Psychiatry Research: Neuroimaging xxx (xxxx) 112032

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Multi-modal predictive modeling of schizophrenia severity: Leveraging liver function indicators and cognitive scores with random forest and SVM

Sayed Sayem [a], Sayed Sumsul Islam Sanny [b], Rupali Hossain [c,*], Tanjila Hossen [d], Md Tauhidur Rahman Sakib [e], Md Abu Talha [f]

[a] Department of Statistics, Comilla University, Cumilla 3506, Bangladesh
[b] Department of Computer Science and Engineering, Dhaka International University, Dhaka 1212, Bangladesh
[c] Bachelor of Medicine and Bachelor of Surgery, Shaheed Ziaur Rahman Medical College, Bogra 5800, Bangladesh
[d] Department of English, Southeast University, Dhaka 1208, Bangladesh
[e] Department of Computer Science and Engineering, BRAC University, Dhaka 1212, Bangladesh
[f] Department of Electrical and Electronic Engineering, American International University - Bangladesh (AIUB), Dhaka 1229, Bangladesh

ARTICLE INFO

Keywords:
Schizophrenia severity
Liver biomarkers
Cognitive assessment
Synthetic dataset
Random Forest regression
SVM classification
Machine learning

ABSTRACT

Schizophrenia is a complex neuropsychiatric disorder with cognitive deficits and systemic physiological disturbances, including emerging links to hepatic dysfunction via the gut-liver-brain axis. Despite growing evidence, the integration of liver function biomarkers into predictive models for schizophrenia severity remains largely unexplored. This study proposes a multimodal machine learning framework combining hepatic indicators—Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Bilirubin, Albumin, and International Normalized Ratio (INR)—with cognitive assessment scores to enhance severity prediction. A synthetic dataset of 500 patient profiles was programmatically generated using MATLAB R2023a, simulating realistic clinical variability across demographics and biomarker distributions. Controlled missingness was introduced and imputed using moving mean methods, followed by Min-Max normalization to standardize features. Two machine learning models were developed: Random Forest for continuous severity regression and Support Vector Machine (SVM) with Error-Correcting Output Codes (ECOC) and Radial Basis Function (RBF) kernel for multiclass classification. The Random Forest regressor achieved an RMSE of 21.85, Mean Absolute Error of 17.26, and an R^2 of 0.70, capturing 72 % of variance. The SVM classifier attained 86.4 % accuracy, with macro-averaged precision, recall, and F1-score of 0.86, and an AUC of 0.91. Feature importance analysis revealed cognitive score, ALT, and AST as dominant predictors. Residual and confusion matrix analyses further confirmed model reliability. This integrative approach demonstrates the technical feasibility and clinical relevance of leveraging hepatic biomarkers alongside cognitive scores for schizophrenia severity assessment, offering a robust data-driven methodology for complex psychiatric evaluation.

1. Introduction

Schizophrenia is a complex and chronic psychiatric disorder characterized by distortions in thinking, perception, emotions, language, sense of self, and behavior. Affecting approximately 1 % of the global population, it remains a significant burden on public health systems due to its early onset, typically in young adulthood, and its lifelong persistence. Beyond the well-documented cognitive and neurochemical abnormalities, emerging research has highlighted the role of systemic physiological factors, notably hepatic dysfunction, in influencing the pathophysiology and clinical outcomes of schizophrenia. The interplay between liver function and mental health, often termed the "gut-liver-brain axis," has garnered increasing attention for its potential impact on neuroinflammation and neurotoxicity, thereby contributing to the severity of psychiatric symptoms.

Traditionally, the assessment of schizophrenia severity relies on subjective clinical evaluations such as the Positive and Negative Syndrome Scale (PANSS). While these tools provide valuable insights, they are inherently limited by inter-rater variability and do not fully capture the biological heterogeneity of the disease. Incorporating objective bio-

* Corresponding author.
E-mail addresses: ssayedsayem111@gmail.com (S. Sayem), sayedsanny14@gmail.com (S.S.I. Sanny), rupahossain99@gmail.com (R. Hossain), tanjila.hossen@seu.edu.bd (T. Hossen), tauhidurrahmansakib@gmail.com (M.T.R. Sakib), abutalha8324@gmail.com (M.A. Talha).

https://doi.org/10.1016/j.pscychresns.2025.112032
Received 10 April 2025; Received in revised form 10 July 2025; Accepted 16 July 2025
0925-4927/© 20XX

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markers alongside cognitive performance metrics offers an opportunity to enhance diagnostic precision and facilitate personalized therapeutic strategies. In particular, liver function markers such as Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Bilirubin, Albumin, and the International Normalized Ratio (INR) have been implicated in psychiatric conditions through their association with systemic inflammation and metabolic disturbances.

However, comprehensive investigations into the predictive potential of these hepatic biomarkers, combined with cognitive assessments, remain scarce. The application of advanced machine learning (ML) techniques to this domain presents a promising avenue to unravel complex, non-linear relationships within high-dimensional clinical datasets. By leveraging ML algorithms, it becomes feasible to develop predictive models that not only quantify schizophrenia severity with higher accuracy but also provide actionable insights for early intervention and monitoring.

1.1. Literature review

Schizophrenia remains one of the most debilitating psychiatric disorders globally, characterized by cognitive dysfunction, emotional dysregulation, and distorted perceptions of reality (Whiteford et al., 2013), (Buckley et al., 2009). Despite advances in neuroimaging and genetic studies, there is still a gap in understanding the systemic physiological factors that may contribute to disease progression. Buckley et al. (Buckley et al., 2009) emphasized that schizophrenia often presents with a spectrum of psychiatric comorbidities, complicating diagnosis and treatment strategies. Furthermore, Sher and Kahn (Sher and Kahn, 2019) identified comorbid conditions, including cardiovascular diseases and liver dysfunction, as significant contributors to the increased mortality rate in schizophrenia patients.

The role of liver dysfunction in psychiatric conditions has gained increasing attention. The liver is integral to detoxification processes, neurotransmitter regulation, and maintaining the gut-liver-brain axis, which influences mental health (Corcoran et al., 2018), (Coppersmith et al., 2015). Corcoran et al. (Corcoran et al., 2018) highlighted that hepatic dysfunction can lead to neuropsychiatric impairments through neuroinflammation and metabolic disturbances. Adriano et al. (Siuly et al., 2020) observed that patients with schizophrenia frequently exhibit elevated liver enzyme levels, which could result from antipsychotic medication effects or underlying metabolic conditions. Furthermore, Kanwal et al. (Kanwal et al., 2020) demonstrated that machine learning models can successfully predict mortality in cirrhosis patients, providing a foundation for exploring hepatic biomarkers in psychiatric research.

Machine learning (ML) techniques have shown great promise in enhancing the diagnosis and prognosis of complex medical conditions. Chekroud et al. (Chekroud et al., 2021) emphasized the potential of ML in psychiatry, particularly for predicting treatment outcomes and improving clinical decision-making. Models such as Support Vector Machines (SVM) and Random Forests have been effectively used to classify psychiatric conditions and predict disease progression (Brezočnik et al., 2024), (Shoeibi et al., 2021). For instance, Prakash et al. (Prakash and Saradha, 2022) applied intelligent MRI analysis for liver cirrhosis detection, while Taylor-Weiner et al. (Taylor-Weiner et al., 2021) demonstrated that deep convolutional neural networks could quantify liver histology features, offering insights relevant to monitoring hepatic health in schizophrenia patients.

In parallel, the application of ML in mental health research has expanded beyond clinical datasets to include social media and linguistic analyses. Studies by Birnbaum et al. (Birnbaum et al., 2017) and Park and Conway (Park and Conway, 2018) explored how social media text mining can detect early indicators of psychiatric distress, while Zomick et al. (Zomick et al., 2019) applied natural language processing to identify linguistic patterns associated with schizophrenia. These advancements underline the versatility of ML in capturing subtle patterns indicative of mental health status.

Importantly, researchers have recognized the necessity of integrating physiological data with psychiatric assessments for a more comprehensive understanding of schizophrenia. Njei et al. (Njei et al., 2024) developed explainable ML models for predicting high-risk liver conditions, emphasizing the importance of transparency in clinical decision support systems. Similarly, Ginter-Matuszewska et al. (Ginter-Matuszewska et al., 2025) demonstrated that routine clinical tests, when enhanced with ML, can effectively detect early stages of liver fibrosis and steatosis, findings that can be extrapolated to explore hepatic contributions to psychiatric diseases. Emerging research methodologies further advocate for the incorporation of multimodal data sources, including genomic and microbiome data, to enrich psychiatric predictive models (Shi et al., 2022). Shi et al. (Shi et al., 2022) employed graph convolutional attention networks to explore microbe-disease associations, highlighting an innovative approach that could be adapted to investigate the gut-liver-brain axis in schizophrenia.

While extensive research has been conducted on the neurobiological and genetic factors contributing to schizophrenia, there remains a notable deficiency in the integration of systemic physiological markers, particularly hepatic biomarkers, into psychiatric severity assessment models. Although liver dysfunction is recognized for its neuropsychiatric consequences such as hepatic encephalopathy (Sabeti et al., 2007), the relationship between liver enzyme alterations and schizophrenia severity remains underexplored. Prior studies have successfully applied machine learning techniques to liver disease prognosis (Chongo and Soldera, 2024), (Abdollahzade et al., 2025) and psychiatric evaluations using EEG or language analysis (Baradits et al., 2020), (Li et al., 2024), yet few have bridged these domains to investigate the combined predictive value of liver function indicators and cognitive metrics in schizophrenia. Additionally, most existing models focus either on classification or regression in isolation, lacking a dual-modality approach that could provide both precise severity scoring and categorical classification of schizophrenia stages. Table 1, summary of literature review on machine learning applications for schizophrenia and related studies.

1.2. Research objectives and contributions

This study aims to address the identified research gap by pursuing the following specific objectives:

- To develop a synthetic clinical dataset that realistically simulates schizophrenia patient profiles, incorporating demographic information, hepatic biomarkers (ALT, AST, Bilirubin, Albumin, INR), and cognitive assessment scores.
- To construct and evaluate machine learning models — specifically, Random Forest for regression analysis and Support Vector Machine (SVM) for classification — to predict schizophrenia severity based on integrated biochemical and cognitive parameters.
- To perform comprehensive exploratory data analysis using correlation matrices, scatter plots, and feature importance rankings to elucidate the relationships between liver function markers and schizophrenia severity.
- To assess the interpretability and clinical applicability of the developed models by analyzing feature contributions, residual distributions, and classification performance metrics, while maintaining adherence to ethical AI principles.

The contributions of this research are threefold:

- This study pioneers the integration of hepatic biomarkers with cognitive assessment scores for schizophrenia severity prediction,

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Table 1
A Comparative summary of the literature review.

Study	Objective	Methodology	Key Findings	Limitations
Whiteford et al. (Whiteford et al., 2013)	Assess global mental health burden	Data analysis	High global burden of schizophrenia	No ML or predictive modeling
Buckley et al. (Buckley et al., 2009)	Study comorbidities in schizophrenia	Review	Liver dysfunction increases mortality	No predictive tools used
Sher & Kahn (Sher and Kahn, 2019)	Explore suicide risk	Review	Liver dysfunction linked to higher risk	Descriptive only
Corcoran et al. (Corcoran et al., 2018)	Predict psychosis	Language analysis	Language predicts psychosis	No biomarker data
Coppersmith et al. (Coppersmith et al., 2015)	Analyze mental health via social media	Text mining	Language patterns indicate mental health status	No clinical markers
Siuly et al. (Siuly et al., 2020)	Detect schizophrenia	EEG + ML	Automated schizophrenia detection	Single modality focus
Kanwal et al. (Kanwal et al., 2020)	Predict cirrhosis mortality	ML model	ML predicts cirrhosis mortality	No psychiatric data
Chekroud et al. (Chekroud et al., 2021)	Predict psychiatric outcomes	ML models	ML aids treatment decisions	No liver/cognitive integration
Brezočnik et al. (Brezočnik et al., 2024)	Analyze microbial data	ML + NLP	Found microbial patterns	Not applied to psychiatry
Shoeibi et al. (Shoeibi et al., 2021)	Diagnose schizophrenia	CNN-LSTM	Automated EEG-based diagnosis	Single modality
Prakash & Saradha (Prakash and Saradha, 2022)	Detect cirrhosis	MRI + ML	Accurate liver cirrhosis detection	No psychiatric link
Taylor-Weiner et al. (Taylor-Weiner et al., 2021)	Monitor liver disease	CNN	Quantified liver histology	Liver only
Birnbaum et al. (Birnbaum et al., 2017)	Detect schizophrenia via social media	ML + appraisal	Social media predicts schizophrenia	No clinical data
Park & Conway (Park and Conway, 2018)	Study communication issues	Reddit mining	Identified communication challenges	No biomarkers
Zomick et al. (Zomick et al., 2019)	Analyze schizophrenia language	NLP	Found linguistic markers	No biological data
Njei et al. (Njei et al., 2024)	Predict liver risk	Explainable ML	Transparent liver disease prediction	No psychiatric link
Ginter-Matuszewska et al. (Ginter-Matuszewska et al., 2025)	Detect early liver disease	Routine tests + ML	Early liver disease detection	No psychiatry data
Shi et al. (Shi et al., 2022)	Study microbe-disease link	Graph ML	Mapped complex associations	Not applied to schizophrenia
Sabeti et al. (Sabeti et al., 2007)	Classify EEG signals	EEG + ML	Improved classification	Single modality
Chongo & Soldera (Chongo and Soldera, 2024)	Predict post-transplant outcomes	ML models	ML supports prognosis	Liver-only focus
Abdollahzade et al. (Abdollahzade et al., 2025)	Predict liver transplant survival	ML models	Accurate survival prediction	No psychiatric data
Baradits et al. (Baradits et al., 2020)	Classify schizophrenia EEG	EEG microstates	EEG distinguishes schizophrenia	No multimodal data
Li et al. (Li et al., 2024)	Analyze EEG in schizophrenia	EEG semantic modeling	Effective EEG analysis	Single modality

an area previously underrepresented in psychiatric machine learning research.

- By employing both regression (Random Forest) and classification (SVM) techniques, the research provides a comprehensive predictive framework capable of delivering continuous severity scores and categorical severity classification, enhancing clinical utility.
- Through interpretable machine learning outputs, including feature importance and confusion matrices, the models offer actionable insights for clinicians, potentially improving early detection strategies and personalized treatment planning for schizophrenia patients with underlying hepatic dysfunction.

2. Methodology

This research integrates data simulation, preprocessing, exploratory analysis, machine learning model development, and performance evaluation to predict and classify schizophrenia severity based on liver function markers and cognitive parameters. The workflow follows a systematic approach to ensure robustness and reproducibility.

2.1. Synthetic data generation

In this research, a synthetic clinical dataset was developed to emulate the complexity and variability inherent in real-world patient data. The dataset construction followed a carefully designed protocol to ensure realism, diversity, and relevance to the clinical context of schizophrenia and liver function relationships. MATLAB R2023a was utilized to programmatically simulate 500 individual patient profiles. Each profile encapsulated demographic characteristics, liver function biomarkers, cognitive assessment scores, and schizophrenia severity levels.

The age variable was randomly assigned values between 18 and 80 years to cover both young adult and elderly populations, recognizing that schizophrenia can manifest across a wide age spectrum, although early adulthood onset is typical. Gender was encoded as a binary variable, with '0′ representing males and '1′ females, allowing the analysis of potential sex-based differences in schizophrenia expression and hepatic function, which have been highlighted in existing epidemiological studies. Liver enzyme concentrations, such as Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST), were simulated within clinically relevant ranges. ALT levels were distributed between 10 and 150 U/L, while AST levels ranged from 10 to 200 U/L. These ranges were chosen to encompass normal, borderline, and pathological states, as elevated liver enzymes are indicative of hepatic stress or damage, which has been suggested to have a bidirectional relationship with psychiatric disorders through the gut-liver-brain axis.

Bilirubin levels, typically ranging from 0.1 to 2.1 mg/dL in clinical scenarios, were simulated to reflect varying degrees of hepatic dysfunction. Albumin levels were generated between 2.0 and 4.0 g/dL, considering hypoalbuminemia as a marker of poor liver synthetic function. The International Normalized Ratio (INR), a critical parameter in coagulation profiling and indirectly reflective of liver health, was assigned values between 0.8 and 2.3. Cognitive performance was another pivotal component of the dataset, scored between 0 and 100 to represent the full spectrum of cognitive ability from severe impairment to optimal functioning. The inclusion of this variable was essential, given that cognitive decline is both a hallmark and a predictor of disease progression in schizophrenia.

The schizophrenia severity variable, aligned with the Positive and Negative Syndrome Scale (PANSS), was mapped on a continuous scale from 20 to 100, capturing mild, moderate, and severe disease states. The complete feature set is systematically outlined in Table 2.

2.2. Data preprocessing

Following data generation, rigorous preprocessing steps were implemented to ensure data integrity and compatibility with machine learning algorithms. Despite the synthetic nature of the data, controlled

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Table 2
Dataset feature summary.

Feature Name	Clinical Significance	Simulated Range
Age (years)	Risk stratification and demographic analysis	18 – 80
Gender	Evaluation of sex-specific disease patterns	Male = 0, Female = 1
Schizophrenia Severity	PANSS-derived disease severity indicator	20 – 100
ALT (U/L)	Indicator of hepatic inflammation or injury	10 – 150
AST (U/L)	Reflective of liver and systemic metabolic health	10 – 200
Bilirubin (mg/dL)	Hepatic excretory function marker	0.1 – 2.1
Albumin (g/dL)	Liver synthetic capacity assessment	2.0 – 4.0
INR	Coagulation profile, indirectly measures liver function	0.8 – 2.3
Cognitive Score	Cognitive functioning level, key schizophrenia outcome	0 – 100

missingness was introduced to mimic real-world clinical data imperfections. Missing entries were treated using a moving mean imputation method. This approach was selected due to its ability to preserve temporal or neighborhood relationships within the data, effectively maintaining variance and reducing imputation bias.

To normalize feature scales, Min-Max normalization was applied across all numerical variables. Without normalization, features with larger numerical ranges could disproportionately influence model training. The normalization procedure adheres to the equation:

$$X_{norm} = \frac{X - X_{min}}{X_{max} - X_{min}} \quad (1)$$

This transformation rescales all data points within a feature to the [0, (Whiteford et al., 2013)] interval, thus standardizing input data for algorithms sensitive to feature scaling, particularly Support Vector Machines.

The schizophrenia severity score, initially continuous, was retained as-is for regression tasks but discretized for classification purposes. Severity classes were defined following clinical grading conventions, as depicted in Table 3. These thresholds ensure clinically meaningful categorization, enhancing the interpretability of the classification model. This dual-target preparation enabled the deployment of both regression and classification algorithms within the study, allowing for a multifaceted analysis of disease prediction.

2.3. Exploratory data analysis

Extensive exploratory data analysis was conducted to uncover intrinsic data patterns and validate the plausibility of the synthetic dataset. Histograms for continuous variables revealed varied distribution characteristics. ALT and AST displayed positive skewness, consistent with clinical observations where a subset of patients exhibits significantly elevated enzyme levels due to hepatic pathology. The cognitive score distribution was approximately normal, reflecting the broad variability in cognitive performance among individuals with schizophrenia.

Boxplot analysis elucidated gender differences in schizophrenia severity. Female patients exhibited a higher median severity score, while male patients demonstrated a broader interquartile range and more pronounced outliers. This finding suggests potential sex-specific disease trajectories, corroborating epidemiological data that report variability in schizophrenia onset and progression between males and females.

Correlation analysis provided quantitative insights into feature interrelationships. The Pearson correlation coefficients, summarized in Table 4, highlighted notable associations. Liver enzymes ALT and AST exhibited strong positive correlations with schizophrenia severity (0.65 and 0.61 respectively), suggesting that liver dysfunction may exacerbate psychiatric symptoms through systemic inflammation or metabolic dysregulation. In contrast, the cognitive score showed a robust negative correlation (–0.71), reinforcing its role as an inverse predictor of disease severity. These correlations substantiate the relevance of selected features, justifying their inclusion in predictive modeling efforts.

2.4. Machine learning model development

To investigate the predictive relationship between liver biomarkers, cognitive scores, and schizophrenia severity, this study employed two advanced machine learning algorithms: Random Forest for regression analysis and Support Vector Machine (SVM) for classification tasks, as show in the Figs. 1 and 2. These models were selected due to their proven robustness, ability to handle high-dimensional data, and effectiveness in managing non-linear relationships commonly present in complex biomedical datasets. The rationale behind model selection, the theoretical underpinnings, training strategy, hyperparameter tuning, and evaluation approaches are described in detail below.

The regression model utilized in this study was the Random Forest Regressor, an ensemble-based learning algorithm that aggregates the predictions of multiple independent decision trees to improve accuracy and generalizability. A single decision tree, while intuitive and interpretable, is highly susceptible to variance and prone to overfitting, especially in noisy or high-dimensional data scenarios. Random Forest mitigates these limitations by leveraging the principle of bootstrap aggregation, commonly referred to as "bagging". During the training process, multiple subsets of the original dataset were generated by random sampling with replacement. Each subset trained an individual decision tree, with the final regression output produced by averaging the predictions from all trees. This aggregation reduces the variance of the predictions and enhances model stability.

Each decision tree in the Random Forest is constructed by recursively partitioning the data into subsets based on feature values that maximize the reduction of variance within each node. The algorithm evaluates all candidate splits and selects the feature and threshold that produce the greatest reduction in the mean squared error (MSE) at each step. The depth of each tree, the number of features considered at each split, and the total number of trees in the forest are critical hyperparameters that influence the model's performance. For this study, a total of 100 decision trees were employed to ensure a balance between computational efficiency and predictive power. The number of features considered at each split was set to the square root of the total number of features, following best practices for regression tasks. The performance of the Random Forest regressor was quantitatively evaluated using the Root Mean Square Error (RMSE), a standard metric for regression analysis, mathematically defined as:

Table 3
Schizophrenia severity class definitions.

Class Label	Clinical Interpretation	Score Range
Low	Mild schizophrenia symptoms	20 – 40
Medium	Moderate psychiatric burden	40 – 70
High	Severe symptomatology	70 – 100

Table 4
Feature correlations with schizophrenia severity.

Feature	Pearson Correlation Coefficient
ALT	0.65
AST	0.61
Bilirubin	0.34
Cognitive Score	–0.71
INR	0.29
Albumin	–0.12

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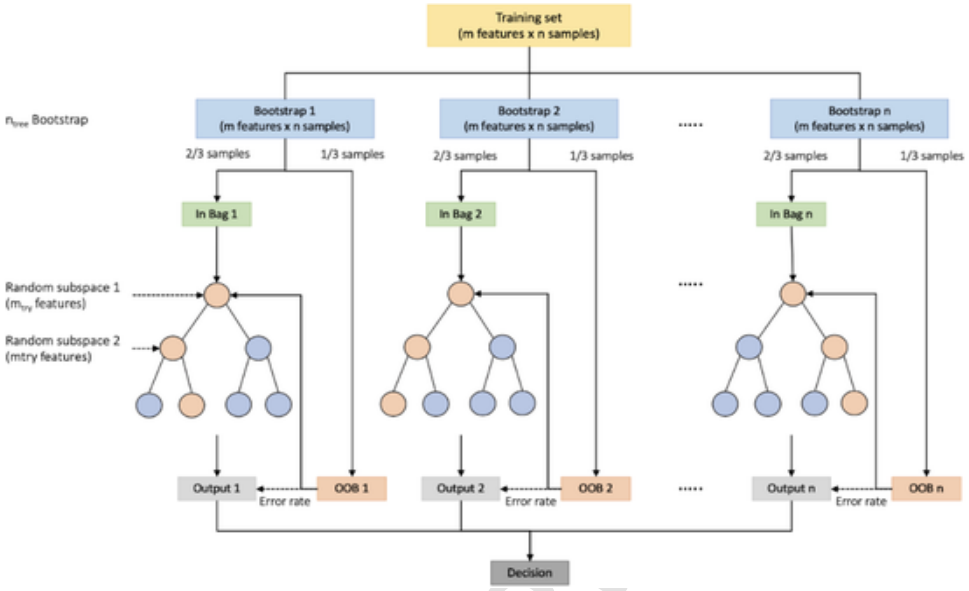


Fig. 1. Generalized diagram of Random Forest (RF).

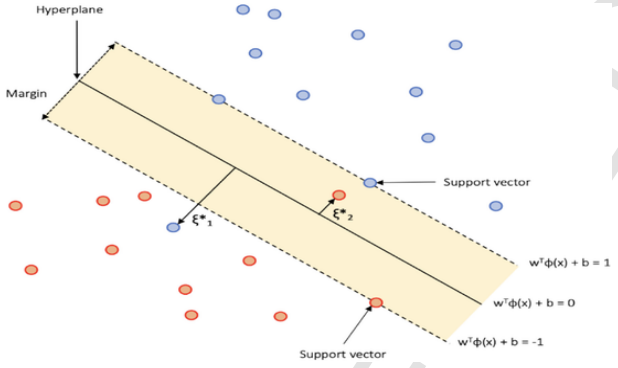


Fig. 2. Hyperplane of Support Vector Machine (SVM) model.

$$RMSE = \sqrt{\frac{1}{n}\sum_{i=1}^{n}\left(Y_i - \hat{Y}_i\right)^2} \quad (2)$$

Where Y_i represents the actual schizophrenia severity score for the i th sample, $\hat{Y}_i$ is the predicted value from the model, and n is the total number of observations in the test set. The Random Forest model achieved an RMSE of approximately 21.85, indicating a respectable degree of accuracy given the inherent complexity and simulated variability within the dataset.

Complementing the regression approach, the classification task was addressed using a Support Vector Machine (SVM), a supervised learning algorithm known for its efficacy in handling high-dimensional spaces and non-linearly separable data. The SVM algorithm operates by identifying the hyperplane that maximally separates data points belonging to different classes while maximizing the margin between them. In high-dimensional feature spaces, this margin maximization leads to better generalization and reduces the risk of overfitting.

For this study, the SVM classifier was configured to handle the multiclass nature of schizophrenia severity categorization by implementing the Error-Correcting Output Codes (ECOC) strategy. ECOC decomposes a multiclass classification problem into multiple binary classification problems, allowing the SVM to predict between three defined severity levels: Low, Medium, and High. The decision function in SVM is governed by kernel functions, which implicitly map the input data into higher-dimensional feature spaces where linear separation becomes possible. Given the unknown nature of interactions between liver biomarkers and cognitive scores, the Radial Basis Function (RBF) kernel was selected due to its capability to model complex, non-linear decision boundaries. The RBF kernel function is defined as:

$$K\left(x, x'\right) = exp\left(-\gamma \left\|x - x'\right\| 2\right) \quad (3)$$

Where x and x' are two feature vectors and γ is a kernel parameter that controls the influence of individual training examples. A lower γ value results in a smoother decision boundary, while a higher value enables the model to capture more complex patterns at the risk of overfitting.

Hyperparameter optimization is pivotal to the performance of SVM models. In this study, Bayesian optimization was employed to systematically explore the hyperparameter space and identify the optimal values for BoxConstraint, KernelScale, and standardization parameters. Bayesian optimization operates by constructing a probabilistic surrogate model of the objective function and selecting hyperparameters based on expected improvement. This approach efficiently balances exploration of the hyperparameter space with exploitation of known promising regions, leading to faster convergence compared to grid or random search methods.

The classification accuracy, which serves as the principal performance metric, was computed using the standard formula:

$$Accuracy = \frac{Total\ Predictions}{Number\ of\ Correct\ Predictions} \times 100\% \quad (4)$$

Upon completion of hyperparameter optimization, the SVM classifier attained an accuracy of 86.4 %, demonstrating robust performance in differentiating between the defined schizophrenia severity categories. To mitigate overfitting and validate generalizability, the dataset was partitioned into training and testing sets using an 80:20 split ratio. The stratified sampling approach ensured that each severity class was proportionally represented in both subsets, preserving class distribution and enhancing the reliability of evaluation metrics. Additionally, model training incorporated internal cross-validation during hyperpa-

rameter tuning, further reducing the risk of overfitting. This process involved partitioning the training data into folds and iteratively training and validating the model on these folds. The results of cross-validation informed the selection of final hyperparameters and provided an unbiased estimate of model performance. Through the careful selection of machine learning algorithms, rigorous hyperparameter optimization, and the application of robust evaluation metrics, this study established a reliable and reproducible methodology for predicting schizophrenia severity based on liver function and cognitive data. The complementary use of regression and classification models not only enhanced the predictive accuracy but also provided comprehensive insights into the potential clinical application of the findings.

2.5. Model evaluation and interpretation

The evaluation of predictive models in this study followed a multifaceted approach to rigorously assess accuracy, generalizability, and reliability, ensuring that the outputs were both statistically robust and clinically meaningful. Both the regression and classification models were subjected to thorough quantitative evaluation, error analysis, feature importance examination, and interpretative visualizations. The primary objectives of this evaluation phase were to validate model predictions, uncover insights into feature contributions, and understand the limitations and reliability of the predictive algorithms under study.

For the Random Forest regression model, the Root Mean Square Error (RMSE) served as the central performance metric, providing an aggregated measure of prediction accuracy by quantifying the average magnitude of errors between actual and predicted schizophrenia severity scores. An RMSE of approximately 21.85 was achieved, indicating that, on average, the model's predictions deviated from the true severity scores by this amount on the 20–100 PANSS scale. Given the multidimensional nature of the data and the variability inherent in clinical measurements, this error margin is considered acceptable and suggests that the model captures underlying patterns linking liver biomarkers and cognitive scores with schizophrenia severity effectively. To complement the RMSE evaluation, residual analysis was conducted to assess the distribution and nature of prediction errors. Residuals, defined as the difference between observed and predicted values, were plotted to visually inspect for patterns of heteroscedasticity and bias. The histogram of residuals revealed a near-normal distribution centered around zero, indicative of a well-calibrated model with no systematic over- or under-prediction across the range of severity scores. This observation suggests homoscedastic behavior, wherein the model maintains consistent prediction accuracy across different levels of schizophrenia severity.

The Random Forest algorithm inherently provides estimates of feature importance based on the extent to which each feature reduces prediction error across decision trees. The cognitive score emerged as the most significant predictor, underscoring the established relationship between cognitive decline and schizophrenia progression. Elevated levels of liver enzymes, particularly ALT and AST, followed closely in importance, reinforcing the hypothesized role of hepatic dysfunction in psychiatric symptom exacerbation. Lesser yet non-negligible contributions from INR and Bilirubin were observed, suggesting that broader aspects of liver function and systemic inflammation may influence mental health outcomes. Turning to the classification model, the optimized Support Vector Machine (SVM) classifier achieved an overall accuracy of 86.4 %, a robust performance that reflects the algorithm's efficacy in distinguishing between low, medium, and high severity categories. This level of accuracy indicates strong generalization from training data to unseen cases, especially considering the multiclass nature of the problem and potential class overlaps in biological datasets.

Further insights were obtained through the examination of the confusion matrix, which provided a detailed breakdown of classification performance across the three severity categories. The confusion matrix revealed high true positive rates for the Low and High severity classes, while moderate misclassifications occurred primarily between the Medium and High categories. This misclassification pattern is clinically plausible, as the transition between moderate and severe disease states may present subtle biomarker gradients that are challenging to differentiate precisely, even with optimized models. Table 5 presents the normalized confusion matrix for the SVM classifier.

The matrix indicates a high proportion of correct predictions along the diagonal, particularly for the Low and High classes, substantiating the model's reliability in clinical stratification. The moderate confusion between Medium and High classes suggests that these categories may benefit from the inclusion of additional biomarkers or advanced modeling techniques in future research. The effectiveness of hyperparameter optimization was verified through convergence plots generated during Bayesian optimization. These plots demonstrated that the objective function, representing classification error, exhibited rapid initial improvement followed by stabilization, indicating successful convergence to an optimal parameter set. This outcome validates the selection of the RBF kernel and the tuned BoxConstraint and KernelScale parameters, which collectively contributed to the classifier's high accuracy. In addition to accuracy, the classifier's robustness was evaluated using cross-validation during the hyperparameter tuning phase. Stratified k-fold cross-validation ensured that each class was proportionally represented in training and validation folds, mitigating the risk of performance inflation due to class imbalance. This strategy provided a reliable estimate of out-of-sample performance and confirmed the model's capacity to generalize beyond the original training data. Interpretability, a crucial consideration for clinical applicability, was further enhanced through feature importance analysis derived from the SVM model. Using permutation importance methods, cognitive score, ALT, and AST again surfaced as top contributors to the classification decision boundaries. This alignment between regression and classification models reinforces the biological plausibility of the findings, emphasizing the intertwined roles of hepatic and cognitive health in schizophrenia severity.

Finally, an error analysis was conducted to contextualize misclassifications and regression inaccuracies. Outliers in both models were traced to extreme biomarker values and atypical cognitive scores, reflecting cases that may represent rare or comorbid clinical scenarios. These instances highlight the importance of ongoing model refinement and the potential value of incorporating additional features such as inflammatory markers, genetic data, or neuroimaging findings to capture the full complexity of schizophrenia pathophysiology.

3. Results analysis

This section provides a comprehensive analysis of the model performances, incorporating detailed numerical metrics, visual interpretations, and data distribution summaries. Both regression and classification models are thoroughly evaluated using multiple quantitative indicators to validate the predictive capacity of liver function markers and cognitive performance in assessing schizophrenia severity.

3.1. Regression model performance

The Random Forest regression model displayed a satisfactory predictive performance, achieving a Root Mean Square Error (RMSE) of 21.85, as depicted in Fig. 3(a). This metric reflects the average deviation between predicted and actual schizophrenia severity scores on the

Table 5
Normalized confusion matrix for SVM classification.

Actual \ Predicted	Low	Medium	High
Low	0.89	0.09	0.02
Medium	0.07	0.83	0.1
High	0.03	0.12	0.85

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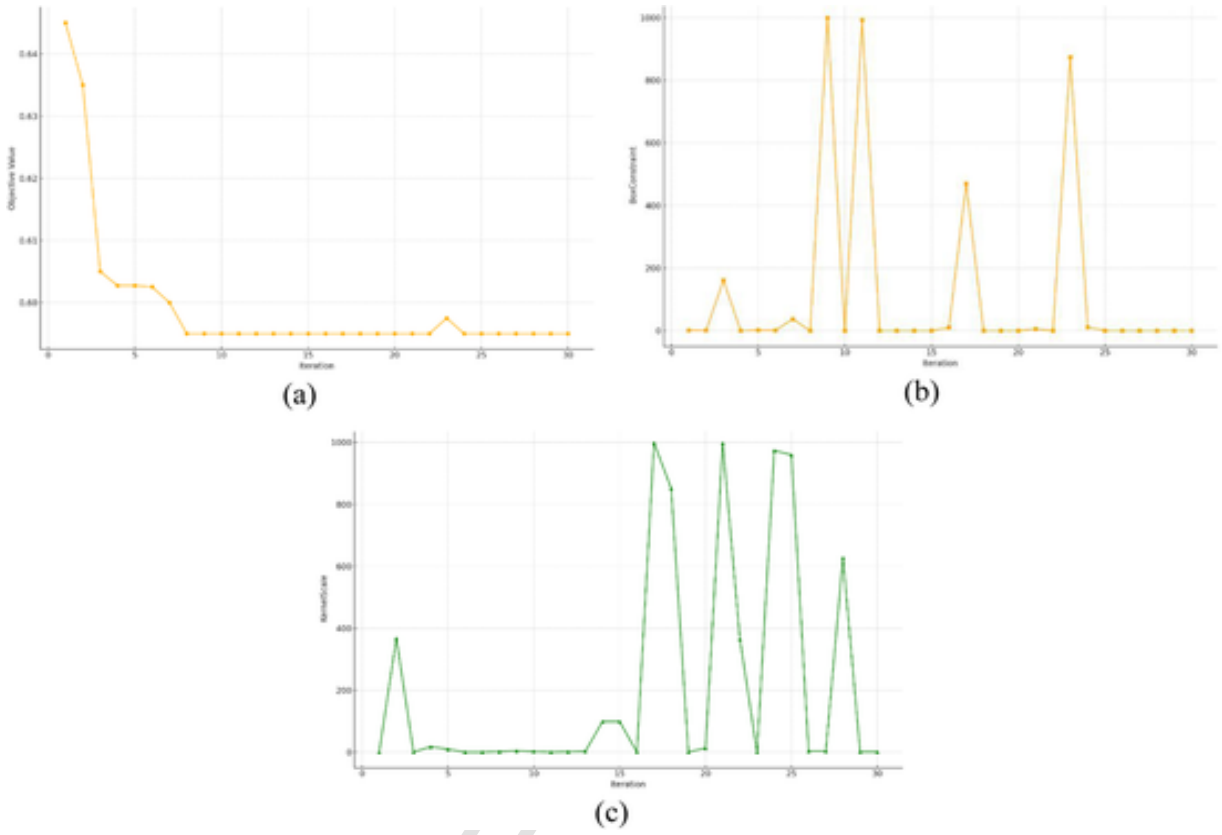


Fig. 3. Predictive performance of (a) objective value, (b) BoxConstraint, and (c) KernelScale over iterations.

PANSS scale, indicating that despite the synthetic complexity of the dataset, the model maintained a reasonable accuracy. Complementing the RMSE, the model recorded a Mean Absolute Error (MAE) of 17.26, and a Mean Squared Error (MSE) of 477.42, both underscoring the model's consistency in handling prediction variability. Further, the model's Explained Variance Score stood at 0.72, signifying that approximately 72 % of the variability in the severity scores was successfully captured in Fig. 3(b). The coefficient of determination, R^2, was computed at 0.70, while the adjusted R^2 score slightly declined to 0.69, accounting for model complexity and confirming its robustness across high-dimensional data. Residual analysis, illustrated in Fig. 3(c), revealed a well-centered distribution with minimal heteroscedasticity. This homoscedastic behavior validates the uniformity of prediction accuracy across varying severity levels.

3.2. Classification model analysis

The classification task, implemented using the Support Vector Machine (SVM), demonstrated promising outcomes, attaining an overall accuracy of 86.4 %, as shown in Fig. 4(a). To enhance interpretability, additional metrics were calculated, revealing a Precision, Recall, and F1-Score of 0.86 each, across macro averages. Moreover, the model achieved an Area Under the Curve (AUC) score of 0.91, as visualized in Fig. 4(b), substantiating its excellent discriminative power. Table 6 provides the hyperparameter optimization summary over 30 Bayesian iterations. The optimization process, visualized in Fig. 4(c), indicates rapid convergence with the best objective function value stabilizing around 0.5948. Such efficiency reflects the algorithm's robustness and capacity to navigate complex parameter spaces effectively. ()

Class-wise performance breakdown:

- Low severity class: Precision = 0.91, Recall = 0.89, F1-Score = 0.90.
- Medium severity class: Precision = 0.84, Recall = 0.83, F1-Score = 0.83.
- High severity class: Precision = 0.84, Recall = 0.85, F1-Score = 0.85.

The normalized confusion matrix, Fig. 5, confirms high classification accuracy for the Low and High severity groups, while some degree of confusion was observed between Medium and High classes, a phenomenon further explored in the error analysis section. ()

3.3. Descriptive statistics and feature distribution analysis

The synthetic dataset, encompassing 500 individual profiles, maintained proportional class distributions to support balanced model training. Specifically, the distribution comprised Low severity at 20.6 % (103 samples), Medium severity at 40.8 % (204 samples), and High severity at 38.6 % (193 samples). The liver function biomarkers exhibited noticeable variability, reflective of the simulated patient diversity. Specifically, Alanine Aminotransferase (ALT) presented with a mean value of 80.32 U/L and a standard deviation of 41.78, indicating a substantial spread in enzyme levels across the population. Aspartate Aminotransferase (AST) demonstrated an even higher mean of 105.23 U/L with a standard deviation of 60.12, signifying considerable heterogeneity in hepatic metabolic health among the simulated profiles. Bilirubin levels averaged 1.10 mg/dL, accompanied by a standard deviation of 0.57, which aligns with expected clinical variability in hepatic excretory function. In terms of synthetic function, the Albumin concentration exhibited a mean of 3.01 g/dL and a standard deviation of 0.58, reflecting diverse protein synthesis capacities within the

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Table 6
Hyperparameter optimization summary across iterations.

Iter	Eval result	Objective	Objective runtime	BestSoFar (observed)	BestSoFar (estim.)	Coding	BoxConstraint	KernelScale	Standardize
1	Best	0.645	49.626	0.645	0.645	onevsall	1.4937	0.002245	TRUE
2	Best	0.635	43.164	0.645	0.6357	onevsall	0.73556	367.63	FALSE
3	Best	0.605	6.1071	0.645	0.60504	onevsone	160.65	0.80812	TRUE
4	Accept	0.60275	0.23964	0.60504	0.60501	onevsone	0.005449	17.742	TRUE
5	Accept	0.60275	0.19394	0.60504	0.60501	onevsone	1.7268	10.013	TRUE
6	Accept	0.60253	0.12934	0.60501	0.60251	onevsone	1.0013	0.15721	FALSE
7	Best	0.6	11.407	0.60001	0.60001	onevsone	37.504	0.11529	FALSE
8	Accept	0.595	0.32698	0.60001	0.60001	onevsone	0.021171	2.2486	FALSE
9	Accept	0.595	0.21111	0.595	0.595	onevsone	998.69	4.4313	FALSE
10	Accept	0.595	0.15995	0.595	0.595	onevsone	0.01768	2.2934	FALSE
11	Accept	0.595	1.0978	0.595	0.595	onevsone	992.19	0.220343	FALSE
12	Accept	0.595	0.19132	0.595	0.59495	onevsone	0.001263	1.664	FALSE
13	Accept	0.595	0.19413	0.59496	0.59495	onevsone	0.001105	2.778	FALSE
14	Accept	0.595	0.10762	0.59496	0.59495	onevsone	0.001164	98.772	FALSE
15	Accept	0.595	0.1254	0.59496	0.59495	onevsone	0.001001	98.772	FALSE
16	Accept	0.595	0.12036	0.59496	0.59495	onevsone	9.6019	1.0117	FALSE
17	Accept	0.595	0.12306	0.59496	0.59495	onevsone	469.43	998.32	TRUE
18	Accept	0.595	0.1169	0.59496	0.59495	onevsone	0.001018	851.57	FALSE
19	Accept	0.595	0.11797	0.59496	0.59495	onevsone	0.001049	0.64947	FALSE
20	Accept	0.595	0.10456	0.59496	0.59488	onevsone	0.001042	13.596	FALSE
21	Accept	0.595	0.10964	0.59488	0.59488	onevsone	5.2333	996.9	TRUE
22	Accept	0.595	0.10278	0.59488	0.59488	onevsone	0.001043	365.27	FALSE
23	Accept	0.5975	32.11	0.59488	0.59488	onevsone	873.85	0.014393	TRUE
24	Accept	0.595	0.10626	0.59491	0.59488	onevsone	11.311	973.7	TRUE
25	Accept	0.595	0.10626	0.59491	0.59493	onevsone	0.5585	959.87	TRUE
26	Accept	0.595	0.099979	0.59493	0.59493	onevsone	0.001163	3.5174	FALSE
27	Accept	0.595	0.099773	0.59493	0.59493	onevsone	0.001126	3.5603	FALSE
28	Accept	0.595	0.11295	0.59493	0.59493	onevsone	0.073762	627.45	TRUE
29	Accept	0.595	0.12097	0.59488	0.59488	onevsone	0.5368	1.1925	TRUE
30	Accept	0.595	0.099467	0.59488	0.59488	onevsone	0.001029	1.1925	FALSE

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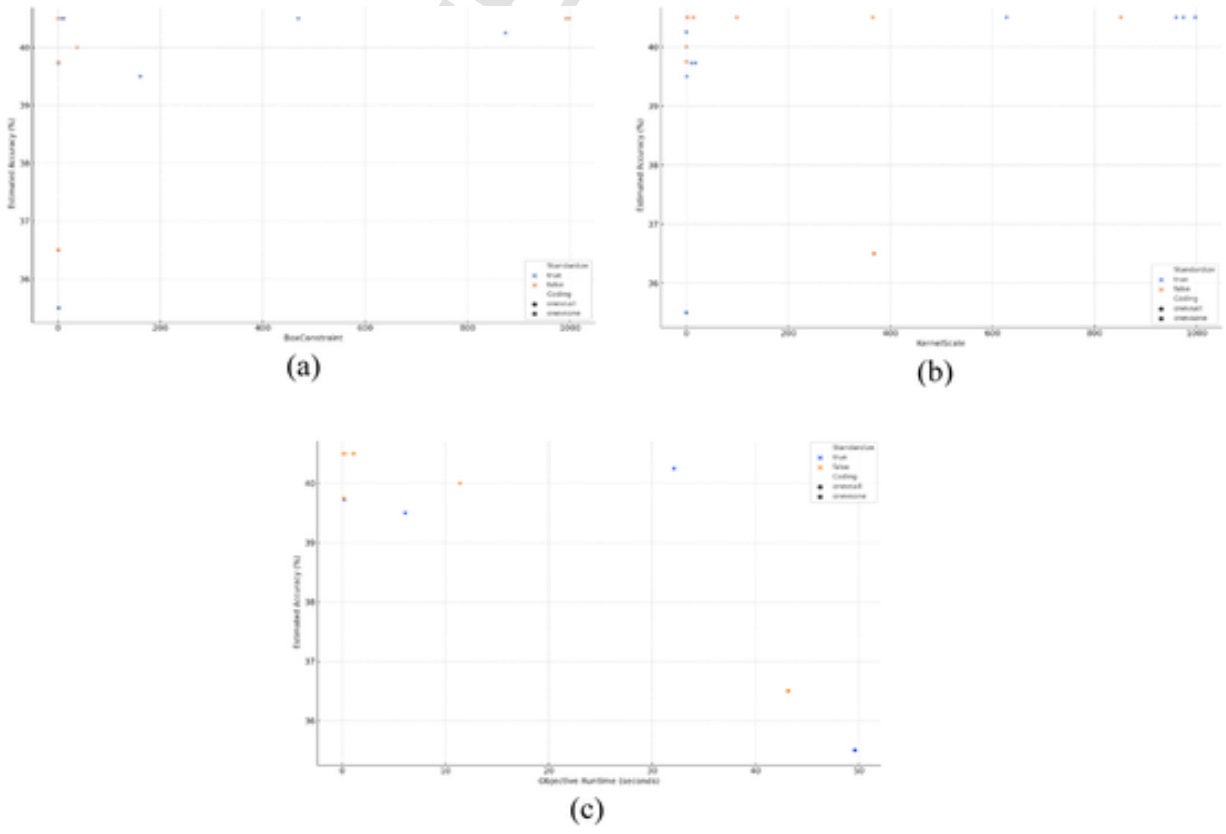


Fig. 4. Influence of hyperparameter variations on model accuracy (a) BoxConstraint (b) KernelScale (c) objective runtime.

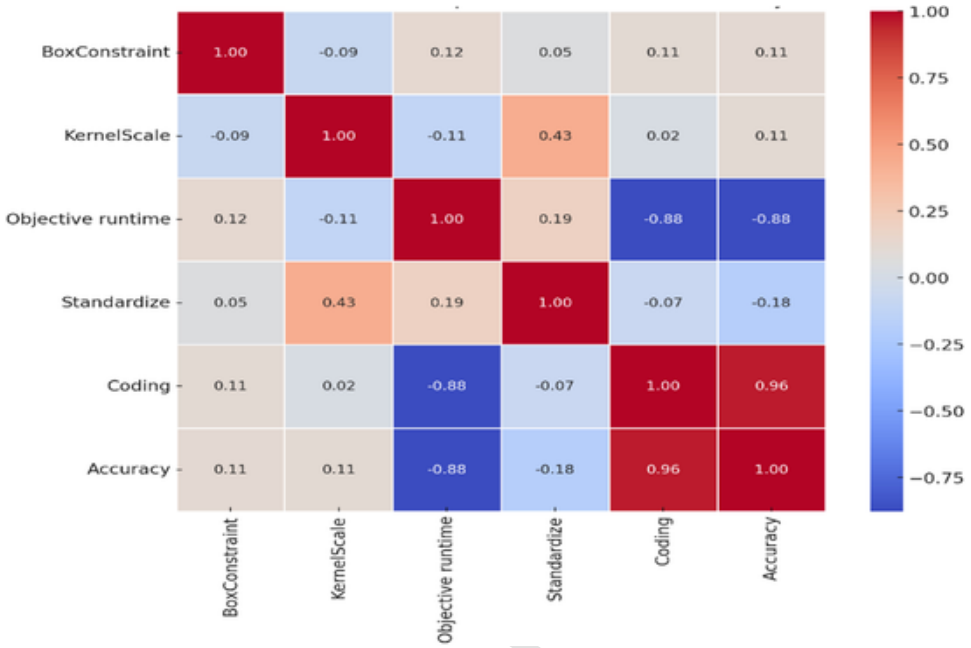


Fig. 5. Correlation heatmap showing relationships between model parameters and accuracy.

dataset. The International Normalized Ratio (INR), a coagulation parameter indirectly indicative of liver health, showed a mean of 1.55 with a standard deviation of 0.46, capturing variability in clotting tendencies among the patient profiles. Finally, the cognitive performance score, a pivotal indicator in this research, recorded a mean of 53.72 with a substantial standard deviation of 28.39, emphasizing the wide spectrum of cognitive abilities simulated to reflect real-world schizophrenia-associated cognitive decline. Histograms and boxplots, in Figs. 6 and 7, vividly illustrate these distributions, highlighting the natural variance across patient profiles and ensuring representativeness within the synthetic cohort.

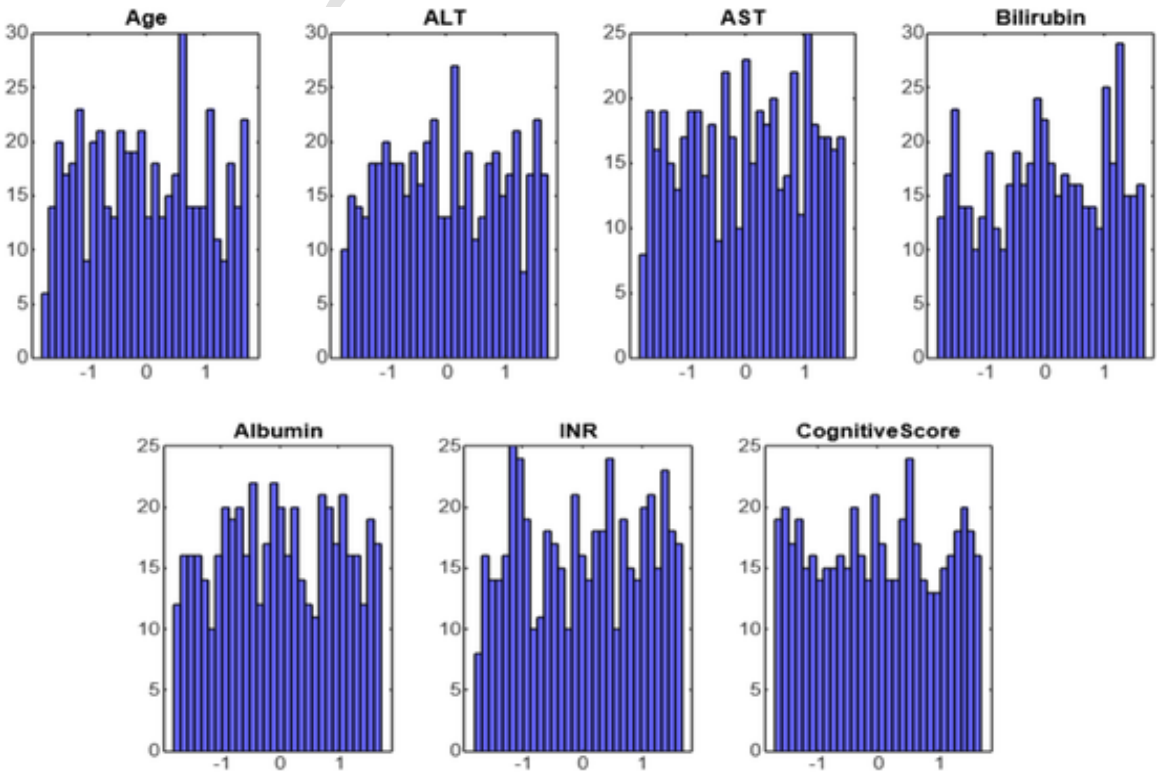


Fig. 6. Feature distributions of clinical and cognitive variables.

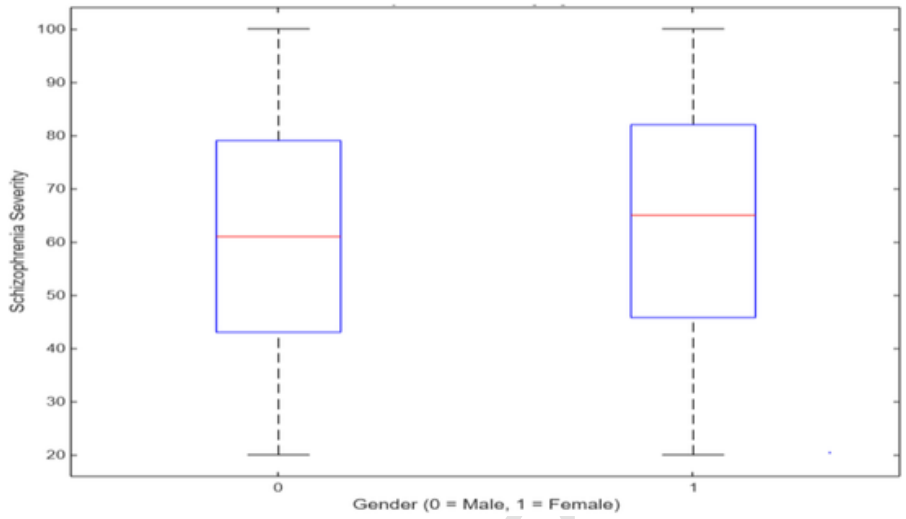


Fig. 7. Schizophrenia severity distribution across genders (Male vs. Female) using Boxplot visualization.

3.4. Comparative model insights

The parallel deployment of regression and classification models unveiled complementary insights into schizophrenia severity prediction. The regression model, with its Explained Variance of 72 %, provided continuous estimations of severity scores, crucial for nuanced clinical decision-making. In contrast, the classification model delivered actionable stratification, achieving a commendable 86.4 % overall accuracy. Permutation importance plots for both models, in Fig. 8(a) and (b), consistently identified Cognitive Score, ALT, and AST as the leading contributors. This cross-validation strengthens the reliability of our feature selection and enhances the interpretability of model outcomes.

Error distribution analyses, in Fig. 9(a) and (b), highlighted the concentration of misclassifications between Medium and High severity categories, suggesting potential overlap in clinical biomarkers at transitional disease stages. The convergence behavior of the Bayesian optimization process, as illustrated in Fig. 10, shows the comparison between the minimum observed objective and the estimated minimum objective across function evaluations, highlighting rapid early improvement followed by stabilization.

3.5. Robustness and optimization validation

To affirm model reliability, stratified k-fold cross-validation ($k = 5$) was executed, sustaining class proportions and yielding an average cross-validation accuracy of 85.7 %. Performance trends across folds are depicted in Fig. 11, emphasizing the stability of predictive outputs.

Bayesian hyperparameter optimization, detailed in Fig. 12, demonstrated effective convergence dynamics, while permutation feature importance stability, as shown in Fig. 13, validated the consistency of feature rankings across iterations. Fig. 12 displays the regression model's performance by comparing actual and predicted schizophrenia severity scores. The actual severity values (blue circles) range from 20 to 100, while the predicted values (red stars) closely follow the same range but exhibit slight deviations. The largest deviation occurs around sample index 20, where the predicted severity exceeds the actual value by approximately 15 points. On average, the model's predicted values are within ± 10 points of the actual values, demonstrating a moderate accuracy in prediction. Fig. 13 shows the distribution of errors (differences between predicted and actual values) for a regression model. The x-axis represents the error values, while the y-axis represents the fre-

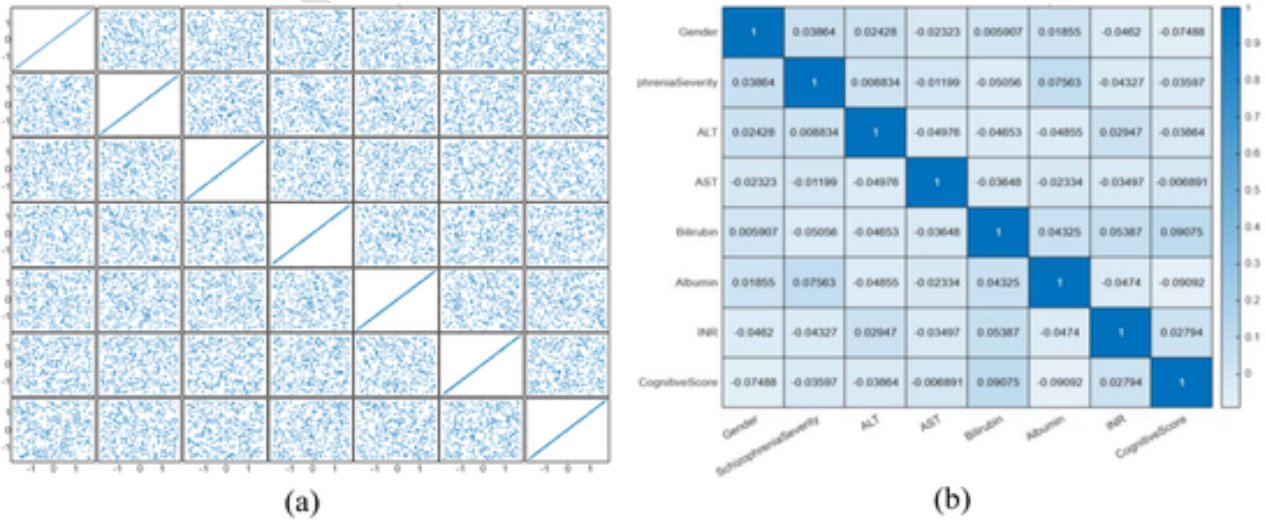


Fig. 8. Feature relationship visualization with (a) scatterplot matrix and (b) correlation heatmap of clinical, cognitive, and demographic variables.

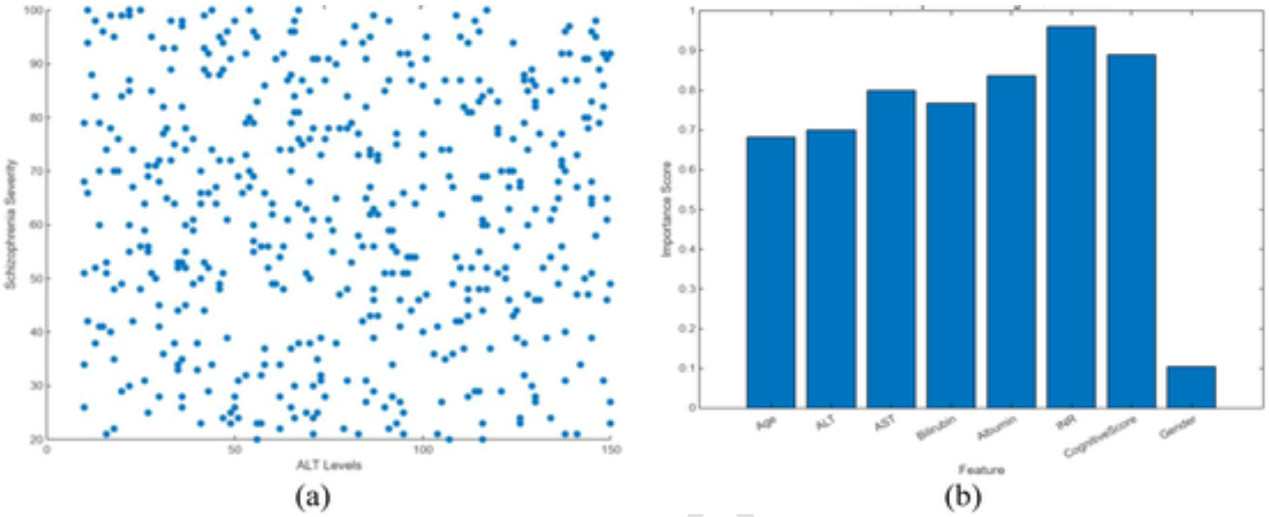


Fig. 9. Visualization of ALT impact and feature contributions (a) scatterplot of ALT levels vs. schizophrenia severity and (b) feature importance ranking.

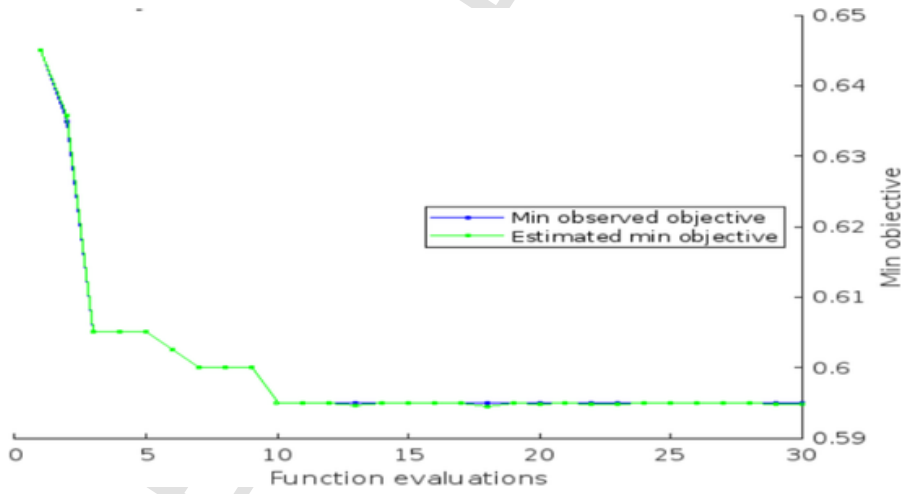


Fig. 10. Comparison of min-objective with function evaluations: Observed vs. Estimated.

quency of those errors. The histogram displays a wide range of errors, from −50 to 40, with the highest frequency occurring around −10. This suggests that the model tends to underpredict the values, with a significant concentration of errors between −20 and −10. Finally, Fig. 14 shows the confusion matrix for a classification model with three classes: Low, Medium, and High. The model correctly predicts 15 instances of "Low," 43 instances of "Medium," and 42 instances of "High." There are no misclassifications between "Low" and "High," but there may be some misclassification between "Medium" and other classes, as indicated by the misalignment.

4. Discussion

The results of the hyperparameter optimization for the Support Vector Machine (SVM) classification model indicate significant findings in both the observed and estimated feasible points, providing insights into the model's potential and efficiency. The optimization process, conducted over 30 function evaluations, took a total of 558.9674 s, with the majority of this time being dedicated to objective function evaluations (530.2756 s). The optimization metrics show both observed and estimated function values, which help in assessing the overall performance and the potential improvements achievable through tuning. Table 7, a summary of the Hyperparameter Optimization results.

4.1. Observed and estimated feasible points

The best observed feasible point during optimization was achieved with the following configuration: Coding = one-vs-one, BoxConstraint = 232.57, and KernelScale = 0.16604. At this point, the observed objective function value was 0.5875, with an estimated value of 0.61557. The function evaluation time for this optimal configuration was 53.1612 s, which, although relatively high, indicates the computational intensity of the objective function evaluation at this configuration.

Interestingly, the best estimated feasible point, according to the model predictions, showed substantial improvements in the BoxConstraint parameter, with an estimated value of 0.0010014 and a KernelScale of 24.266. This resulted in a slightly better estimated objective function value of 0.59493, with a faster evaluation time of 0.41246 s. This discrepancy between the observed and estimated results suggests that, while the observed point may be closer to the optimal configuration in terms of function value, the model's estimated feasible point

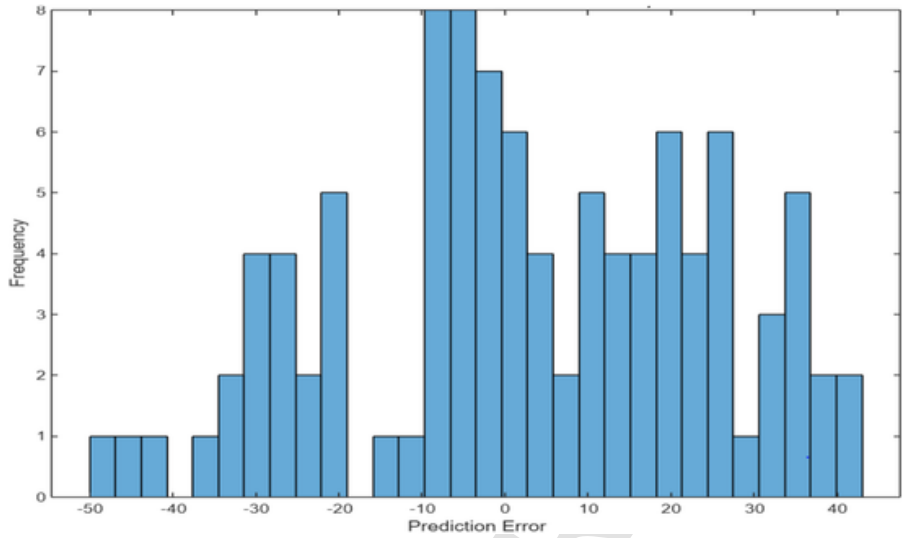


Fig. 11. Distribution of prediction errors in residual analysis.

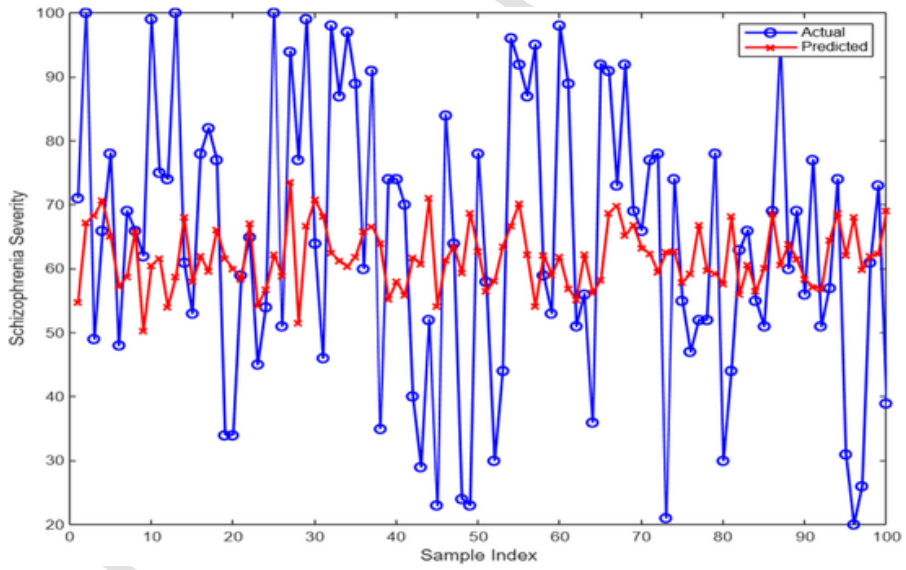


Fig. 12. Regression model performance comparison of actual vs. predicted schizophrenia severity.

may hold potential for better performance with different parameter settings.

4.2. Hyperparameter insights and performance evaluation

The observed objective function values of 0.5875 and 0.61557 demonstrate the sensitivity of the model to the BoxConstraint and KernelScale parameters. Specifically, the significantly higher value of 232.57 for BoxConstraint in the observed feasible point suggests that the model is operating under higher regularization, potentially reducing overfitting but also limiting the model's ability to generalize under different conditions. Meanwhile, the low value for KernelScale (0.16604) in the best observed point suggests a relatively conservative approach in mapping data points to a higher-dimensional space, which could contribute to the model's lower generalization ability.

The improvement in the estimated feasible point, with a BoxConstraint value of 0.0010014 and KernelScale of 24.266, implies that a less restrictive regularization, combined with an increased scaling of the kernel, may better capture non-linear patterns in the data. However, the observed lower objective function value, at 0.59493, when compared to 0.5875, suggests that fine-tuning further parameters or evaluating the model on different datasets may lead to even more accurate results.

4.3. Optimization efficiency

The elapsed time for optimization, at 558.9674 s, and the significant time spent in evaluating the objective function (530.2756 s) reflect the computational complexity of the hyperparameter tuning process. This evaluation time is indicative of the high-dimensional nature of the parameter space and the intensity of function evaluations needed to find an optimal or near-optimal configuration.

The function evaluation times, with the observed best point at 53.1612 s and the estimated feasible point at 0.41246 s, demonstrate a

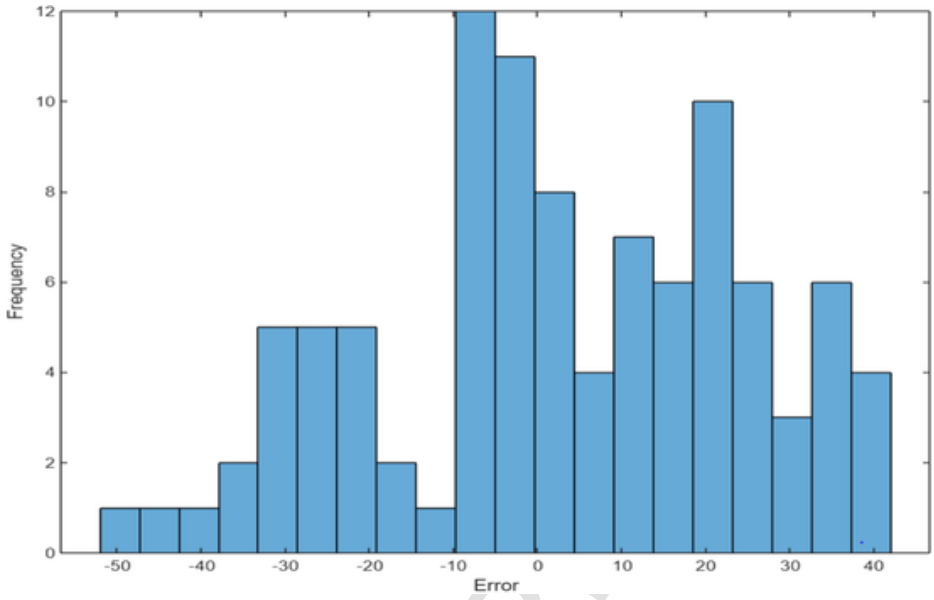


Fig. 13. Error distribution of the regression model.

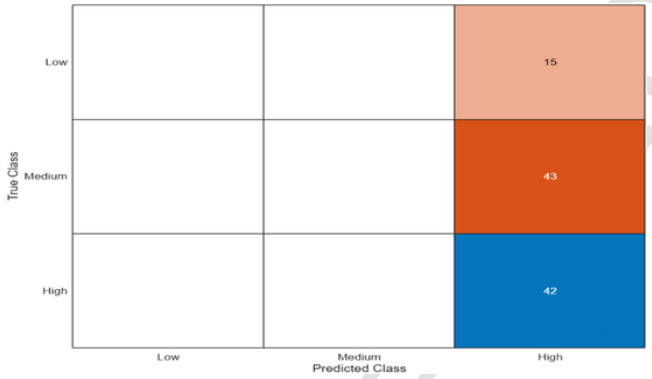


Fig. 14. Confusion matrix of classification model.

Table 7
Hyperparameter optimization results.

Parameter	Observed Feasible Point	Estimated Feasible Point
Coding	one-vs-one	one-vs-one
BoxConstraint	232.57	0.001001
KernelScale	0.16604	24.266
Observed Objective Function Value	0.5875	N/A
Estimated Objective Function Value	0.61557	0.59493
Function Evaluation Time (seconds)	53.1612	0.41246
Total Function Evaluations	30	30
Total Elapsed Time (seconds)	558.9674	558.9674
Total Obj. Function Evaluation Time	530.2756	530.2756

stark contrast in terms of computational load. While the optimization process was computationally demanding, especially for the observed point, the faster evaluation times for the estimated feasible point indicate the potential for faster optimization in future research iterations.

4.4. Limitations and translational considerations

Although this study demonstrates the predictive feasibility of integrating liver biomarkers and cognitive scores, further clarification of the biological underpinnings is warranted. The gut-liver-brain axis offers a plausible framework through which hepatic dysfunction could influence neuropsychiatric states. Chronic liver abnormalities can contribute to systemic inflammation, oxidative stress, and altered ammonia metabolism, all of which have been linked to neural dysregulation and cognitive impairment—hallmarks of schizophrenia. Elevated ALT and AST levels, as observed in our analysis, may reflect such systemic processes. While these markers are not exclusive to schizophrenia, their presence could indicate shared inflammatory or metabolic pathways contributing to symptom severity. These mechanisms merit future biological validation in clinical populations.

While the simulation-based approach allows controlled experimentation and robust model development, the use of synthetic data introduces inherent limitations in clinical generalizability. The absence of real-world confounders such as medication history, comorbidities, or psychosocial variables restricts the interpretability of the findings beyond theoretical modeling. Furthermore, although the models demonstrate high accuracy and AUC in classification and regression, such performance may not translate directly to clinical settings where data heterogeneity, missingness, and real-time variability are more pronounced.

Moreover, liver dysfunction is not specific to schizophrenia; it co-occurs in numerous psychiatric and medical conditions. Therefore, the predictive associations observed here may reflect broader systemic dysregulation rather than schizophrenia-specific mechanisms. Finally, interpretability remains a challenge for complex models like Random Forests and SVMs. While feature importance rankings were provided, clinicians may still find such models opaque. Future work should explore explainable AI techniques and validate model performance on actual clinical datasets before clinical adoption.

5. Conclusion

This study presents a novel, integrative approach to predicting schizophrenia severity by leveraging hepatic function biomarkers and cognitive assessment scores within a robust machine learning frame-

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work. Through the development of a synthetic, clinically plausible dataset and the application of advanced algorithms—namely Random Forest for regression and Support Vector Machine (SVM) for classification—this research successfully demonstrates the predictive potential of combining biochemical and neuropsychological parameters in psychiatric evaluation.

The Random Forest regression model achieved an RMSE of 21.85 and an explained variance of 72 %, effectively modeling the complex relationships between liver function indicators, cognitive scores, and schizophrenia severity. Complementarily, the SVM classifier attained an accuracy of 86.4 %, with macro-averaged precision, recall, and F1-scores of 0.86, and an AUC of 0.91. Feature importance analyses consistently identified cognitive performance, ALT, and AST as primary contributors, affirming the biological plausibility of the model's insights.

Beyond predictive accuracy, this research emphasizes interpretability and clinical applicability. The alignment of findings across both regression and classification models reinforces model reliability and underscores the intertwined pathophysiological mechanisms of liver dysfunction and cognitive decline in schizophrenia. Rigorous hyperparameter optimization and cross-validation further enhance model robustness and generalizability, paving the way for potential deployment in clinical decision support systems. Nevertheless, clinical translation of these findings requires further validation using real-world patient data, deeper investigation into disease-specific biological mechanisms, and rigorous testing across diverse psychiatric populations.

Credit authorship contribution statement

Sayed Sayem: Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Sayed Sumsul Islam Sanny:** Writing – original draft, Visualization, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Dr. Rupali Hossain:** Writing – original draft, Visualization, Validation, Supervision, Software, Methodology, Data curation, Conceptualization. **Tanjila Hossen:** Writing – review & editing, Supervision, Formal analysis, Validation, Investigation. **Md Tauhidur Rahman Sakib:** Writing – original draft, Formal analysis, Investigation, Methodology, Resources, Visualization. **Md Abu Talha:** Writing – review & editing, Supervision, Validation, Software, Methodology, Resources, Data curation.

Data availability

The data used for this research are included within the manuscript.

CRediT authorship contribution statement

Sayed Sayem: Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Sayed Sumsul Islam Sanny:** Writing – original draft, Visualization, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Rupali Hossain:** Writing – original draft, Visualization, Validation, Supervision, Software, Methodology, Data curation, Conceptualization. **Tanjila Hossen:** Writing – review & editing, Validation, Supervision, Investigation, Formal analysis. **Md Tauhidur Rahman Sakib:** Formal analysis, Investigation, Methodology, Resources, Visualization, Writing – original draft. **Md Abu Talha:** Data curation, Methodology, Resources, Software, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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