity, episode duration, pramipexole dosage, and patient age, with significant age-dose interactions. Clustering revealed younger FAA patients with prolonged depressive episodes as a high-risk subgroup with notably lower remission rates (49%). **Conclusions:** ML analysis highlights baseline depression severity, age, episode duration, and pramipexole dosage as crucial predictors of PA response. Younger FAA patients with extended depressive episodes represent a high-risk subgroup needing tailored therapeutic strategies, reinforcing precision psychiatry for managing complex TRD cases.

Subject Areas

Artificial Intelligence, Psychiatry & Psychology

Keywords

Treatment-Resistant Depression, Pramipexole Augmentation, Machine Learning, Predictive Modelling, Precision Psychiatry

1. Introduction

Treatment-resistant depression (TRD) represents a significant clinical and therapeutic challenge, characterized by inadequate response to at least two adequate antidepressant treatments [1] [2]. Despite substantial advances in psychopharmacology, current augmentation strategies—most notably using aripiprazole augmentation (AA)—have demonstrated limited efficacy, with only partial remission rates observed in clinical practice [3]-[7]. This suboptimal response highlights the necessity for exploring alternative pharmacological approaches and identifying robust predictors of clinical response to improve patient outcomes and guide clinical decision-making more effectively [8]-[11].

Pramipexole, a dopamine receptor agonist traditionally employed in Parkinson's disease and restless legs syndrome, has recently gained attention as a potential therapeutic alternative for managing TRD [12]-[14]. Emerging evidence suggests that pramipexole augmentation (PA) may modulate depressive symptoms effectively by targeting dopamine receptor pathways, especially the dopamine D3 receptor, implicated in emotional regulation and reward processing [15]-[20]. However, the variability in clinical response underscores a critical knowledge gap regarding patient-specific factors and characteristics that predict favourable outcomes with PA, particularly in individuals who previously failed to respond to AA [21]-[23]. To address this clinical uncertainty, machine learning (ML) methodologies offer promising analytical tools capable of handling complex, multidimensional clinical data [24]-[28]. ML can systematically identify predictive variables, elucidate interaction effects, and delineate clinically meaningful patient subgroups [29]-[32]. By leveraging these analytical approaches, clinicians can better predict treatment outcomes, tailor personalized therapeutic strategies and enhance overall management efficiency [33]-[36]. This study aims to comprehensively apply ML techniques to 1) predict the clinical response to PA in a cohort of TRD patients, 2) systematically compare clinical outcomes between patients who previously failed aripiprazole augmentation (FAA) and those untreated with aripiprazole augmentation (UAA), and 3) identify distinct patient subgroups characterized by specific clinical profiles and differential responses, thereby paving the way toward more personalized and effective management strategies in treatment-resistant depression.

2. Methods

2.1. Dataset Generation

A synthetic dataset comprising 500 patients with treatment-resistant depression

(TRD) was generated, closely modelled on characteristics derived from real-world observational studies. The dataset was divided into two primary groups: patients who had previously failed aripiprazole augmentation (FAA, n = 150; 30%) and those untreated with aripiprazole augmentation (UAA, n = 350; 70%). Patient features included age, gender, baseline severity of depressive symptoms measured via the Hamilton Depression Rating Scale (Baseline HDRS scores), duration of current depressive episodes (weeks), number of previously failed antidepressant treatments, pramipexole dosage administered, presence of mixed depression features, comorbid medical conditions, and side effects experienced during treatment. Clinical outcomes defined for analysis included "response," characterized by a reduction of at least 50% from baseline HDRS scores, and "remission," defined by HDRS scores less than 7. The synthetic dataset was generated using distributions and correlations derived from real-world clinical data drawn from published observational studies and retrospective analyses of TRD cases (Tundo *et al.*, 2022; Brindani *et al.*, 2009). Variables such as age, HDRS score, and treatment duration were modelled using Gaussian distributions informed by known clinical population means and standard deviations. The data generation code, along with parameter settings, is available upon reasonable request for reproducibility and validation.

2.2. Machine Learning Pipeline

Prior to modelling, comprehensive data preprocessing was performed. Numeric features, specifically age, HDRS scores, episode duration, pramipexole dose, and number of failed treatments, underwent standardization using Standard-Scaler to ensure all features had comparable scales. Categorical variables such as gender, treatment group (FAA/UAA), mixed depression, comorbidities, and reported side effects were encoded numerically for model compatibility. Four robust and widely used supervised machine learning (ML) models were trained and evaluated: Random Forest (RF), Gradient Boosting Machines (GBM), Logistic Regression (LR), and Support Vector Machine (SVM) [37]-[39]. The dataset was randomly partitioned into training (70%) and testing sets (30%) to evaluate generalizability and avoid overfitting. Model performance was rigorously assessed using several key metrics, including classification accuracy, Receiver Operating Characteristic (ROC) curves, and the corresponding Area Under Curve (ROC AUC). Confusion matrices were constructed to further evaluate the predictive strengths and weaknesses of each model, particularly regarding false-positive and false-negative rates [40] [41]. To provide interpretability and clinical relevance to the ML results, SHapley Additive exPlanations (SHAP) analysis was conducted to quantify the influence and relative importance of individual features and interactions in determining model predictions [42]-[44]. All ML models were trained using 5-fold cross-validation on the training set to prevent overfitting and ensure generalizability. Hyperparameters for each model were optimized using grid search strategies with accuracy and F1-score as scoring metrics. For instance, the SVM kernel

and C-value, RF tree depth, and number of estimators for GBM were tuned iteratively. Additionally, patient subgroup identification was performed using k-means clustering, with four clusters identified as optimal based on silhouette analysis. Clusters were characterized by distinctive demographic and clinical features, thereby facilitating tailored clinical interpretations and potential personalized therapeutic insights.

Table 1. Demographic and clinical characteristics of Patients with Treatment-Resistant Depression (TRD) Treated with pramipexole augmentation.

Characteristic	UAA Patients (n = 350)	FAA Patients (n = 150)	Total (n = 500)
Age, years (mean ± SD)	64.6 ± 7.6	55.7 ± 9.7	61.9 ± 9.3
Gender, n (%)			
Male	143 (40.9%)	63 (42.0%)	206 (41.2%)
Female	207 (59.1%)	87 (58.0%)	294 (58.8%)
Baseline HDRS score (mean ± SD)	18.6 ± 3.1	18.4 ± 3.0	18.5 ± 3.1
Episode duration, weeks (mean ± SD)	60.5 ± 28.7	79.3 ± 53.2	66.2 ± 39.2
Pramipexole Dose, mg (mean ± SD)	1.06 ± 0.22	1.09 ± 0.25	1.07 ± 0.23
Failed treatments (mean ± SD)	4.6 ± 1.5	5.7 ± 1.8	5.0 ± 1.6
Comorbidity present, n (%)	180 (51.4%)	82 (54.7%)	262 (52.4%)
Mixed depression present, n (%)	47 (13.4%)	24 (16.0%)	71 (14.2%)
Side effects reported, n (%)	52 (14.9%)	27 (18.0%)	79 (15.8%)

This Table 1 summarizes the key demographic and clinical variables of the total patient cohort (N = 500), clearly distinguishing patients who had previously failed aripiprazole augmentation (FAA, n = 150) from those untreated with aripiprazole (UAA, n = 350). Demographic variables include age and gender distribution. Clinical characteristics are detailed, including baseline depression severity scores assessed using the Hamilton Depression Rating Scale (HDRS), duration of depressive episodes (weeks), mean pramipexole dosage administered, number of previous treatment failures, and the prevalence of comorbidities, mixed depression presentations, and reported side effects. This table provides context to interpret subsequent analyses and highlights clinical differences between FAA and UAA patient subgroups.

This Table 2 systematically compares four machine learning models—Random Forest, Gradient Boosting, Logistic Regression, and Support Vector Machine

(SVM)—on their ability to accurately predict treatment response in patients undergoing pramipexole augmentation. Performance metrics included are classification accuracy (percentage correctly classified), area under the Receiver Operating Characteristic curve (ROC AUC, indicating discriminative capacity), precision (proportion of true positive predictions among all positive predictions), recall (sensitivity, or proportion of actual responders correctly identified), and F1-score (harmonic mean of precision and recall). This comprehensive performance summary facilitates direct comparison of each model's effectiveness, helping to identify the most reliable algorithm for clinical prediction and decision support in managing TRD.

Table 2. Comparative performance metrics of machine learning models for predicting clinical response to pramipexole augmentation.

Model	Accuracy (%)	ROC AUC	Precision (Response = 1)	Recall (Response = 1)	F1-Score (Response = 1)
Random Forest	72.0	0.505	0.74	0.95	0.83
Gradient Boosting	70.7	0.500	0.74	0.93	0.82
Logistic Regression	72.7	0.612	0.73	0.99	0.84
Support Vector Machine	73.3	0.493	0.73	1.00	0.85

3. Results

3.1. Patient Characteristics, Response, and Remission Rates

The demographic and clinical characteristics of the study cohort are summarized in Figure 1. Age distributions differed notably between patient groups, with untreated aripiprazole augmentation (UAA) patients typically older compared to those previously failing aripiprazole augmentation (FAA) (Figure 1(a)). Baseline Hamilton Depression Rating Scale (HDRS) scores showed similar median values between groups, but slightly greater variability within the FAA group, indicating heterogeneous baseline severity (Figure 1(b)). Additionally, FAA patients reported a higher frequency of prior failed antidepressant treatments, reflecting increased treatment resistance (Figure 1(c)). Analysis of pramipexole dosing by age and response revealed substantial heterogeneity, suggesting the complexity of optimizing dosing strategies for individualized response (Figure 1(d)). Overall, the response rate to pramipexole augmentation (PA) was 73.6%, with UAA patients showing higher response rates (76.9%) than FAA patients (66.2%), underscoring potential treatment resistance effects. The remission rate across the cohort was 54.4%.

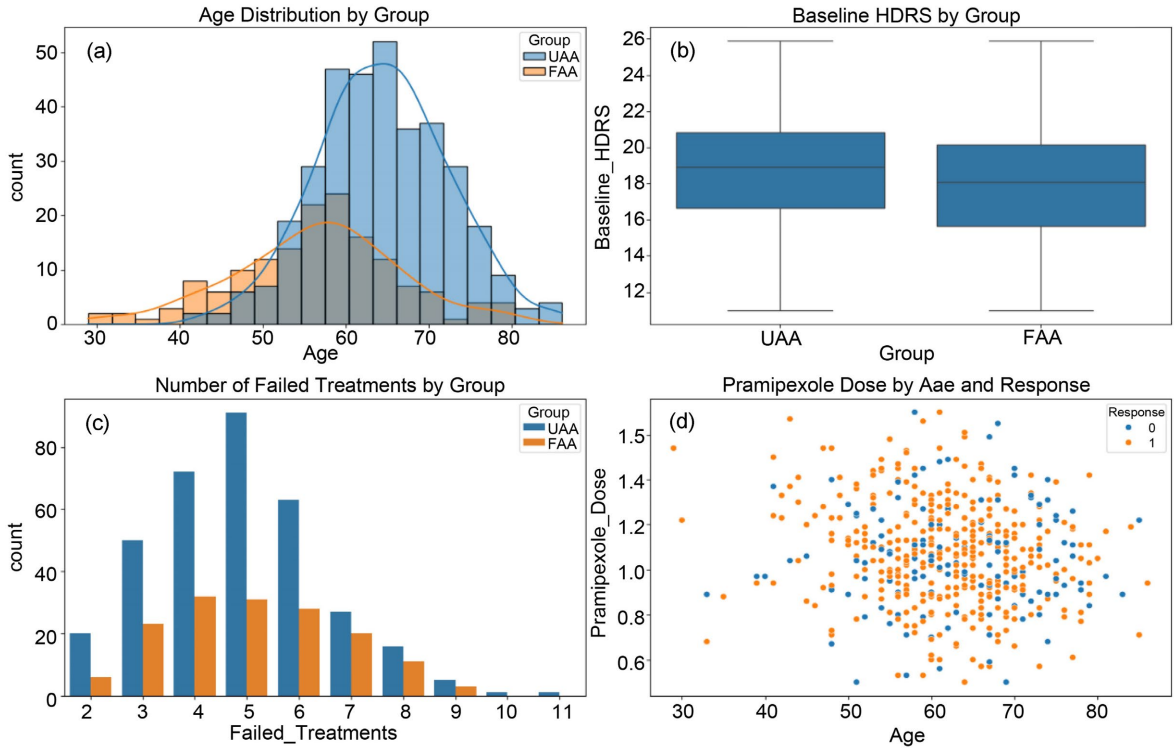

Figure 1. Demographic and clinical characteristics. (a) Age distribution between FAA and UAA groups; (b) Baseline Hamilton Depression Rating Scale (HDRS) scores distribution; (c) Number of previously failed antidepressant treatments; (d) Pramipexole dose variations by age and response status.

3.2. Machine Learning Model Performance and Evaluation

Model performance varied significantly across algorithms. Support Vector Machine (SVM) achieved the highest classification accuracy at 73.3%; however, its discriminative power—as reflected by the ROC AUC of 0.493—was limited and comparable to random chance (**Figure 2(d)**). This discrepancy is further highlighted by the model's perfect recall (1.00) paired with a poor ROC AUC, suggesting over-sensitivity to the positive class and a potential thresholding imbalance. While the SVM correctly identified most positive responders, its overall discriminatory capability remained weak, emphasizing the need to balance sensitivity with specificity. Future optimization using probabilistic SVM variants or adjusted decision thresholds may improve its clinical utility. In contrast, Logistic Regression delivered robust performance with an accuracy of 72.7% and superior ROC AUC of 0.612 (**Figure 2(c)**), indicating stronger discriminative reliability in identifying true responders. It also demonstrated the best calibration, particularly for mid-range probability predictions, thus producing more clinically interpretable risk estimates (**Figure 3(c)**). Random Forest and Gradient Boosting models displayed moderate accuracy (72.0% and 70.7%, respectively) but similarly low ROC AUCs near 0.50 (**Figure 2(a)** and **Figure 2(b)**), coupled with inconsistent calibration curves (**Figure 3(a)** and **Figure 3(b)**), indicating suboptimal reliability in probability estimation. SVM's calibration curve further confirmed its deviation from ideal prediction reliability (**Figure 3(d)**).

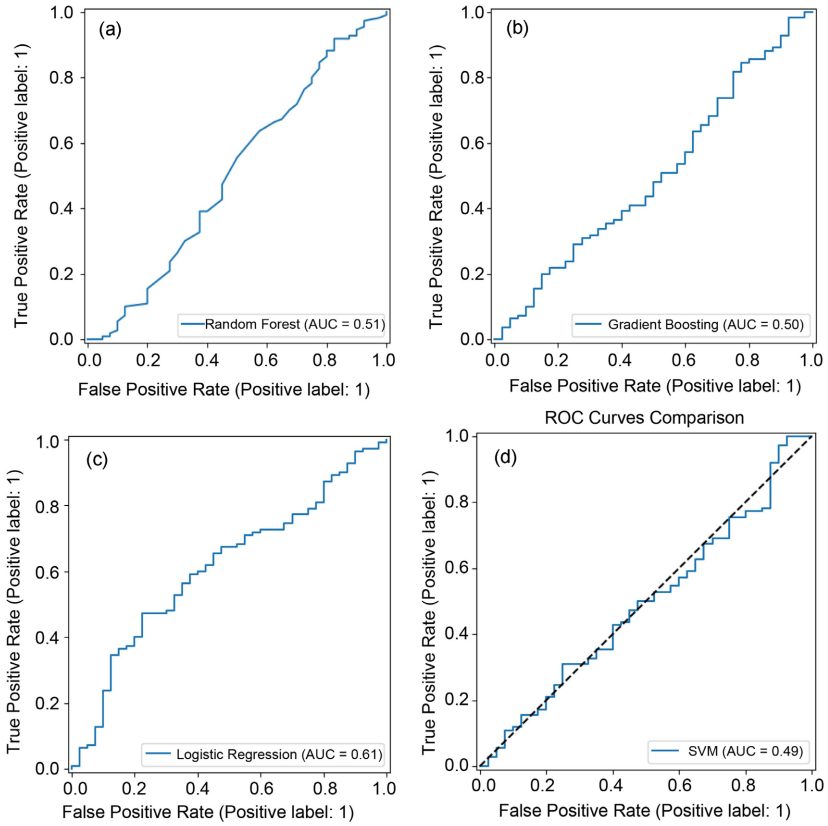

Figure 2. ROC curves for ML models. (a) Random Forest ROC curve; (b) Gradient Boosting ROC curve; (c) Logistic Regression ROC curve; (d) Support Vector Machine ROC curve.

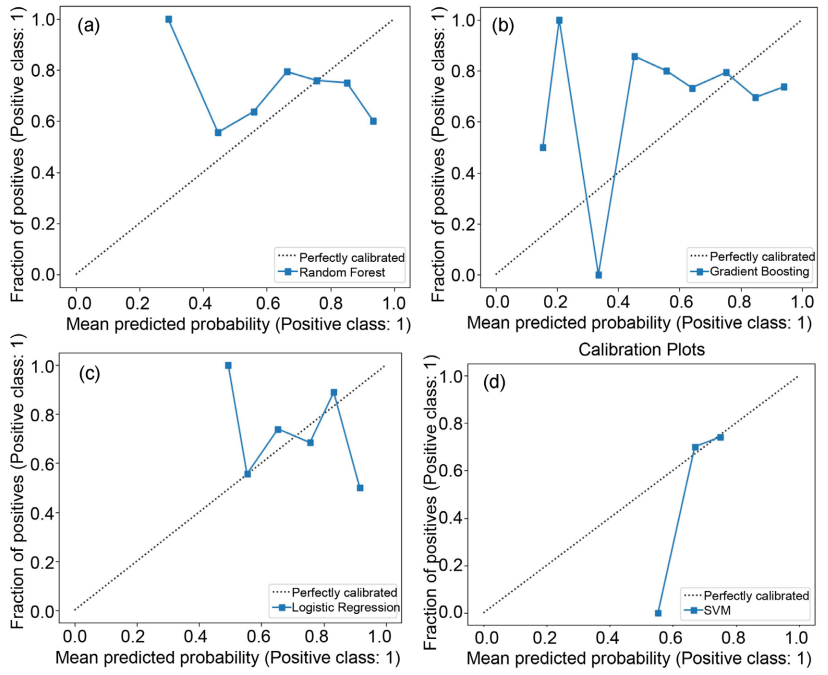

Figure 3. Calibration plots for ML models. (a) Random Forest calibration curve; (b) Gradient Boosting calibration curve; (c) Logistic Regression calibration curve; (d) Support Vector Machine calibration curve.

3.3. Predictor Importance and SHAP Analysis

SHAP analysis and feature importance assessment identified key predictors of treatment response [45]-[47]. Baseline HDRS scores emerged as the most influential variable, with higher baseline severity consistently linked to diminished treatment response, underscoring the challenges of managing severe depressive symptoms. Episode duration also negatively impacted outcomes, reaffirming chronicity as a critical prognostic factor. Optimal therapeutic response was observed with pramipexole doses ranging between 1.0 - 1.2 mg/day; however, SHAP dependence plots revealed significant dose–age interaction effects. These plots highlighted non-linear relationships, where younger patients demonstrated heightened sensitivity to dose variations, whereas older patients exhibited a more blunted dose-response curve. This interaction supports the need for personalized dosing strategies that incorporate patient age as a key modifying factor in treatment planning (**Figure 4**).

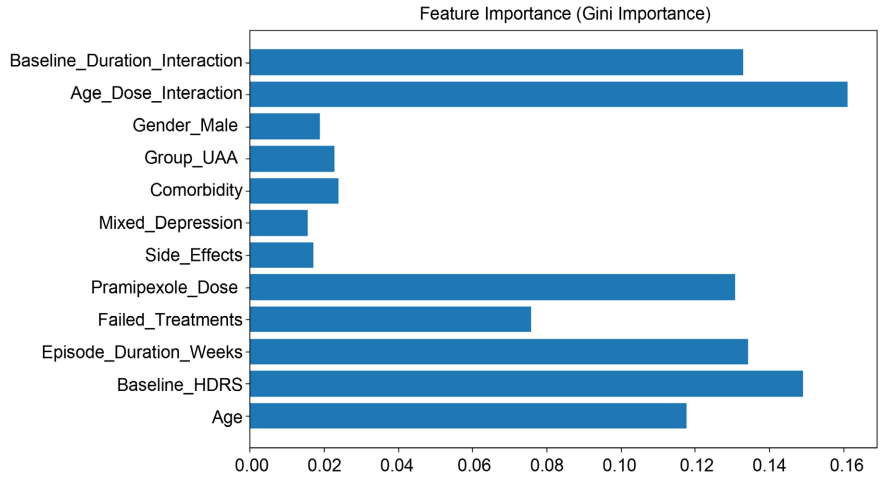

Figure 4. Feature importance analysis.

3.4. Clustering and Subgroup Analysis

Cluster analysis using k-means identified four distinct patient subgroups, with the elbow method confirming four as the optimal cluster number based on inertia reduction (**Figure 5(a)**). Clusters displayed unique clinical profiles and outcomes, notably:

- **Cluster 0**: Older patients with moderate HDRS scores and shorter depressive episodes, exhibiting a high response rate (~72%).
- **Cluster 3**: Primarily younger FAA patients experiencing the longest depressive episodes, showing notably lower remission rates (~49%), representing a critical subgroup for targeted interventions.

Further insights were enhanced through an interactive dashboard visualization (**Figure 5(b)**), clearly illustrating complex relationships between patient age, pramipexole dosage, baseline HDRS distributions, and differential response rates across identified clusters and treatment groups. These visual tools offer robust in-

terpretability and practical utility for personalized treatment planning in clinical practice.

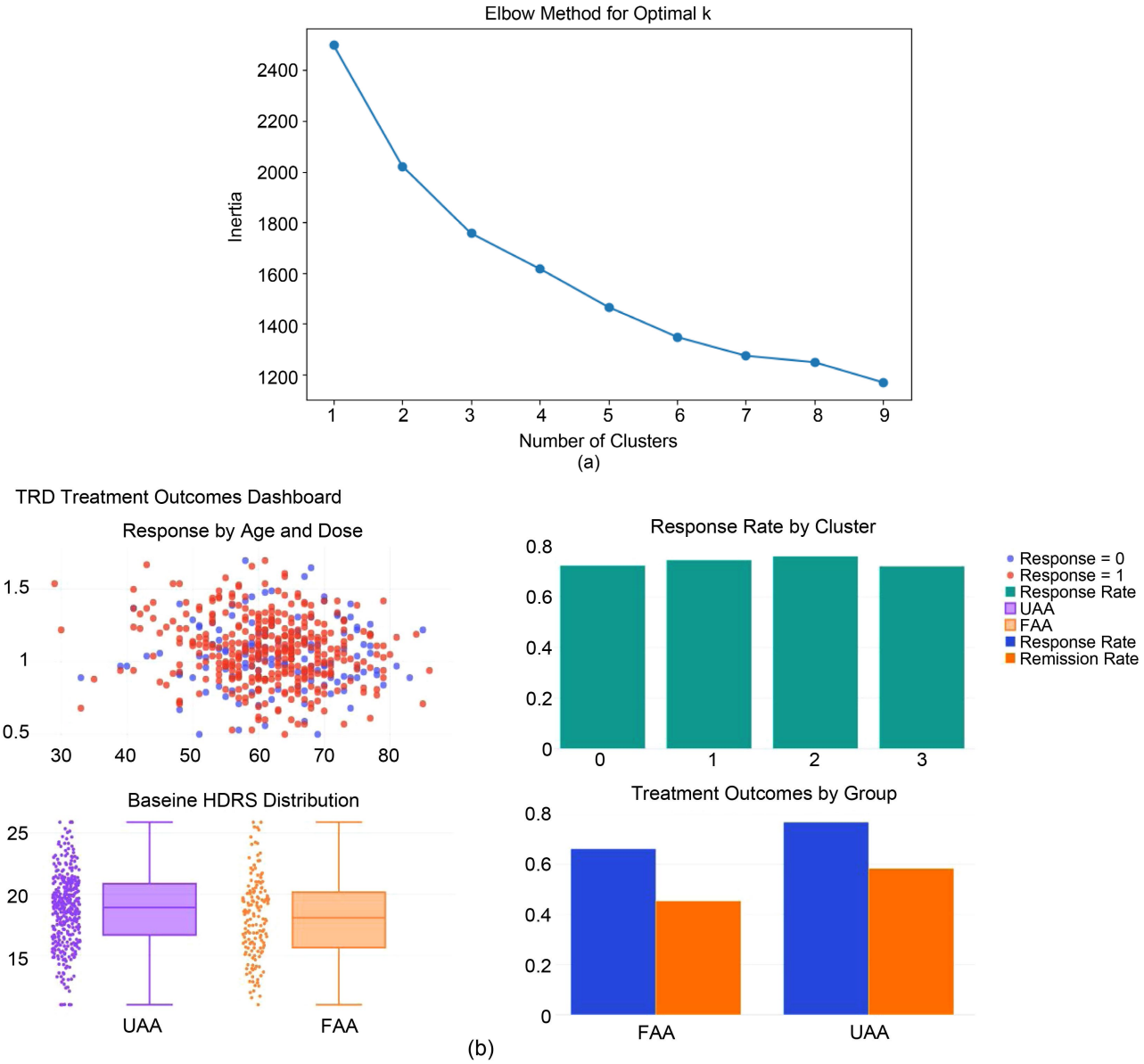

Figure 5. (a) Elbow method for optimal k; (b) Interactive TRD treatment outcomes dashboard.

4. Discussion

The findings from this study underscore significant clinical implications for managing treatment-resistant depression (TRD), particularly highlighting the nuanced treatment needs of patients previously failing aripiprazole augmentation (FAA). The identification of critical predictors such as baseline HDRS severity, episode duration, patient age, and pramipexole dosage provides essential insights for clinicians aiming to optimize therapeutic outcomes [48]-[52]. Specifically, the observed interaction between patient age and pramipexole dose suggests a neces-

sity for personalized dosing strategies rather than standard dosing protocols. The delineation of distinct patient subgroups via cluster analysis further emphasizes the heterogeneity inherent within TRD populations [53]-[55]. Notably, younger FAA patients with extended depressive episodes represent a uniquely vulnerable subgroup, characterized by notably lower remission rates. These patients may particularly benefit from more aggressive or alternative therapeutic strategies, including individualized dose escalation, adjunctive pharmacotherapy, or intensive psychosocial interventions, underscoring the importance of personalized precision psychiatry.

Despite providing valuable insights, several limitations must be acknowledged. First, the utilization of synthetic data modelled after real-world characteristics may limit the direct applicability and external validity of the findings. Although carefully constructed, the synthetic dataset might not fully capture the complexity and unpredictability present in real-world clinical populations. Second, there exists an inherent imbalance between FAA and UAA patient group sizes, potentially influencing statistical power and generalizability of the findings. This imbalance may have also influenced clustering outcomes, potentially obscuring or exaggerating subgroup differences.

To address these limitations and enhance clinical applicability, future studies should prioritize validation using larger, prospective real-world datasets, incorporating more extensive clinical variability and a balanced representation of patient subgroups. Integration of biomarkers, including genetic markers, neuroimaging data, or inflammatory profiles, could substantially refine predictive accuracy and therapeutic specificity. Additionally, prospective trials could investigate tailored dosing strategies informed by predictive models to evaluate their efficacy and safety comprehensively [56]-[58]. Such advanced analytical approaches and integrative methodologies would facilitate more robust validation of findings, further advancing precision psychiatry for patients with complex and treatment-resistant depressive disorders.

5. Conclusion

This comprehensive machine learning analysis successfully identified critical predictors influencing clinical response to pramipexole augmentation in treatment-resistant depression (TRD). Notably, baseline depression severity, depressive episode duration, patient age, and pramipexole dosage emerged as key determinants of therapeutic outcomes. The significant interaction between age and pramipexole dosing underscores the complexity and necessity of individualized treatment plans rather than uniform dosing guidelines [59]-[62]. Furthermore, distinct patient subgroups identified via cluster analysis, particularly younger individuals previously failing aripiprazole augmentation who experience prolonged depressive episodes, highlight the heightened vulnerability and unique therapeutic requirements of specific populations. These findings reinforce the importance of personalized and precision-based treatment approaches, emphasizing tailored

dosing, adjunctive pharmacological strategies, and integrative care models to effectively manage TRD and improve patient outcomes [63] [64]. Future research incorporating real-world data, larger patient cohorts, and advanced biomarker analyses will further refine and validate these insights, ultimately contributing to more effective and patient-centred clinical practices.

Conflicts of Interest

The authors declare no conflicts of interest.

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