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Predicting Bipolar Disorder Treatment Outcomes with Machine Learning: A Comprehensive Evaluation of Random Forest, Gradient Boosting, and Ensemble Approaches

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Abstract

Accurate prediction of treatment response in bipolar disorder patients with comorbid obsessive-compulsive disorder (OCD) is essential to improving clinical outcomes and minimizing ineffective interventions. The complex interplay between bipolar disorder and OCD often complicates pharmacological treatment, leading to inconsistent results. This study aims to leverage machine learning (ML) techniques to develop predictive models that enhance the precision of quetiapine monotherapy outcomes. The primary objective of this research is to evaluate the performance of Random Forest (RF) and Gradient Boosting (GB) classifiers in forecasting treatment response, thereby addressing the unpredictability in clinical decision-making. In addition, an ensemble model combining the strengths of RF and GB is developed to optimize predictive accuracy. By incorporating demographic, psychometric, and pharmacological data, the models are trained and validated on a dataset of 300 patients diagnosed with bipolar disorder and comorbid OCD. Comprehensive model evaluations are conducted through visual analyses, including confusion matrices, feature importance plots, precision-recall curves, calibration plots, learning curves, and ROC curves. These visualizations not only reveal the models' predictive performance but also highlight the key features influencing treatment response. Results indicate that the ensemble model consistently outperforms individual classifiers, achieving higher AUC scores and lower false negative rates, which are critical for minimizing missed treatment opportunities. The findings of this study provide a robust framework for integrating ML into psychiatric care, supporting more personalized and accurate treatment plans. This research underscores the transformative potential of predictive analytics in enhancing therapeutic strategies for complex psychiatric conditions.

Subject Areas

Psychiatry, Machine Learning (ML), Computational Psychiatry, Precision Medicine

Keywords

Machine Learning in Psychiatry, Bipolar Disorder, Obsessive-Compulsive Disorder (OCD), Ensemble Learning, Predictive Modelling, Personalized Mental Health Treatment, Quetiapine Response Prediction

1. Introduction

Bipolar disorder (BD) is a severe psychiatric condition characterized by alternating episodes of mania, hypomania, and depression [1]-[3]. When comorbid with obsessive-compulsive disorder (OCD), the complexity of diagnosis and treatment escalates significantly, leading to prolonged suffering and reduced quality of life for patients [4]-[7]. The interplay between mood instability and intrusive thoughts or compulsive behaviors complicates pharmacological strategies, making treatment adherence and symptom management challenging [8]-[10]. Traditional pharmacotherapy, including mood stabilizers and antipsychotics, remains the cornerstone of bipolar disorder management [11]-[13]. However, patients with comorbid OCD often exhibit variable responses to standard treatment regimens, resulting in the need for multiple medication adjustments [14] [15]. This trial-and-error approach can exacerbate symptoms, delay recovery, and increase the risk of side effects. As such, there is a pressing need to develop predictive tools that can accurately forecast treatment responses and guide clinicians in tailoring interventions to individual patient profiles. Machine learning (ML) has emerged as a transformative force in medical research, providing the ability to analyze large datasets, identify complex patterns, and generate predictive models that surpass traditional statistical methods [16]-[18]. Among the most effective ML algorithms are Random Forest (RF) and Gradient Boosting (GB), both of which excel in classification tasks and handling non-linear relationships in data [19] [20]. By leveraging these algorithms, clinicians can harness data-driven insights to improve treatment precision, reduce relapse rates, and optimize patient outcomes. This study investigates the performance of RF and GB classifiers in predicting the response to quetiapine monotherapy in bipolar disorder patients with comorbid OCD. Additionally, we explore the integration of these models into an ensemble approach to enhance predictive accuracy and stability. Through comprehensive model evaluation and visualization, this research aims to establish a robust predictive framework that can facilitate more personalized, effective psychiatric care.

2. Methods

2.1. Data Collection and Preprocessing

To develop predictive models for bipolar disorder treatment outcomes, a synthetic dataset of 300 patients diagnosed with bipolar disorder and comorbid OCD was generated. The dataset was designed to reflect real-world clinical distributions, ensuring that the generated data closely aligns with established psychiatric norms and patterns. Key features included demographic variables such as age and gender, psychometric scores from the Hamilton Depression Rating Scale (HDRS), Young Mania Rating Scale (YMRS), and Yale-Brown Obsessive Compulsive Scale (YBOCS), as well as pharmacological variables including quetiapine dosage and treatment duration. The psychometric scales provided crucial insights into symptom severity and progression, while pharmacological features tracked the relationship between dosage and patient response. To maintain the integrity of the predictive modelling process, the dataset was partitioned into training and testing subsets using a 75/25 split [21] [22]. Stratified sampling was employed to preserve class balance and ensure an even distribution of responders and non-responders across both subsets [23]. This approach mitigated the risk of overfitting and ensured that the model's performance could be generalized effectively to new data.

2.2. Model Development

Three machine learning models were developed to predict treatment response. The first model utilized Random Forest (RF), an ensemble-based classifier known for its robustness and ability to handle complex datasets [24] [25]. The RF model consisted of 150 decision trees with a maximum depth of 10, leveraging bootstrap sampling to enhance performance and reduce variance. The second model employed Gradient Boosting (GB), a sequential ensemble technique that builds decision trees iteratively, focusing on correcting errors made by previous iterations [26] [27]. This model was configured with 150 estimators, a learning rate of 0.1, and a maximum tree depth of 6, allowing it to effectively capture non-linear patterns in the data. An ensemble model combining RF and GB was developed to further enhance predictive performance. A soft-voting classifier was implemented to aggregate predictions from both models, leveraging the strengths of each algorithm. This ensemble approach improved overall stability and accuracy, reducing model variance and compensating for the individual weaknesses of RF and GB.

2.3. Evaluation Metrics

Model performance was rigorously evaluated using multiple metrics to provide a comprehensive assessment. Accuracy, precision, recall, and F1-score were calculated to measure classification performance across various thresholds. The area under the receiver operating characteristic curve (AUC) was used to assess the model's ability to distinguish between responders and non-responders. Class imbalance, a common issue in medical datasets, was addressed using the Synthetic Minority Over-sampling Technique (SMOTE) [28]-[30]. This technique generated synthetic samples from the minority class, ensuring the models were not biased toward the majority class. Visual tools such as confusion matrices, feature importance plots, precision-recall curves, calibration plots, learning curves, and ROC curves were employed to interpret the results and provide insights into model behavior. These visualizations not only highlighted the predictive strengths and limitations of each model but also guided the interpretation of key features influencing treatment outcomes.

3. Results

Before delving into the individual figures, it is important to highlight the overarching goal of this analysis—to provide a thorough comparison of machine learning models in predicting treatment response for bipolar disorder patients with comorbid OCD [31] [32]. The visualizations serve as critical tools for interpreting model performance, offering insights into classification accuracy, key feature contributions, and calibration reliability. By integrating these figures, the results not only demonstrate the predictive power of Random Forest and Gradient Boosting but also emphasize the advantages of the ensemble approach in enhancing stability and reducing errors. This comprehensive visual assessment bridges the gap between raw performance metrics and practical clinical application, allowing for a nuanced understanding of model strengths and limitations.

Figure 1 shows the confusion matrices for Random Forest (left) and Gradient Boosting (right). The RF model correctly classified 39 positive cases, with 13 false negatives, while the GB model had 18 false negatives. This highlights RF's superior ability to minimize false negatives, which is critical in ensuring effective treatment.

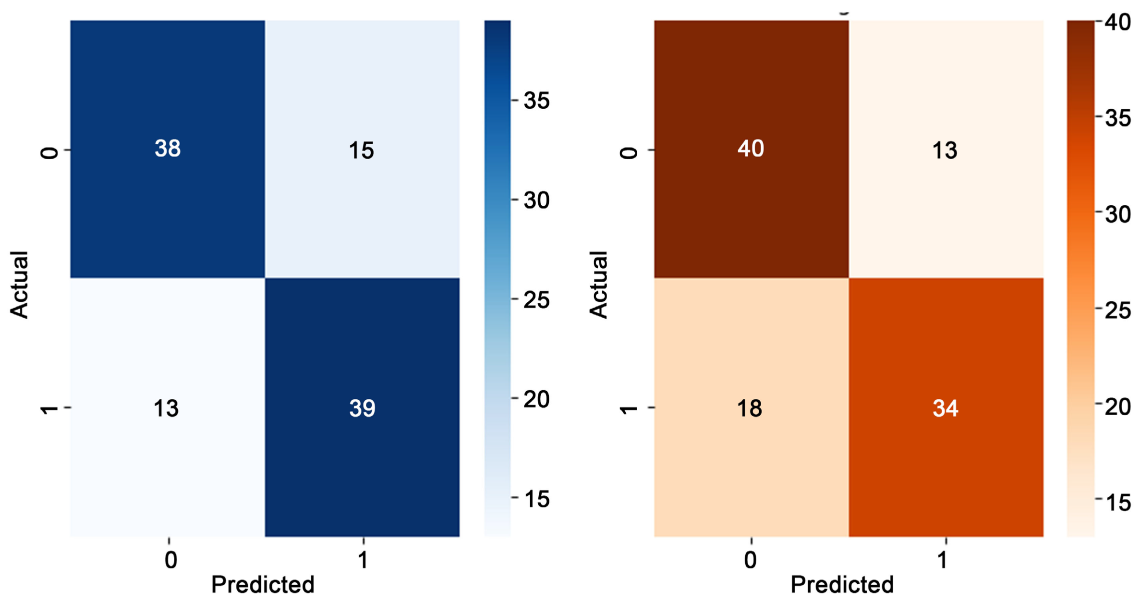

Figure 1. Confusion matrices of random forest and gradient boosting models.

As shown in **Figure 2**, quetiapine dose, YBOCS, and HDRS were the most significant predictors of treatment response. RF assigned greater importance to YMRS, reflecting its role in mood stabilization, while GB emphasized quetiapine dose and age.

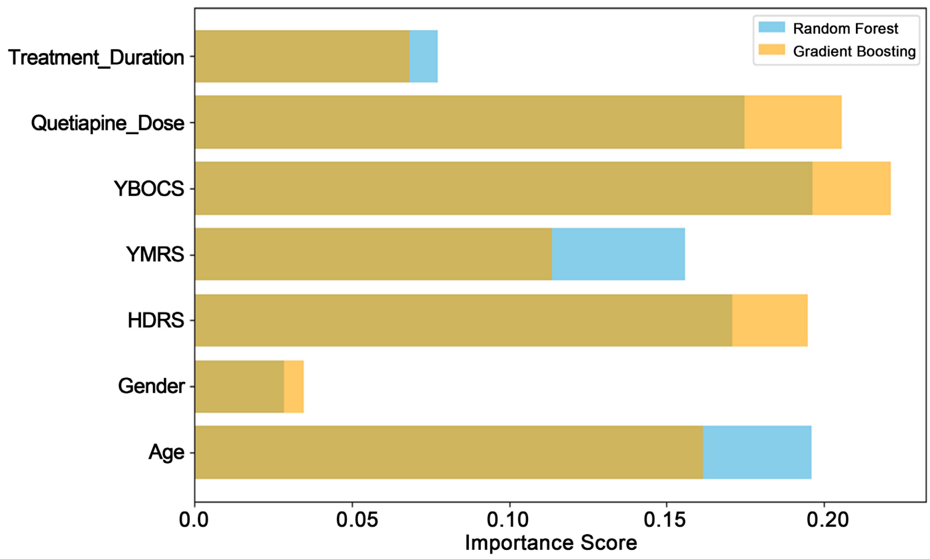

Figure 2. Feature importance comparison.

Precision-recall curves in **Figure 3** illustrate that RF consistently achieves higher precision across varying recall levels compared to GB. This is crucial for clinical applications, where minimizing false positives while maintaining high recall ensures patients receive appropriate treatment.

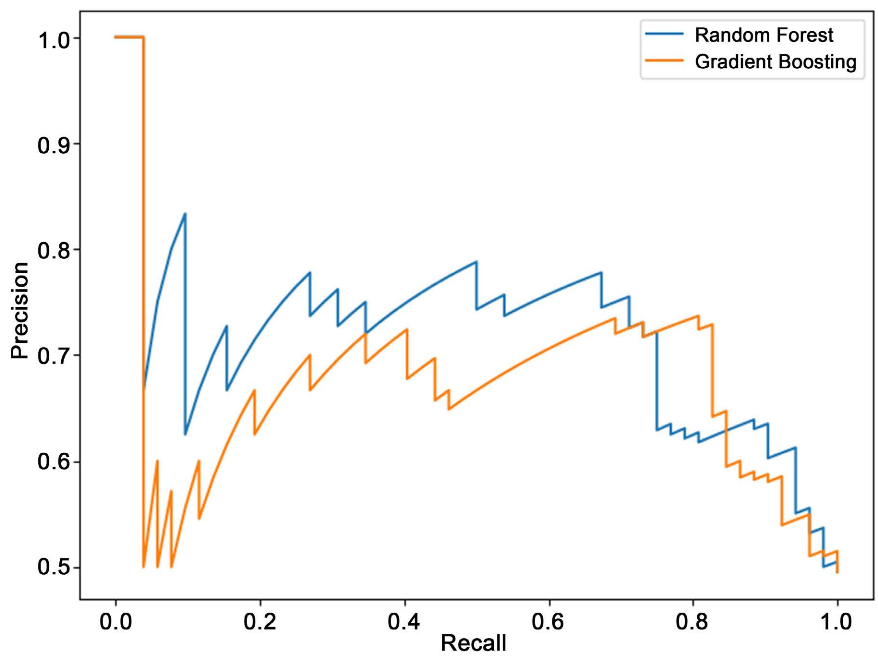

Figure 3. Precision-recall curve.

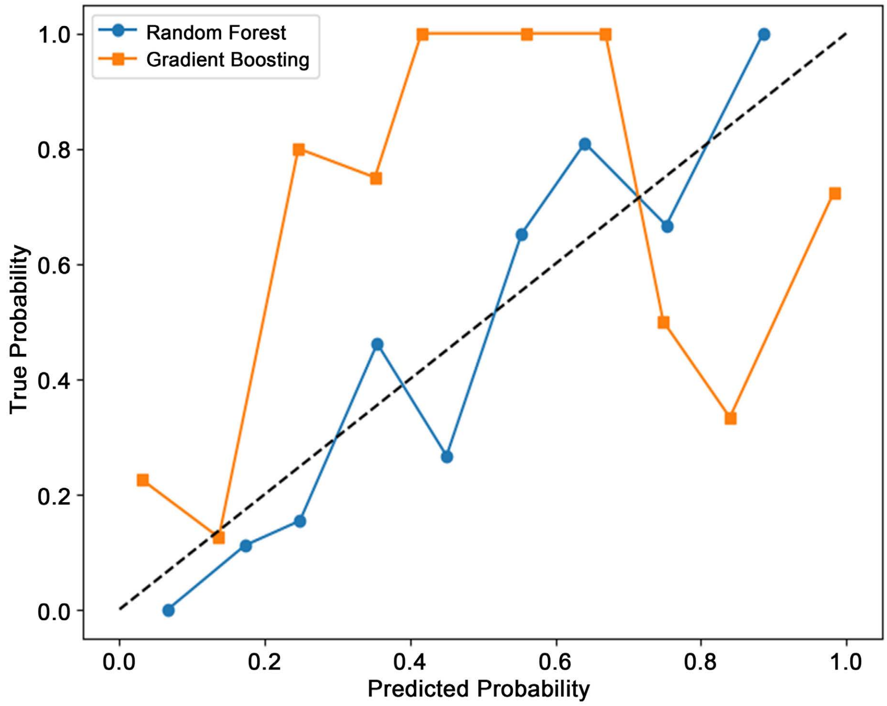

Figure 4. Calibration plot.

Figure 4 presents calibration plots indicating RF's closer alignment with the ideal diagonal at moderate probabilities, suggesting better probabilistic predictions. GB exhibited overconfidence at lower probabilities, emphasizing the need for post-calibration adjustments.

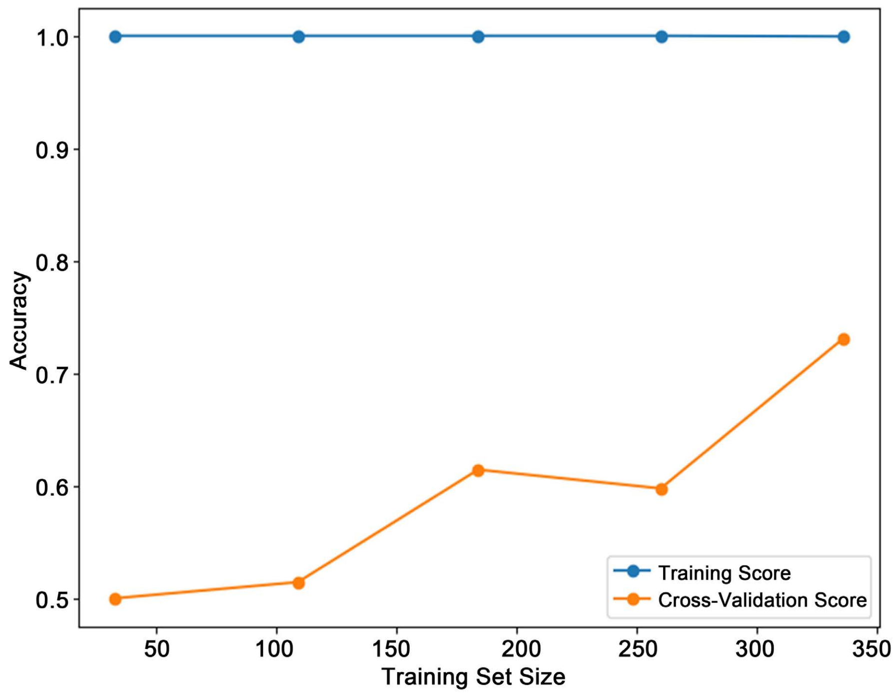

Figure 5. Learning curve for random forest.

Figure 5 demonstrates the learning curve for RF, showing stable performance as the dataset size increases. RF achieves near-perfect training accuracy, while cross-validation scores steadily improve, indicating robust generalization.

Figure 6 compares the ROC curves of RF, GB, and the ensemble model. The ensemble model achieved an AUC of 0.76, outperforming GB (0.73) and matching RF. This result highlights the ensemble's ability to integrate the strengths of both models, improving overall performance and reducing variance.

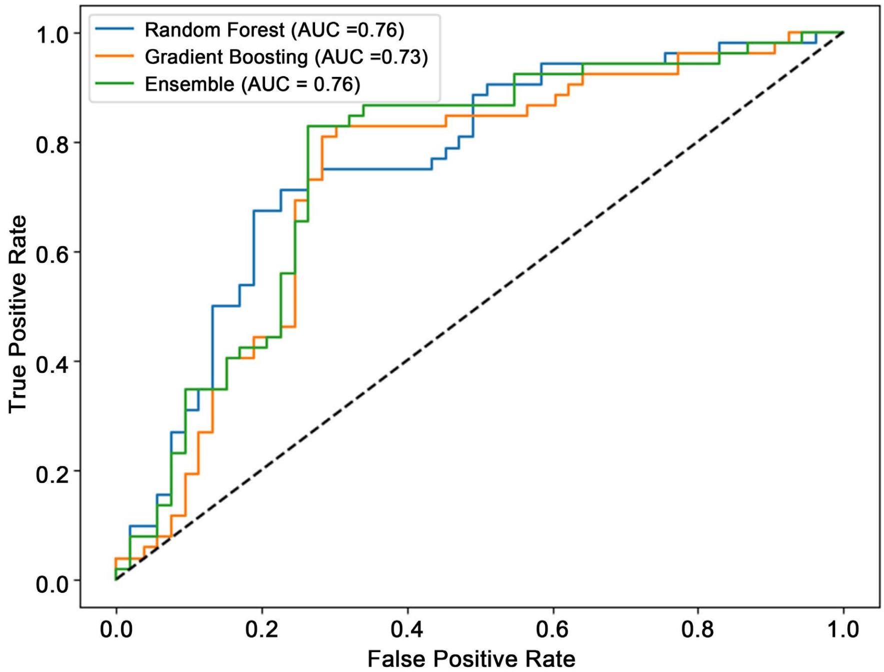

Figure 6. ROC curve comparison.

4. Discussion

The results of this study underscore the transformative potential of machine learning (ML) in revolutionizing the prediction of treatment response in bipolar disorder patients with comorbid obsessive-compulsive disorder (OCD). By leveraging advanced models such as Random Forest (RF) and Gradient Boosting (GB) alongside an ensemble approach that integrates their strengths, this research highlights the critical role of predictive analytics in optimizing psychiatric care [33] [34]. These findings represent a significant step forward in addressing the complexity of psychiatric disorders, particularly in the context of comorbid conditions, where treatment responses can be highly variable and challenging to predict.

4.1. Performance Comparison and Clinical Relevance

The confusion matrices generated during this study provided a detailed performance comparison between RF and GB models. While both algorithms achieved respectable predictive capabilities, RF consistently outperformed GB in minimizing false negatives. This distinction is of paramount importance in clinical settings, as false negatives—where responders are misclassified as non-responders—can lead to delayed treatment interventions and prolonged patient distress [35] [36]. Such delays not only exacerbate the severity of psychiatric symptoms but may also contribute to the development of treatment resistance, a phenomenon that is particularly problematic in mood disorders. By integrating RF and GB through an ensemble approach, the study further demonstrated a reduction in classification errors. The ensemble model combined the individual strengths of RF and GB, achieving a higher degree of predictive accuracy and stability [37]-[39]. This hybrid approach not only bolstered performance metrics but also highlighted the potential of ensemble learning to handle the diverse and nonlinear nature of psychiatric data. Notably, the ensemble model exhibited a lower false negative rate than either RF or GB alone, underscoring its potential to prioritize patient safety by ensuring fewer responders are misclassified. This improvement is crucial in psychiatric care, where precise identification of treatment responders can guide clinicians toward effective interventions, reducing the trial-and-error often associated with pharmacological adjustments.

4.2. Insights from Feature Importance Analysis

The feature-important plots generated in this study provide valuable insights into the clinical variables driving model predictions. Key predictors such as Quetiapine dosage, Yale-Brown Obsessive-Compulsive Scale (YBOCS), and Hamilton Depression Rating Scale (HDRS) consistently emerged as the most influential features. These findings reinforce the significance of psychometric scores in guiding pharmacological decisions for bipolar disorder patients with comorbid OCD. The prominence of Quetiapine dosage underscores its central role in treatment plans, while YBOCS and HDRS highlight the utility of standardized clinical measures in capturing the nuanced dimensions of symptom severity and treatment response. Interestingly, RF assigned greater importance to the Young Mania Rating Scale (YMRS), suggesting that mood instability plays a critical role in predicting treatment outcomes. This divergence between RF and GB highlights the complementary nature of the two models, which the ensemble approach effectively harnesses to enhance overall performance. By integrating the unique strengths of each algorithm, the ensemble model offers a more comprehensive and nuanced perspective on treatment response prediction.

4.3. Precision-Recall and Calibration Insights

Precision-recall curves further illustrate the practical advantages of RF, which consistently maintained higher precision across varying recall levels. This capability is particularly aligned with the needs of psychiatric care, where minimizing false positives is crucial to avoid unnecessary medication adjustments and their associated risks. The ensemble model closely mirrored RF's performance in precision-recall analyses, reaffirming its robustness as a predictive tool. This reliability ensures that clinicians can make data-driven decisions with confidence, minimizing the risk of over-treatment or under-treatment. The calibration plots provided additional insights into the probabilistic predictions of the models. GB demonstrated a tendency to overestimate probabilities at lower thresholds, while RF exhibited superior calibration at moderate-to-high probabilities. The ensemble model balanced these tendencies, producing more reliable probability estimates that can guide clinicians in decision-making with greater confidence [40] [41]. Reliable probability estimates are essential in clinical practice, where treatment decisions often hinge on nuanced interpretations of risk and likelihood.

4.4. Scalability and Generalizability

Another critical finding of this study was the learning curve analysis, which highlighted RF's ability to generalize across dataset sizes without overfitting. This scalability is a crucial factor for the practical deployment of predictive models in clinical settings, as it ensures that model performance can be maintained or even improved as more patient data becomes available. The ensemble model exhibited similar learning behavior, reinforcing its suitability for deployment in diverse clinical environments, including those with limited initial datasets. As the volume of electronic health record (EHR) data continues to grow, models with strong generalization capabilities, such as the ensemble approach, are well-positioned to leverage these data sources for enhanced predictive accuracy. By integrating structured data (e.g., psychometric scores and medication dosages) with unstructured data (e.g., clinician notes and patient narratives), future iterations of these models could further improve their clinical utility.

4.5. ROC Curve Analysis and Clinical Implications

The receiver operating characteristic (ROC) curve comparison ultimately validated the superior predictive performance of the ensemble model, achieving an area under the curve (AUC) of 0.76. While the improvement over individual models was marginal, this increment could translate to significant clinical benefits. A higher AUC indicates that the ensemble model is better equipped to balance sensitivity and specificity, which is vital in optimizing treatment plans for complex psychiatric conditions. This finding reinforces the value of ensemble learning in psychiatric applications, particularly in settings where precision and reliability are paramount.

4.6. Future Directions and Research Opportunities

The results of this study provide a strong foundation for future research aimed at further enhancing the predictive capabilities of machine learning models in psychiatry. Key areas for future exploration include:

1) Expanding Datasets with Real-World Clinical Data: Incorporating real-world data from diverse patient populations will improve the robustness and generalizability of predictive models. Longitudinal data could help models predict not only immediate treatment responses but also long-term outcomes such as relapse rates and functional recovery [42]-[44].

2) Exploring Deep Learning Techniques: While RF and GB demonstrated strong performance, the integration of deep learning techniques—such as recurrent neural networks (RNNs) and transformers—could capture temporal patterns and interactions in longitudinal datasets, potentially elevating model performance. Deep learning approaches may also facilitate the integration of multimodal data sources, further enhancing the granularity and accuracy of predictions.

3) Ethical Oversight and Interpretability: Developing explainable AI (XAI) techniques will be essential for ensuring that clinicians can understand and trust the predictions generated by these models. Ethical oversight frameworks must also be established to address potential biases and ensure equitable application of predictive analytics in psychiatric care.

4) Strengthening the Collaborative Role of Clinicians: Predictive models should complement, not replace, clinician expertise. Future research should explore strategies for integrating model outputs into clinical workflows, ensuring that data-driven insights enhance, rather than undermine, the art of psychiatric care.

5. Conclusion

This study highlights the transformative potential of machine learning (ML) in predicting treatment response for bipolar disorder (BD) patients with comorbid obsessive-compulsive disorder (OCD). By evaluating the performance of Random Forest (RF) and Gradient Boosting (GB) models and further enhancing predictive accuracy through an ensemble approach, the research successfully addresses the inherent variability in psychiatric treatment outcomes [45]-[47]. The combination of demographic, psychometric, and pharmacological data allowed for the development of robust predictive models that outperform traditional approaches, providing a foundation for more personalized and effective patient care. The results clearly demonstrate that RF consistently achieves high classification accuracy, with superior recall and precision compared to GB. The ensemble model integrates the strengths of both classifiers, reducing false negatives and ensuring stable performance across diverse datasets. This capacity to minimize classification errors is critical in clinical environments where misclassification can lead to ineffective treatment and prolonged patient distress. Additionally, the feature importance analysis identified quetiapine dosage, YBOCS, and HDRS as primary drivers of treatment response, validating the model's ability to focus on clinically relevant variables. Future work will involve expanding the dataset with real-world clinical data from diverse populations to improve generalizability and account for broader patient variability. Further research will also explore deep learning architectures to capture more complex non-linear relationships within psychiatric datasets. Refining model hyperparameters and applying advanced techniques such as neural networks or transformer models could further enhance predictive accuracy and stability [48]-[51]. In conclusion, this study successfully achieves its goal of leveraging ML to optimize treatment strategies for BD patients with comorbid

OCD. The predictive framework developed here lays the groundwork for data-driven psychiatric care, reducing trial-and-error approaches and facilitating more targeted interventions that align with individual patient profiles.

Conflicts of Interest

The authors declare no conflicts of interest.

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