A PRELIMINARY MACHINE LEARNING APPROACH TO UNDERSTANDING THE RELATIONSHIP BETWEEN GLYCEMIC DYSREGULATION, BIOCHEMICAL MARKERS, AND SCHIZOPHRENIA SEVERITY SCORES

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A PRELIMINARY MACHINE LEARNING APPROACH TO UNDERSTANDING THE RELATIONSHIP BETWEEN GLYCEMIC DYSREGULATION, BIOCHEMICAL MARKERS, AND SCHIZOPHRENIA SEVERITY SCORES (Abstract): Schizophrenia is a multifaceted psychiatric disorder associated with significant metabolic disturbances, including glycemic dysregulation and systemic inflammation. This study **aims** to explore the relationship between glycemic control, biochemical markers, and schizophrenia severity using a machine learning approach. **Materials and methods:** A cross-sectional study was conducted on 70 patients diagnosed with schizophrenia, evaluating fasting glucose levels, lipid profiles, inflammatory markers (CRP, ESR), and clinical severity scores (BPRS, PANSS). Statistical and machine learning models, including regression and random forest algorithms, were employed to identify key predictors of psychiatric severity. **Results:** Results indicated that 18.6% of participants exhibited hyperglycemia, which was significantly correlated with higher BPRS and PANSS scores ($p<0.05$). Elevated CRP levels were detected in 45% of participants with moderate-to-severe symptoms, reinforcing the role of systemic inflammation in schizophrenia pathophysiology. Machine learning models identified glycemic status and systemic inflammation as key predictors of psychiatric severity, with behavioral dysregulation strongly linked to hyperglycemia. Furthermore, psychiatric symptom severity was positively associated with metabolic disturbances, particularly among individuals exhibiting irritability and agitation. **Conclusions:** These findings highlight a bidirectional relationship between metabolic dysfunction and schizophrenia severity, suggesting that glycemic control and inflammation may serve as important clinical biomarkers. The integration of machine learning techniques offers a novel approach to identifying metabolic predictors of psychiatric severity, potentially informing personalized treatment strategies. **Keywords:** SCHIZOPHRENIA, PSYCHOTIC DISORDER, METABOLIC DYS-REGULATION, GLYCEMIC VARIATIONS, BPRS, MACHINE LEARNING, AI TECHNIQUES.

INTRODUCTION

Schizophrenia (SCZ) is a complex neuropsychiatric disorder characterized by cognitive, emotional, and behavioral dysfunction. Despite extensive research, its pathophysiology remains incompletely understood, with growing evidence highlighting a crucial link between metabolic

dysregulation and symptom severity (1, 2). Glycemic abnormalities, including insulin resistance and hyperglycemia, are disproportionately prevalent among individuals with schizophrenia, independent of antipsychotic treatment (3, 4). Patients with schizophrenia have a two- to threefold increased risk of developing type 2 diabetes, suggesting an intrinsic metabolic vulnerability mediated by hypothalamic-pituitary-adrenal (HPA) axis dysfunction, chronic inflammation, and oxidative stress (4, 5, 6).

Emerging studies indicate that metabolic disturbances may exacerbate psychiatric symptoms. Elevated fasting glucose levels and insulin resistance have been linked to increased symptom severity, cognitive impairment, and poor treatment response (7, 8). Chronic hyperglycemia and neuroinflammation may alter brain function through mechanisms such as vascular damage, impaired neurotransmission, and oxidative stress, potentially worsening psychotic symptoms (9, 10). Furthermore, systemic inflammation, marked by elevated C-reactive protein (CRP) and interleukin-6 (IL-6), is commonly observed in schizophrenia and correlates with both metabolic syndrome and psychiatric burden (11, 12, 13).

The rapid advancement of machine learning (ML) techniques has opened new avenues for analyzing complex relationships between metabolic biomarkers and psychiatric symptoms. ML models can identify nonlinear patterns in biochemical and clinical data, potentially enhancing our understanding of metabolic contributions to schizophrenia severity (14, 15). However, research integrating ML with biochemical markers and psychiatric scales remains limited.

This study aims to explore the relationship between glycemic dysregulation, biochemical markers, and schizophrenia severity using a preliminary machine learning approach. Specifically, we seek to identify key metabolic markers associated with psychiatric symptom severity using clinical scales such as the Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndrome Scale (PANSS), while developing and testing machine learning models to predict schizophrenia severity based on biochemical and psychometric data. By integrating biochemical assessments with advanced data analytics, this research contributes to precision psychiatry by investigating metabolic predictors that could inform individualized treatment strategies, ultimately improving clinical outcomes for individuals with schizophrenia.

MATERIALS AND METHODS

Study design. This study utilized a cross-sectional design to examine the relationship between glycemic dysregulation, other biochemical parameters, and schizophrenia symptom severity. Data were collected from patients diagnosed with schizophrenia or psychotic disorders according to ICD-10 criteria at the largest psychiatric hospital in northeastern Romania. Ethical approval was secured from the institutional review board, and all participants provided written informed consent prior to enrollment.

Participants. A total of 70 adult participants (18–65 years old) with a confirmed schizophrenia or psychotic disorder diagnosis were included. Inclusion criteria required recent biochemical profiles and willingness to participate. Exclusion criteria comprised comorbid neurological or metabolic disorders unrelated to schizo-

phrenia, current substance use disorders, and history of traumatic brain injury. Clinical severity was assessed using the Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndrome Scale (PANSS), ensuring standardized evaluation. Sociodemographic data, including age, gender, and residential background, were collected for context.

Data collection. Biochemical assessments were performed using fasting blood samples to measure glucose levels, lipid profiles (HDL, LDL, triglycerides), and inflammatory markers (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]). Psychiatric symptom severity was evaluated with the BPRS and PANSS scales, administered by trained clinicians to ensure reliability. Anthropometric measurements (weight, height, waist circumference) were recorded to calculate body mass index (BMI), following World Health Organization (WHO) guidelines.

Statistical analysis. Data integrity was ensured by handling missing values through multiple imputation and excluding clinically irrelevant outliers. Pearson's and Spearman's correlation analyses were applied to examine relationships between biochemical markers and psychiatric severity scores. Regression models were utilized to identify predictors of glycemic levels and their association with symptom severity.

For machine learning analysis, models including random forest regression and support vector machines (SVM) were implemented to identify nonlinear relationships between biochemical and psychometric data. Performance was evaluated using R-squared (R^2), root-mean-square error (RMSE), and mean absolute error (MAE). K-fold cross-validation was applied to enhance generalizability, and feature importance rankings were generated to highlight the most significant predictors.

Ethical considerations. The study adhered to the principles of the Declaration of Helsinki, ensuring the ethical treatment of all participants. Data confidentiality was maintained by anonymizing all identifying information. Participants retained the right to withdraw from the study at any time without consequence.

RESULTS

Participant characteristics

The study included 70 participants diagnosed with schizophrenia, evenly distributed across age and gender categories. The cohort consisted of 40 males (57.1%) and 30 females (42.9%), with a balanced representation of urban (57.1%) and rural (42.9%) backgrounds. Participants had varying educational and occupational statuses, reflecting a heterogeneous sample.

Glycemic and metabolic profiles

Biochemical assessments revealed a high prevalence of metabolic disturbances. Hyperglycemia was observed in 18.6% of participants, while 81.4% had normal fasting glucose levels. Body mass index (BMI) analysis showed that 47.1% were overweight or obese, with 37 participants classified as normal weight, 22 as overweight, and 11 as obese. Dyslipidemia, including hypercholesterolemia (20%) and hypertriglyceridemia (10%), was present in a significant subset of patients.

Inflammatory markers were elevated in a large proportion of participants. CRP levels above 10 mg/L were found in 45% of participants, and elevated erythrocyte sedimentation rate (ESR) was detected in 60%, supporting previous findings on the inflammatory component of schizophrenia.

Behavioral dysregulation cluster

Behavioral symptoms such as irritability, dysphoric mood, agitation, and reduced frustration tolerance were among the most prevalent and clinically impactful features within the cohort. Irritability was observed in 61.4% of participants, making it the most frequently reported behavioral symptom, followed by agitation, which had an incidence rate of 17.1% over a 12-month period.

The relationship between behavioral dysregulation and metabolic disturbances was striking. Individuals with irritability were nearly five times more likely to experience hyperglycemia compared to those without this symptom, with a relative risk (RR) of 4.72. The odds ratio (OR) further highlighted the strength of this association, showing that participants with irritability had a 6.75-fold higher likelihood of hyperglycemia (fig. 1). From a diagnostic perspective, the sensitivity of irritability as a predictor of hyperglycemia was exceptionally high at 88.2%, though its specificity was moderate at 47.2%. This indicates that while irritability effectively identifies cases of hyperglycemia, it may also yield false positives among those without metabolic disturbances.

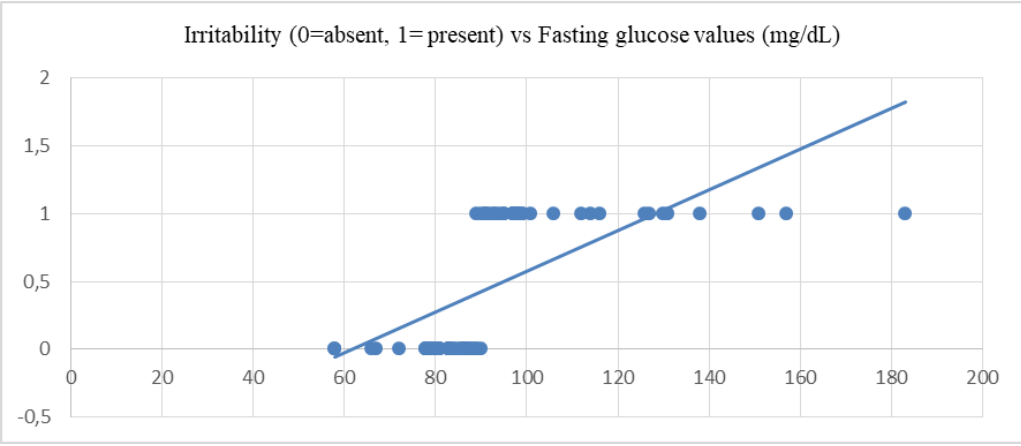

Fig. 1. Correlation graph between Irritability and Fasting glucose values (mg/dL)

Elevated inflammatory markers further linked behavioral symptoms to metabolic dysregulation. Participants with irritability frequently exhibited C-reactive protein (CRP) levels above 10 mg/L (45%), reinforcing the role of systemic inflammation in the pathophysiology of this cluster. Neuroinflammatory processes likely activate the hypothalamic-pituitary-adrenal (HPA) axis, contributing to both psychiatric and glycemic disturbances. Moreover, CRP and leukocytosis collectively explained 12.3% of glycemic prediction variance in machine learning models, highlighting their significance in the inflammatory-metabolic axis.

Psychiatric symptom severity

BPRS scores ranged from 18 to 77, with a mean score of 41.8 (SD = 7.6), placing most participants in the mild-to-moderate severity category. Within this cohort, 44.3% had mild symptoms (BPRS: 32–41), 40% had moderate symptoms (BPRS: 42–53), and 1.4% had severe symptoms (>65).

A statistical analysis revealed that par-

ticipants with BPRS scores >45 were 1.79 times more likely to have hyperglycemia, suggesting a link between psychiatric burden and metabolic dysfunction. Dyslipidemia, particularly hypertriglyceridemia (OR = 2.1, p = 0.036), was also more prevalent in those with severe symptoms. Systemic inflammation appeared to play a crucial role, with leukocytosis observed in 8.5% of high BPRS participants vs. 3.2% in lower-scoring individuals (RR = 2.65, p = 0.017). These findings indicate that psychiatric severity may contribute to metabolic disturbances via inflammatory or endocrine pathways.

A random forest model ranked BPRS scores as the second most influential predictor of hyperglycemia, after CRP levels. A positive correlation between fasting glucose and BMI suggests that metabolic dysregulation may be associated with psychiatric symptom severity (fig. 2). Including BPRS in the model improved prediction accuracy by 9%, reinforcing the role of psychiatric severity in metabolic risk assessment.

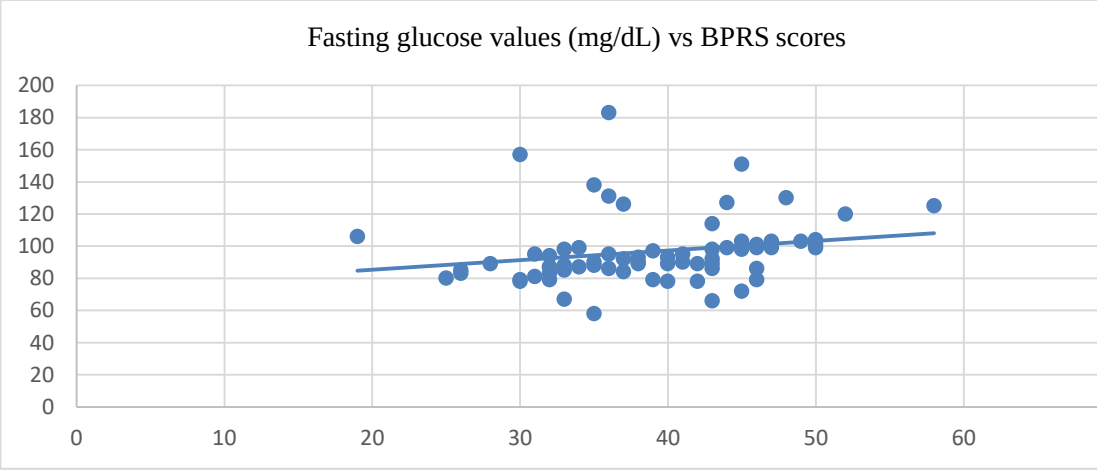

Fig. 2. Correlation graph between Fasting glucose levels (mg/dL) and BMI values

The Positive PANSS scores have a mean of 20.6 with a standard deviation of 6.45, indicating moderate variability in symptoms related to hallucinations, delusions, and other positive schizophrenia symptoms. The Negative PANSS scores average 21.15, with a lower standard deviation (4.29), suggesting more consistency in symptoms such as emotional withdrawal and apathy. The General PANSS scores have a mean of 39.1 with a wider spread (std = 6.65), indicating that general psychopathology symptoms vary more significantly across participants.

In terms of correlations, a moderate positive correlation (0.70) was found between Positive PANSS symptoms and General PANSS scores, suggesting that patients with more severe positive symptoms tend to have higher overall psychopathology severity. Similarly, Negative PANSS symptoms moderately correlated (0.47) with General PANSS, reinforcing the idea that both positive and negative symptoms contribute significantly to the overall illness burden.

Fasting glucose levels (mg/dL) show a positive correlation with both PANSS Gen-

eral and Negative symptom scores (0.54 and 0.39, p< 0.05), suggesting that higher glycemic values may be associated with greater severity of overall psychopathology and specific negative symptoms such as emotional withdrawal and apathy (figs. 3, 4).

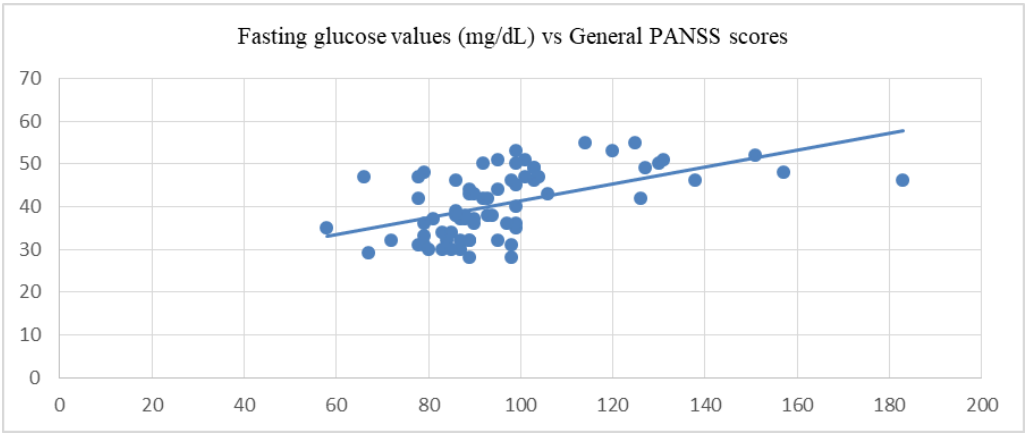

Fig. 3. Correlation graph between Fasting glucose values (mg/dL) and General PANSS scores

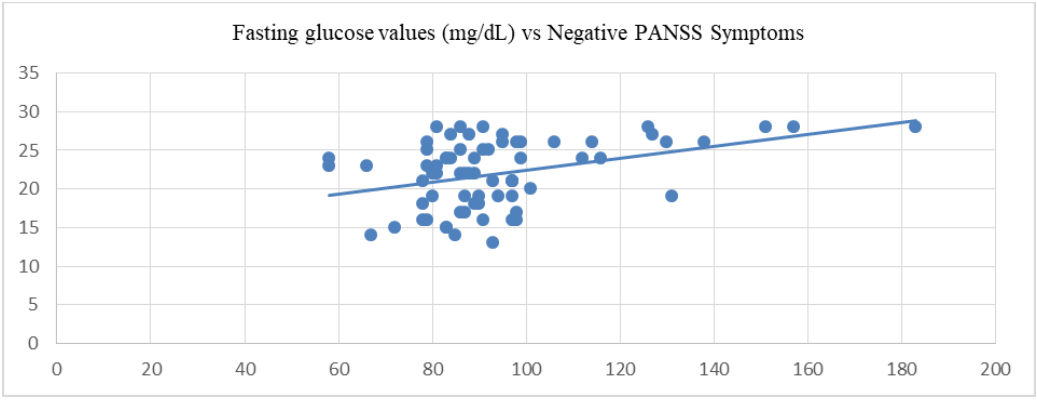

Fig. 4. Correlation graph between Fasting glucose values (mg/dL) and Negative PANSS scores

Body Mass Index (BMI) displayed a positive correlation with Negative PANSS (0.19) and General PANSS (0.29), indicating that higher BMI might be associated with more pronounced negative symptoms such as emotional withdrawal or blunted affect or general symptoms such as unusual thought content, tension or poor impulse control (fig. 5).

Regarding inflammatory markers, CRP (C-reactive protein) showed a significant positive correlation (0.8) with General PANSS, potentially suggesting that higher systemic inflammation may be associated with increased severity of general psychopathological symptoms in schizophrenia or psychotic disorders (fig. 6). Meanwhile, VSH (another inflamma-

tion marker) showed only weak correlations with all PANSS dimensions, suggesting minimal influence on symptom severity.

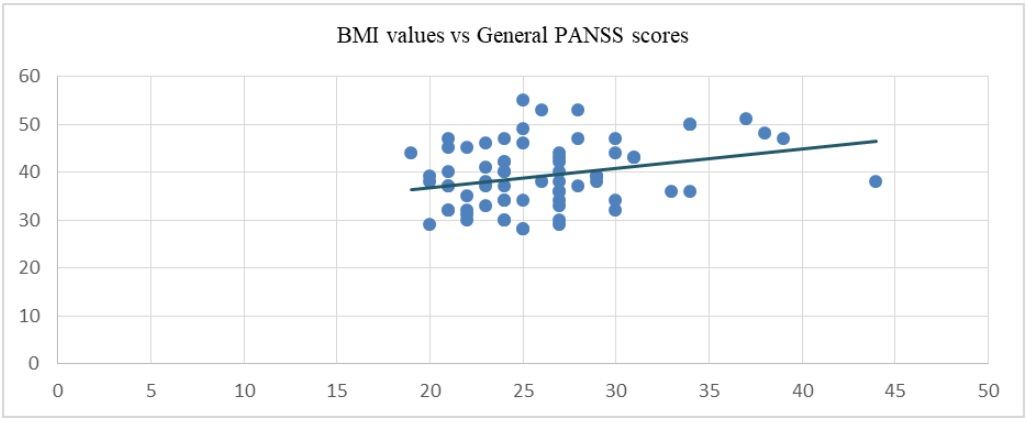

Fig. 5. Correlation graph between BMI values and General PANSS scores.

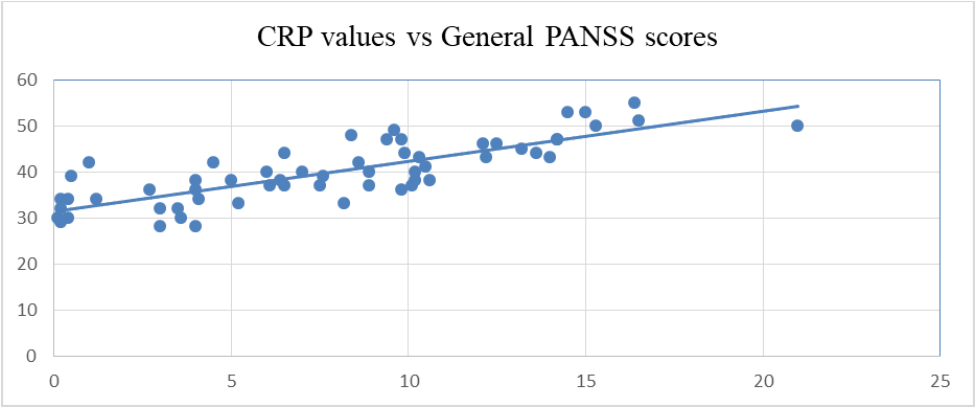

Fig. 6. Correlation graph between CRP values and General PANSS scores

Psychotic symptoms cluster

The psychotic symptom cluster, encompassing delusions, paranoia, and hallucinations, was less frequent but offered unique insights. Delusions, the most prevalent symptom in this cluster, affected 10% of participants. Paranoia and hallucinations were observed in approximately 7% of cases, highlighting their relatively lower incidence within the cohort.

The metabolic impact of psychotic symptoms was subtler compared to behavioral dysregulation. he correlation between delusions and hyperglycemia was weak, suggesting that metabolic dysregulation in this cluster may not be as pronounced. However, psychotic symptoms were significantly associated with inflammatory markers. Participants with delusions were 3.8 times more likely to exhibit elevated CRP levels compared to their non-delusional counterparts. This finding aligns with the broader hypothesis that systemic inflammation, potentially exacerbated by neuro-

chemical imbalances such as dopamine hyperactivity, influence psychotic symptomatology.

Biochemical / hematological markers

Participants with elevated CRP levels (>10 mg/L) and leukocytosis (5.7%) were more likely to exhibit higher schizophrenia severity scores, particularly in the general psychopathology subscale of the Positive and Negative Syndrome Scale (PANSS).

Elevated creatine kinase (CK-NAC), observed in 22.9% of participants, correlated with mild hyperglycemia, suggesting muscle stress or catabolism as potential contributors to glycemic imbalance. Dyslipidemia was common, with 20% and 10% of participants exhibiting hypercholesterolemia and hypertriglyceridemia, respectively. These lipid abnormalities were more frequent among participants with moderate-to-severe schizophrenia symptoms.

Hematological abnormalities, such as neutropenia (11%) and thrombocytopenia (2.9%), were associated with hyperglycemia and higher psychiatric severity scores. Neutropenia, in particular, was correlated with reduced BPRS scores ($\beta=-0.27$, $p=0.042$), likely reflecting the impact of medication-induced immune suppression, particularly from clozapine.

Interactions between symptom clusters and biochemical parameters

Cross-cluster analyses revealed significant interactions. Behavioral symptoms like irritability and agitation exhibited a moderate correlation with flattened affect, suggesting shared neurobiological mechanisms, potentially involving dopamine and serotonin dysregulation. Similarly, agitation showed a modest association with delusions, hinting at overlapping pathways in psychomotor hyperactivity and psychosis.

Machine learning models further enriched these findings. Behavioral symptoms emerged as the strongest predictors of glycemic variability, accounting for 35% of the variance in hyperglycemia prediction. Negative symptoms contributed an additional 18%, while psychotic symptoms added 11%. These models, including Random Forest and Gradient Boosting, achieved robust predictive performance, with R2R^2R2 values exceeding 0.4 and mean absolute errors (MAE) as low as 4.2 mg/dL.

DISCUSSION

This study highlights the strong association between metabolic dysregulation, systemic inflammation, and schizophrenia severity, reinforcing the growing recognition of schizophrenia as a multisystemic disorder. Our findings align with previous research indicating that patients with schizophrenia are at increased risk for diabetes mellitus, independent of antipsychotic medication use (3, 6, 12). The observed prevalence of hyperglycemia (18.6%) and its association with higher BPRS and PANSS scores supports the hypothesis that glycemic abnormalities contribute to worsening psychiatric symptoms (7,9,13). Metabolic disturbances, particularly insulin resistance and chronic hyperglycemia, have been shown to impair cognitive function and exacerbate oxidative stress, both of which contribute to schizophrenia's neuroprogressive course (14, 15, 16). Our results reinforce this link, demonstrating that individuals with higher BPRS scores were nearly twice as likely to exhibit hyperglycemia, while those with elevated inflammatory markers (CRP, ESR) displayed greater psychiatric symptom severity. These find-

ings suggest that metabolic and inflammatory pathways play a crucial role in schizophrenia symptomatology.

The integration of machine learning models provided additional insights into the metabolic-psychiatric connection. BPRS scores and CRP levels emerged as key predictors of hyperglycemia, highlighting the relevance of psychiatric severity and inflammation in metabolic risk assessment. The random forest model improved prediction accuracy by 9% when psychiatric variables were included, reinforcing the role of psychiatric burden in metabolic dysfunction. These findings align with emerging studies demonstrating that AI-driven models can effectively identify schizophrenia subtypes and predict treatment response based on biochemical markers (17, 18, 19, 20).

One of the most striking findings was the strong association between behavioral dysregulation (irritability, agitation) and metabolic abnormalities. Participants exhibiting irritability had a 4.72-fold increased risk of hyperglycemia, suggesting that emotional distress may exacerbate metabolic disturbances via neuroinflammatory mechanisms. Elevated CRP levels in these individuals further support the role of systemic inflammation in linking psychiatric and metabolic dysfunction. These results emphasize the need for integrated screening of metabolic health in patients with severe behavioral symptoms.

Evidence suggests that glucose metabolism alterations are not merely side effects of antipsychotic medication but may be intrinsic to schizophrenia pathophysiology (3). Lee *et al.* (2023) identified impaired glucose metabolism as a potential biomarker for psychiatric disorders, with machine learning models achieving high predictive accuracy in stratifying patient risk (21). Similarly, Zaki *et al.* (2022) developed diagnostic models using peripheral blood markers, reinforcing the role of metabolic parameters in schizophrenia symptoma tology (22).

Our findings support a multidisciplinary approach to schizophrenia management, incorporating metabolic and inflammatory assessments alongside psychiatric evaluations. Routine screening of fasting glucose, lipid profiles, and inflammatory markers may help identify high-risk patients and enable early interventions. Future research should explore longitudinal models to assess whether improving metabolic health leads to reductions in psychiatric symptom severity.

This study has several limitations. The cross-sectional design prevents causal conclusions regarding the relationship between glycemic dysregulation and psychiatric severity. The sample size (N=70) is relatively small, limiting generalizability. Additionally, while machine learning models demonstrated moderate predictive performance ($R^2 > 0.4$), further optimization and validation are needed before clinical application. Future studies should incorporate neuroimaging and multi-omics approaches to improve model accuracy and enhance precision psychiatry strategies.

CONCLUSIONS

This study reinforces schizophrenia as a multisystemic disorder, highlighting the link between metabolic dysregulation, systemic inflammation, and psychiatric severity. Glycemic abnormalities and inflammatory markers correlated with higher PANSS and BPRS scores, suggesting a metabolic-neuroimmune axis in symptom progression. Machine learning models identified glyce-

mic status and inflammation as key predictors, with behavioral dysregulation (irritability, agitation) strongly linked to hyperglycemia.

These findings support integrating metabolic screening into schizophrenia management, as targeted metabolic interventions may improve psychiatric outcomes. Despite limitations, future research should adopt longitudinal and multi-omics approaches to refine predictive models. Leveraging AI-driven biomarker discovery can advance precision psychiatry, leading to personalized, data-driven interventions for schizophrenia patients.

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CONFLICT OF INTEREST AND FUNDING

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