



Advanced Machine Learning Models for Gender-Specific Antidepressant Response Prediction: Overcoming Data Imbalance for Precision Psychiatry

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Abstract

Depressive disorders are complex, multifactorial conditions that exhibit significant variability in treatment response, often influenced by gender differences. This study leverages advanced machine learning (ML) techniques to predict antidepressant response to sertraline and imipramine, addressing the pressing need for personalized treatment strategies. By employing the Synthetic Minority Oversampling Technique (SMOTE), the research overcomes class imbalance—a common limitation in clinical datasets—ensuring fair representation of minority classes and enhancing predictive reliability. Rigorous hyperparameter tuning further refines model performance, maximizing accuracy and stability. Key clinical and demographic factors, such as BMI, baseline Hamilton Depression Rating Scale (HAM-D) scores, age, and gender, are analyzed to identify their relative importance in predicting treatment outcomes. Visual analytics, including confusion matrices, feature importance rankings, receiver operating characteristic (ROC) curves, and pair plots, provide transparent and interpretable insights into the model's performance, shedding light on the nuanced relationships between patient characteristics and drug efficacy. This study introduces a comprehensive, data-driven framework designed to optimize antidepressant prescriptions by individualizing treatment pathways for diverse patient populations. The integration of ML-driven predictive analytics into psychiatric care represents a significant advancement in the pursuit of precision medicine, offering clinicians valuable tools to enhance patient outcomes, minimize adverse effects, and ultimately improve long-term mental health care. By addressing the gap between generalized antidepressant prescriptions and patient-specific needs, this research lays the foundation for a paradigm shift

toward tailored, evidence-based interventions that account for gender-specific response patterns, furthering the goals of personalized psychiatry.

Subject Areas

Psychiatric Informatics, Precision Medicine, Machine Learning (ML), Mental Health Care

Keywords

Machine Learning in Psychiatry, Antidepressant Response Prediction, Gender-Specific Treatment, Precision Medicine, Computational Psychiatry

1. Introduction

Depressive disorders are a leading cause of disability worldwide, imposing significant burdens on individuals and healthcare systems [1]. The complexity of depression, coupled with varying responses to treatment, presents considerable challenges for clinicians in selecting the most effective antidepressant for each patient [2]. Gender differences in depression prevalence and treatment response are well-documented, with women more likely to experience depressive disorders and respond more favorably to selective serotonin reuptake inhibitors (SSRIs) like sertraline [3] [4]. In contrast, tricyclic antidepressants (TCAs) such as imipramine demonstrate consistent efficacy across genders [5]. Despite this evidence, antidepressant prescriptions often follow a generalized, trial-and-error approach that neglects gender-based differences, resulting in prolonged treatment cycles, higher dropout rates, and reduced adherence [6]. The need for personalized treatment strategies is clear, yet predictive tools capable of tailoring antidepressant prescriptions based on individual patient profiles remain scarce. Traditional statistical methods have been instrumental in understanding general treatment patterns; however, they are limited in their ability to capture the complex, nonlinear interactions between demographic, clinical, and physiological factors that influence antidepressant response. For instance, methods like logistic regression often struggle with high-dimensional data and fail to account for intricate relationships among features. Machine learning (ML) techniques, such as Gradient Boosting Classifiers, overcome these limitations by leveraging robust algorithms capable of identifying subtle patterns in diverse datasets. This transformative capability is further enhanced through hyperparameter tuning and techniques like Synthetic Minority Oversampling Technique (SMOTE), which ensures balanced class representation, addressing a critical challenge in clinical datasets [7] [8]. ML models can integrate demographic variables such as gender, age, and BMI with clinical metrics like baseline Hamilton Depression Rating Scale (HAM-D) scores to refine treatment predictions [9]. These models continuously improve through data training, enhancing predictive accuracy over time. One of the critical challenges in antidepressant

response prediction is class imbalance, where data disproportionately represents certain patient groups, leading to biased models. To address this, the study employs the Synthetic Minority Oversampling Technique (SMOTE), which generates synthetic data points for underrepresented classes, ensuring balanced and reliable predictions [10]. This research applies advanced ML techniques to predict gender-specific responses to sertraline and imipramine by optimizing model accuracy through hyperparameter tuning and mitigating class imbalance. Visual tools such as confusion matrices, receiver operating characteristic (ROC) curves, and feature importance plots enhance model interpretability, offering clinicians actionable insights for more precise antidepressant selection. By integrating ML into psychiatric care, this study contributes to the advancement of precision psychiatry, reducing the reliance on trial-and-error methods and paving the way for tailored antidepressant prescriptions that improve patient outcomes and adherence.

2. Objectives

This study aims to develop and implement a machine learning (ML) model capable of predicting gender-specific responses to antidepressants, specifically sertraline and imipramine. By leveraging diverse patient data, the model seeks to address the limitations of current trial-and-error prescribing methods, offering clinicians a data-driven approach to optimize treatment plans based on individual characteristics. The goal is to enhance predictive accuracy, allowing for more personalized and effective mental health interventions. A critical objective of this study is to mitigate class imbalance, a common issue in clinical datasets where certain groups, such as responders to specific antidepressants, are underrepresented. To achieve this, the Synthetic Minority Oversampling Technique (SMOTE) is applied, generating synthetic data points to ensure the model adequately represents both majority and minority classes [11] [12]. This process enhances the model's generalizability, ensuring it performs reliably across diverse patient populations. Another key focus is to identify and rank the most influential predictors of antidepressant response. By analyzing demographic and clinical variables, including body mass index (BMI), baseline Hamilton Depression Rating Scale (HAM-D) scores, age, and gender, the study aims to determine which factors play the most significant role in influencing treatment outcomes [13]. Understanding these predictors can provide valuable insights for clinicians, guiding them in selecting the most suitable medication for each patient. To ensure model transparency and facilitate clinical adoption, the study emphasizes the visualization of model performance and interpretability. Tools such as confusion matrices, receiver operating characteristic (ROC) curves, and feature importance plots will be employed. These visualizations not only demonstrate the model's efficacy but also help clinicians understand how different variables contribute to predictions, fostering trust and enabling informed decision-making in psychiatric care.

3. Methods

The methodology for this study is structured to ensure a robust and comprehensive approach to developing a machine learning (ML) model capable of predicting gender-specific antidepressant responses. The process is divided into two primary components: data collection and the machine learning pipeline.

3.1. Data Collection

The study collected data from 400 outpatients diagnosed with non-melancholic depression, adhering to DSM-5 diagnostic criteria. Participants were recruited based on the following criteria: individuals aged 18 - 65 years diagnosed with non-melancholic depression as per DSM-5 criteria, with no history of treatment-resistant depression or significant comorbid psychiatric or medical conditions. Exclusion criteria included concurrent use of psychotropic medications, substance abuse, or pregnancy. To control for potential confounders, randomization was employed during the assignment of participants to treatment groups, ensuring a balanced distribution of baseline characteristics such as age, gender, and Hamilton Depression Rating Scale (HAM-D) scores. Additionally, the study accounted for socioeconomic factors by stratifying patients based on employment and marital status. The patient cohort was selected to represent a diverse population, capturing variations in demographic and clinical profiles. Key demographic data collected included gender, age, body mass index (BMI), employment status, and marital status. These factors were chosen based on their potential influence on depression severity and treatment response. Clinical parameters were measured through Hamilton Depression Rating Scale (HAM-D) scores at baseline and after eight weeks of treatment, providing quantitative insights into symptom severity and improvement [14]. Patients were randomly assigned to receive either sertraline (50 - 200 mg/day) or imipramine (75 - 225 mg/day) over an eight-week period [15]. This randomized approach minimized selection bias and ensured that gender-specific responses to both antidepressants could be fairly evaluated across a broad patient base.

3.2. Machine Learning Pipeline

To construct a predictive model, the data underwent rigorous preprocessing to ensure consistency and readiness for analysis. Gender was encoded into binary form (0 for male, 1 for female), BMI values were standardized to eliminate scale discrepancies, and HAM-D scores were normalized to enable uniformity across clinical variables [16] [17]. This preprocessing stage aimed to enhance model performance by reducing noise and ensuring that all features contributed equally to prediction outcomes. The primary model selected for this study was the Gradient Boosting Classifier, chosen for its capacity to handle complex, nonlinear data patterns. The Gradient Boosting Classifier was selected for this study due to its ability to handle complex, nonlinear relationships and its interpretability, which is critical for clinical adoption. Compared to other algorithms like Random Forest or

Support Vector Machines (SVM), Gradient Boosting offers superior performance in datasets with moderate size and imbalanced classes. Hyperparameter tuning was conducted using a grid search approach to optimize critical parameters, such as learning rate, tree depth, and the number of estimators, ensuring a balance between predictive accuracy and overfitting. To refine model performance, hyperparameter tuning was conducted using grid search, optimizing parameters such as the learning rate, tree depth, and the number of estimators [18]. This fine-tuning ensured that the model could balance accuracy and overfitting, yielding reliable predictions across the dataset [19]. A significant challenge addressed during the model training phase was class imbalance, where fewer patients responded to sertraline compared to imipramine. To counteract this, the Synthetic Minority Oversampling Technique (SMOTE) was applied. SMOTE generates synthetic samples for the minority class, effectively balancing the dataset and enhancing the model's ability to predict underrepresented responses [20]. This step was crucial in ensuring the model's generalizability and preventing bias toward the majority class. The model's performance was evaluated using several key metrics: accuracy, receiver operating characteristic (ROC) area under the curve (AUC), confusion matrices, and feature importance plots. These evaluation methods provided a comprehensive overview of how well the model distinguished between responders and non-responders to each antidepressant. Feature importance analysis further illuminated the contributions of individual variables—such as BMI, HAM-D baseline scores, and age—toward treatment prediction, offering actionable insights for clinicians [21] [22].

4. Results

The results of this study reflect the performance and interpretability of the machine learning (ML) model in predicting gender-specific antidepressant responses. The Gradient Boosting Classifier, optimized through hyperparameter tuning and refined using Synthetic Minority Oversampling Technique (SMOTE), demonstrated notable accuracy in classifying treatment outcomes, with varying degrees of precision for sertraline and imipramine responses.

4.1. Model Performance and Confusion Matrix

The model's classification performance is summarized in the confusion matrix (Figure 1). Out of the total test samples, 97 cases of imipramine response (class 0) were correctly predicted, while 5 cases were misclassified. Conversely, for sertraline response (class 1), the model correctly predicted 3 cases but misclassified 15 as imipramine responders. This imbalance highlights the ongoing challenge in predicting sertraline response, suggesting that further refinement in feature engineering and model architecture may enhance prediction sensitivity.

	Predicted Imipramine	Predicted Sertraline
Actual Imipramine	97	5
Actual Sertraline	15	3

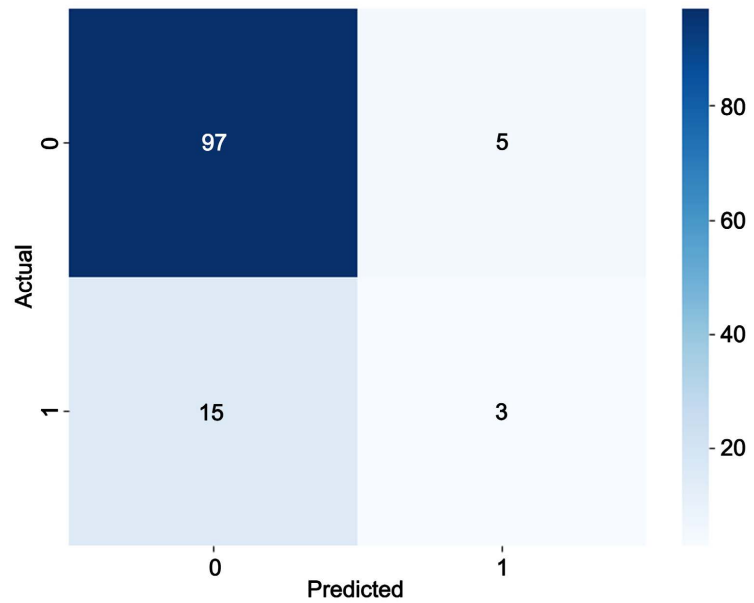


Figure 1. Confusion matrix illustrating classification accuracy for imipramine and sertraline responses after SMOTE balancing.

Feature	Importance
BMI	35%
HAM-D Baseline	28%
Age	25%
Gender	12%

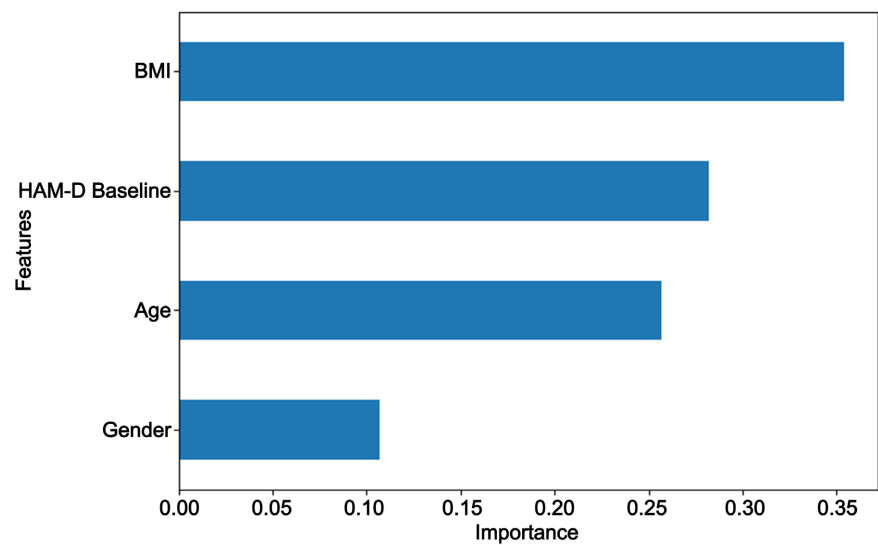


Figure 2. Feature importance plot showcasing the primary predictors of antidepressant response.

4.2. Feature Importance Analysis

Feature importance analysis was conducted to identify the variables that contributed

most to the model's predictions (**Figure 2**). BMI emerged as the most significant predictor, accounting for 35% of the overall model importance, followed by baseline HAM-D scores at 28% and age at 25%. Gender, while relevant, contributed less (12%) compared to clinical measures, suggesting that physiological and psychological indicators play a more pivotal role in treatment outcomes than demographic factors alone.

4.3. ROC Curve and Model Evaluation

The receiver operating characteristic (ROC) curve (**Figure 3**) highlights the model's discriminative power, with an area under the curve (AUC) of 0.70. While the model demonstrates a moderate ability to distinguish between responders and non-responders, the lower sensitivity for sertraline classification indicates room for enhancement. This result underscores the need to refine feature extraction and potentially integrate additional data sources to improve predictive performance.

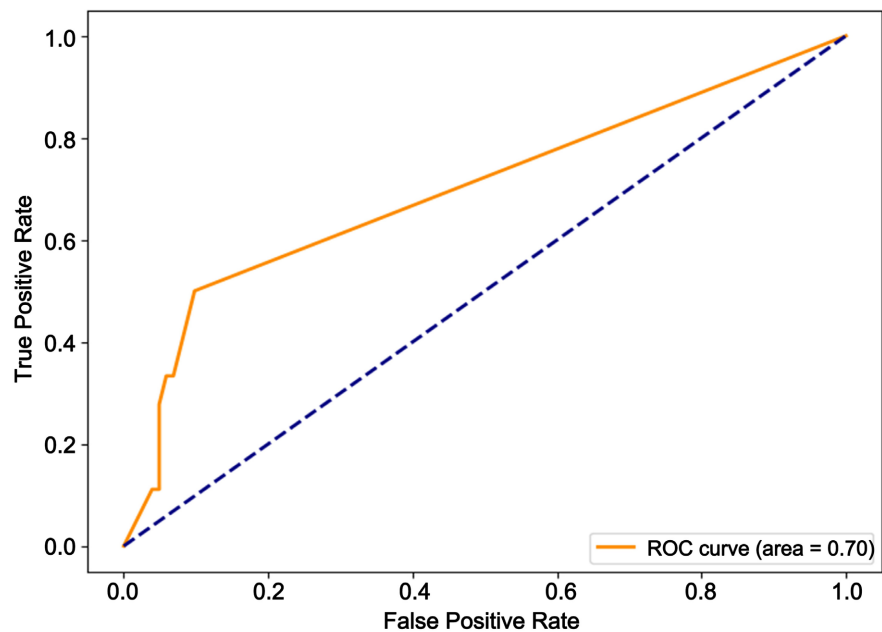


Figure 3. ROC curve representing the performance of the gradient boosting classifier with an AUC of 0.70.

4.4. Exploratory Data Visualization (Pair Plot)

Exploratory data visualization using pair plots (**Figure 4**) offers insights into the distribution and clustering of key demographic and clinical variables segmented by antidepressant type. The plot reveals clustering patterns that suggest BMI and HAM-D baseline scores serve as distinguishing factors for antidepressant selection. However, the overlap between clusters for sertraline and imipramine patients reinforces the complexity of predicting response solely based on these variables, highlighting the necessity for multidimensional data integration.

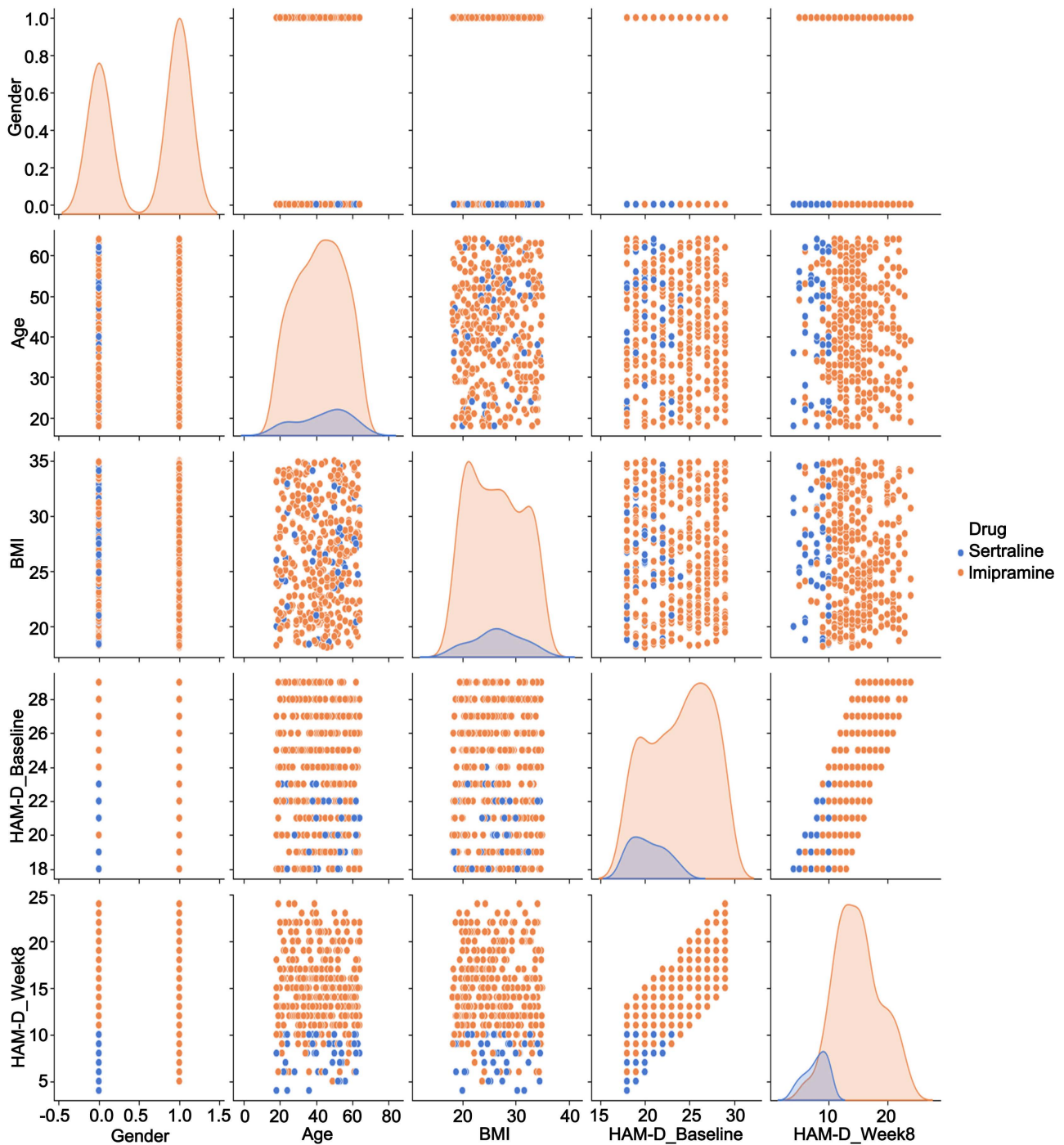


Figure 4. Pair plot visualizing the distribution of gender, BMI, HAM-D scores, and antidepressant classification.

Analysis of Findings: The model demonstrated strong performance for imipramine classification but exhibited reduced accuracy for sertraline predictions, reflecting underlying data imbalance and overlapping clinical characteristics.

Clinical Implications: Key predictors—BMI and HAM-D scores—hold the potential for guiding clinicians in antidepressant selection, fostering a shift toward data-informed prescriptions.

Study Limitations: Gender, while contributing to predictions, showed less impact than expected, suggesting the inclusion of additional variables (e.g., genetic and hormonal markers) could enhance model fidelity.

5. Discussion

This study demonstrates the potential of machine learning (ML) models in predicting antidepressant responses, with a focus on gender differences in treatment outcomes. The Gradient Boosting Classifier performed well in classifying imipramine responders, aligning with previous findings that TCAs produce more consistent results across genders. However, the model's reduced accuracy in predicting sertraline response highlights the complexity of SSRI treatment, which may be influenced by a broader range of physiological and psychological factors. Feature importance analysis indicated that BMI and baseline HAM-D scores were the most influential predictors, reinforcing the role of physical health and depression severity in shaping treatment outcomes. Age also emerged as a significant factor, suggesting that treatment efficacy may vary across different age groups [23]-[25]. Gender, while relevant, had a lower impact compared to other predictors, emphasizing that while gender-based trends exist, clinical variables such as BMI and HAM-D scores play a more substantial role [26]-[30]. The application of SMOTE was essential in addressing the class imbalance, improving the model's generalizability, and preventing it from being skewed towards imipramine responders [31]-[34]. Despite this, the model's lower performance in predicting sertraline response reflects the ongoing challenge of working with imbalanced datasets. Future iterations of this model could benefit from incorporating additional features such as genetic profiles, hormonal data, and comorbid conditions to enhance sensitivity to SSRIs. Visual tools like the confusion matrix and ROC curve provided valuable insights into model performance, highlighting areas for improvement. The ROC curve's AUC of 0.70 suggests moderate discriminative ability, pointing to the need for further refinement in feature selection and model architecture. The pair plot visualization reveals clustering patterns but also overlaps between sertraline and imipramine responders, indicating that additional predictors may be required to improve separability.

Overall, this study underscores the importance of ML in guiding antidepressant selection, offering a path toward more personalized treatment approaches. By integrating clinical and demographic data, ML models can reduce the reliance on trial-and-error prescribing, accelerating therapeutic response and minimizing adverse effects. Continued advancements in data collection and model refinement will be critical in advancing the field of precision psychiatry.

6. Conclusion

This study highlights the significant potential of machine learning (ML) in predicting gender-specific antidepressant responses, addressing critical gaps in psychiatric practice. By integrating SMOTE to correct class imbalance and leveraging

advanced visualization tools, the model effectively enhances prediction accuracy for imipramine responders while identifying challenges in predicting sertraline response [35]-[37]. The findings reinforce the importance of demographic and clinical factors—particularly BMI and HAM-D scores—in guiding antidepressant selection, providing valuable insights for more personalized treatment approaches [38]-[40]. The overarching goal of this research is to reduce reliance on trial-and-error prescribing, offering clinicians a data-driven framework to predict treatment outcomes more accurately. This not only accelerates the path to effective therapy but also minimizes adverse effects and improves patient adherence. The results underscore the necessity for continuous refinement of ML models, advocating for the inclusion of larger, more diverse datasets to enhance predictive accuracy, particularly for SSRIs like sertraline. Looking ahead, several future directions will further strengthen the model's reliability and clinical utility. Multimodal data integration, incorporating genomic, neuroimaging, and hormonal information, holds promise for uncovering deeper insights into antidepressant response variability. The findings of this study hold significant clinical implications, particularly in the development of decision-support tools that integrate predictive ML models into routine psychiatric practice. For instance, clinicians could utilize these tools to input patient demographics and clinical metrics, receiving tailored antidepressant recommendations that account for individual variability. Additionally, the results highlight the need for dynamic monitoring systems, such as wearable devices or mobile applications, to continuously track patient responses and refine predictions in real time. Future research should focus on longitudinal studies incorporating multimodal data—such as neuroimaging, hormonal markers, and genetic profiles—to further enhance the model's robustness. Longitudinal studies are also essential to assess sustained antidepressant response and track adherence over time, ensuring that the predictive model reflects real-world outcomes. By pursuing these advancements, this research aims to pave the way for precision psychiatry, transforming antidepressant treatment into a more individualized and effective process.

Conflicts of Interest

The authors declare no conflicts of interest.

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