

Clinical Severity Scales Differentiate Psychotic from Non- Psychotic Adolescent Depression: A Cross-Sectional Study

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Abstract

Background: Adolescents with major depressive disorder (MDD) who exhibit psychotic symptoms (MDD-Psy) represent a severe subtype associated with greater clinical burden and poorer outcomes. However, objective biomarkers to differentiate MDD-Psy from non-psychotic MDD (MDD-NonPsy) remain limited. This study investigated clinical characteristics and peripheral biomarkers that may distinguish these two subgroups.

Methods: A total of 131 adolescents with major depressive episode were enrolled, including 63 MDD-NonPsy and 68 MDD-Psy. Demographic characteristics, clinical severity scales (Kutcher Adolescent Depression Scale KDAS and Brief Psychiatric Rating Scale BPRS), and peripheral blood biomarkers (complete blood count, biochemical parameters, thyroid function) were assessed. Group comparisons, correlation analyses, binary logistic regression, and receiver operating characteristic (ROC) analyses were performed. False discovery rate (FDR) correction was applied for multiple comparisons.

Results: The MDD-Psy group exhibited significantly higher scores on KDAS total (16.21 ± 2.44 vs. 14.86 ± 1.93 , $p=0.001$), BPRS total (34.56 ± 2.90 vs. 29.19 ± 1.54 , $p<0.001$), and all BPRS subscales except anxiety-depression and emotional withdrawal. After FDR correction, no peripheral biomarker significantly differed between groups. Correlation analyses revealed that hostility remained positively correlated with albumin/globulin ratio after FDR correction ($r=0.272$, $q=0.048$). Binary logistic regression identified thought disturbance as the only independent predictor of psychotic symptoms (OR=14.07, 95% CI: 2.88–68.72, $p=0.001$). ROC analysis demonstrated excellent discriminative performance for thought disturbance (AUC=0.975) and BPRS total score (AUC=0.951).

Conclusions: Clinical severity scales, particularly thought disturbance and BPRS total score, effectively differentiate adolescents with MDD-Psy from those with MDD-NonPsy. While peripheral biomarkers showed limited discriminative value after multiple comparison correction, the association between hostility and albumin/globulin ratio warrants further investigation. These findings support the utility of structured clinical assessment in identifying psychotic features in adolescent depression.

1 Introduction

Major depressive disorder (MDD) represents one of the most prevalent and debilitating psychiatric conditions globally, affecting approximately 15–18% of individuals across their lifetime¹. By 2030, MDD is projected to become the leading cause of disability in high-income countries, imposing substantial personal suffering and socioeconomic burden². Among the various clinical presentations of depression, the presence of psychotic features—including delusions and hallucinations—delineates a particularly severe subtype associated with greater clinical complexity, poorer treatment outcomes, and heightened mortality risk^{3,4}. The recognition and appropriate management of psychotic depression remain critical clinical imperatives, yet significant challenges persist in its accurate identification, particularly in vulnerable populations such as adolescents.

Psychotic depression, initially conceptualized as existing at the severe end of a unidimensional depression continuum, is now recognized as a distinct diagnostic entity characterized by the co-occurrence of mood disturbance and psychosis as independent but interacting pathological dimensions³. Epidemiological studies indicate that approximately 9–20% of adults with MDD experience psychotic features during depressive episodes⁵, with comparable prevalence rates observed in adolescent populations⁶. The clinical significance of this distinction cannot be overstated: individuals with psychotic depression demonstrate longer episode durations, higher recurrence rates, more frequent hospitalizations, greater functional impairment, and substantially elevated suicide risk compared to their non-psychotic counterparts^{3,7,8}. A longitudinal study by Tohen and colleagues found that while 86% of first-episode psychotic depression patients achieved syndromal recovery within two years, only 35% attained functional recovery, underscoring the profound and lasting impact of this condition⁹.

In adolescent populations specifically, the convergence of developmental vulnerability and severe psychopathology presents unique diagnostic and therapeutic challenges. Adolescents with MDD and psychotic features (MDD-Psy) exhibit more severe depressive symptomatology, higher rates of suicidal ideation and attempts, and poorer short-term outcomes compared to those without psychotic features^{6,10,11}. The presence of psychotic symptoms in depressed youth has been associated with increased perceived burdensomeness, thwarted belongingness, and reduced social protective factors—mechanisms that may partially explain the elevated suicide risk observed in this population¹². Furthermore, psychotic features in adolescent depression predict poorer response to conventional antidepressant therapy and may necessitate more intensive treatment approaches, including antipsychotic augmentation or electroconvulsive therapy^{13,14}. Despite these clinical implications, psychotic symptoms in depressed adolescents often remain under-recognized in routine clinical practice, contributing to diagnostic delays and suboptimal treatment allocation^{5,15}.

The pathophysiological mechanisms underlying psychotic depression remain incompletely understood, though accumulating evidence implicates multiple interacting biological systems. Neurobiological investigations have revealed alterations in hypothalamic-pituitary-adrenal axis function, dopaminergic and glutamatergic neurotransmission, and structural and functional brain connectivity in patients with psychotic depression compared to non-psychotic MDD^{16–18}. More recently, inflammatory processes have emerged as potential contributors to the pathophysiology of both mood and psychotic disorders^{19,20}. Elevated levels of pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP), have been documented in individuals with MDD and psychotic disorders, with some studies suggesting that inflammation may be particularly relevant to the psychotic subtype^{21–23}. A prospective population-based study by Khandaker and colleagues demonstrated that higher childhood IL-6 levels were associated with increased risk of both depression and psychotic experiences in young adulthood, supporting a potential causal role for inflammation in the development of psychosis among depressed individuals²⁴.

The search for objective biomarkers to differentiate psychotic from non-psychotic depression has intensified in recent years, driven by the promise of precision psychiatry and the need for biologically-informed diagnostic tools ^{25,26}. Peripheral blood-based markers offer particular advantages due to their accessibility, cost-effectiveness, and potential for integration into routine clinical practice ²⁷. Several lines of investigation have explored inflammatory markers, including complete blood count parameters such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), as proxies for systemic inflammation in psychiatric disorders ^{28,29}. In patients with severe MDD with psychotic features, Kayhan and colleagues reported elevated PLR compared to those with non-psychotic depression, suggesting that platelet-related inflammatory markers may hold particular relevance for the psychotic subtype ³⁰. Similarly, alterations in thyroid function tests have been described in mood disorders, with some evidence linking thyroid dysfunction to psychotic symptoms ^{31,32}. Case reports have documented psychosis as a presenting feature of hypothyroidism, which resolved with thyroid hormone replacement, highlighting the potential importance of thyroid axis assessment in patients presenting with psychotic features ^{33,34}.

Despite these promising leads, the literature on peripheral biomarkers in psychotic depression remains characterized by substantial heterogeneity and methodological limitations. Studies have varied considerably in their diagnostic criteria, sample composition, biomarker selection, and statistical approaches, yielding inconsistent and often conflicting findings ^{35,36}. Many investigations have been limited by small sample sizes, lack of correction for multiple comparisons, inadequate control for potential confounders such as medication exposure and comorbid medical conditions, and failure to validate findings in independent cohorts ^{25,37}. Furthermore, the vast majority of biomarker studies have focused on adult populations, with a striking paucity of research examining peripheral biomarkers specifically in adolescents with psychotic depression ³⁸. Given the developmental differences in immune function, neuroendocrine regulation, and medication exposure between adolescents and adults, findings from adult studies cannot be directly extrapolated to younger populations ³⁹. A recent study by Li and colleagues examining electrolytes and complete blood count in Chinese adolescents with depression found that while calcium, white blood cell count, and neutrophil count were associated with psychotic symptoms, the predictive model demonstrated poor discriminative performance (AUC = 0.598), highlighting the limitations of conventional peripheral markers in this population ⁴⁰.

The clinical assessment of psychotic features in depression has traditionally relied on structured diagnostic interviews and symptom rating scales, which remain the gold standard for identification and severity assessment ⁴¹. Instruments such as the Brief Psychiatric Rating Scale (BPRS) and depression-specific scales with psychosis items provide systematic frameworks for evaluating the presence and severity of psychotic symptoms, as well as associated dimensions of psychopathology ⁴². In adolescents, the Kutcher Adolescent Depression Scale (KDas) has been widely used to assess depressive symptom severity, though its utility in detecting psychotic features specifically has received limited investigation ⁴³. The comparative performance of clinical severity scales versus peripheral

biomarkers in differentiating psychotic from non-psychotic depression has not been systematically evaluated in adolescent populations, representing a significant gap in the literature.

Given the substantial clinical implications of accurately identifying psychotic features in depressed adolescents, and the limitations of current evidence regarding objective biomarkers in this population, rigorous investigation of both clinical and biological markers is urgently needed. Such research should employ robust methodological approaches, including adequate sample sizes, appropriate statistical correction for multiple comparisons, and comprehensive assessment of potential confounding variables⁴⁴. The use of false discovery rate (FDR) correction, as recommended for multiple comparison correction in biomarker discovery studies, is particularly important to minimize type I error while maintaining adequate statistical power. Furthermore, examination of the relationships between clinical symptoms and biological measures may provide insights into pathophysiological mechanisms and identify novel targets for intervention.

The present study was designed to address these knowledge gaps by comprehensively evaluating clinical characteristics and peripheral blood biomarkers in a well-characterized sample of adolescents with major depressive episode, comparing those with and without psychotic features. We hypothesized that: (1) adolescents with MDD-Psy would exhibit more severe psychopathology across multiple clinical domains compared to those with MDD-NonPsy, as reflected in higher scores on depression and general psychopathology rating scales; (2) specific peripheral blood markers, including complete blood count parameters, biochemical indices, and thyroid function tests, would differ between the two groups, potentially reflecting underlying inflammatory or neuroendocrine alterations; and (3) the combination of clinical scale scores and peripheral biomarkers would demonstrate enhanced ability to differentiate MDD-Psy from MDD-NonPsy compared to either modality alone. By applying rigorous statistical methods including FDR correction for multiple comparisons, binary logistic regression, and receiver operating characteristic (ROC) analysis, we sought to identify robust and reproducible predictors of psychotic features in adolescent depression. The ultimate goal of this investigation is to provide evidence-based guidance for clinical assessment and to inform future research directions in the search for clinically useful biomarkers in this vulnerable population.

2 Materials and Methods

2.1 Study Design and Participants

This cross-sectional study was conducted in Zigong Mental Health Center from December 2023 to April 2025. A total of 131 adolescents aged 13–18 years presenting with a major depressive episode were consecutively recruited from inpatient and outpatient psychiatric services. All participants were evaluated using the Structured Clinical Interview for DSM-5 (SCID-5) to confirm the diagnosis of MDD⁴⁵. Participants were allocated into two groups based on the presence or absence of psychotic features: the MDD with psychotic symptoms group (MDD-Psy, n = 68) and the MDD without psychotic symptoms

group (MDD-NonPsy, n = 63). Psychotic features were defined according to DSM-5 criteria as the presence of delusions and/or hallucinations during the current depressive episode.

Inclusion criteria were: (1) age between 13 and 18 years; (2) meeting DSM-5 criteria for a current major depressive episode; (3) ability to understand and complete all study assessments; and (4) provision of written informed consent from participants and their legal guardians. Exclusion criteria included: (1) lifetime diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, or other primary psychotic disorders; (2) intellectual disability or autism spectrum disorder; (3) current or past history of substance use disorder; (4) significant neurological disorders (e.g., epilepsy, traumatic brain injury, central nervous system infections); (5) acute or chronic infectious diseases within the past month; (6) autoimmune disorders or any medical condition known to affect inflammatory markers; (7) use of immunosuppressive or anti-inflammatory medications within the past month; and (8) pregnancy or lactation.

The study protocol was designed to compare clinical characteristics and peripheral biomarker profiles between adolescents with MDD-Psy and MDD-NonPsy, with the primary aim of identifying factors that differentiate these two clinically distinct subgroups.

2.2 Ethical Considerations

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki (2013 revision) and its later amendments [4]. The research protocol was approved by the Ethics Committee of the Zigong Mental Health Center (Approval No. 2023021). All participants and their legal guardians received detailed information about the study objectives, procedures, potential risks, and benefits. Written informed consent was obtained from all legal guardians, and written assent was obtained from all adolescent participants prior to enrollment. Participants were assured of their right to withdraw from the study at any time without consequences for their clinical care.

2.3 Clinical Assessment

All participants underwent comprehensive clinical assessment conducted by trained psychiatrists with at least five years of clinical experience. Diagnostic confirmation was established using the SCID-5. Demographic and clinical characteristics, including sex, age, body mass index (BMI), years of education, age at illness onset, illness duration, episode status (first episode vs. recurrent), family history of mental disorders, and medication status (antidepressant use, antipsychotic use, mood stabilizer use, or being unmedicated), were collected through structured interviews and medical record review.

Depressive symptom severity was assessed using the KDAS⁴⁶, a 11-item clinician-rated instrument specifically developed and validated for adolescents with depression. The KDAS evaluates core depressive symptoms including sad mood, loss of interest, lack of drive, restlessness, and suicidal ideation, with each item scored from 0 (no symptoms) to 3 (severe symptoms).

Psychotic and general psychopathology symptoms were evaluated using the BPRS⁴⁷, a widely used 18-item instrument that assesses a broad range of psychiatric symptoms. Each item is rated on a 7-point Likert scale from 1 (not present) to 7 (extremely severe). Based on established factor analytic studies in psychotic and affective disorders, BPRS items were grouped into five subscales: (1) thought disturbance; (2) activation; (3) hostility; (4) anxiety-depression; and (5) emotional withdrawal. Total BPRS score and subscale scores were calculated for each participant. All clinical assessments were conducted within 72 hours of admission or study enrollment, and raters were blinded to participants' laboratory results.

2.4 Blood Sample Collection and Laboratory Analysis

Peripheral venous blood samples were collected from all participants between 7:00 and 9:00 AM after an overnight fast of at least 10 hours to minimize circadian variation in biochemical parameters. Samples were drawn into vacuum tubes containing EDTA for complete blood count analysis and into plain tubes for serum separation. Blood samples were processed within 2 hours of collection.

Complete blood count parameters, including white blood cell count (WBC), neutrophil count and percentage, lymphocyte count and percentage, monocyte count and percentage, eosinophil count and percentage, basophil count and percentage, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count, mean platelet volume, platelet distribution width, and platelet-large cell ratio, were measured using an automated hematology analyzer (XN-9000, Sysmex Corporation, Kobe, Japan).

Biochemical parameters, including total protein, albumin, globulin, albumin/globulin ratio, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, total bilirubin, direct bilirubin, blood urea nitrogen, creatinine, uric acid, fasting glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and electrolytes (sodium, potassium, chloride, calcium, phosphorus, magnesium), were measured using an automated chemistry analyzer (AU5800, Beckman Coulter, Brea, CA, USA).

Thyroid function parameters, including triiodothyronine (T3), thyroxine (T4), free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH), were measured using electrochemiluminescence immunoassays on a Cobas 6000 analyzer (Roche Diagnostics, Mannheim, Germany). Serum cortisol levels were measured using the same platform. All laboratory analyses were performed by laboratory technicians blinded to clinical diagnoses, and standard quality control procedures were followed throughout the study period.

2.5 Statistical Analysis

Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). Normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR) as appropriate. Categorical variables were expressed as frequencies and percentages.

Group comparisons between MDD-Psy and MDD-NonPsy were performed using independent samples t-tests for normally distributed continuous variables, Mann-Whitney U tests for non-normally distributed continuous variables, and chi-square tests or Fisher's exact tests for categorical variables as appropriate. Given the number of comparisons performed for laboratory parameters, the Benjamini-Hochberg FDR correction was applied to control for type I error inflation due to multiple testing. FDR-adjusted q-values < 0.05 were considered statistically significant for these comparisons.

Pearson or Spearman correlation coefficients, as appropriate based on data distribution, were calculated to examine relationships between clinical severity scales (KDas total and subscales, BPRS total and subscales) and peripheral biomarkers. To address multiple testing in correlation analyses, FDR correction was applied across all correlation coefficients, with $q < 0.05$ indicating statistical significance.

Binary logistic regression analysis with forward stepwise selection (likelihood ratio method) was performed to identify independent predictors of psychotic symptoms (MDD-Psy vs. MDD-NonPsy). All clinical scale scores (KDas total, lack of drive, restlessness, BPRS total, thought disturbance, activation, hostility) and peripheral biomarkers that showed nominal significance ($p < 0.10$) in univariate analyses were entered as candidate variables. The Hosmer-Lemeshow goodness-of-fit test was used to assess model fit, with $p > 0.05$ indicating adequate fit. Results were expressed as odds ratios (OR) with 95% confidence intervals (CI) and associated p-values.

ROC curve analysis was conducted to evaluate the discriminative ability of clinical severity scales in differentiating MDD-Psy from MDD-NonPsy. Area under the curve (AUC) values were calculated with 95% CIs, and the optimal cut-off points were determined using the Youden index (sensitivity + specificity - 1). AUC values were interpreted as excellent (0.90-1.00), good (0.80-0.89), fair (0.70-0.79), poor (0.60-0.69), or fail (0.50-0.59). Statistical significance for ROC analyses was set at $p < 0.05$.

All statistical tests were two-tailed, and significance was set at $p < 0.05$ unless otherwise specified for FDR-corrected analyses. Sample size estimation was performed a priori based on previous studies examining clinical and biomarker differences in psychotic versus non-psychotic depression. Assuming a medium effect size (Cohen's $d = 0.5$) for group differences in primary outcome measures, with $\alpha = 0.05$ and power = 0.80, a minimum of 64 participants per group was required. Our final sample of 131 participants exceeded this requirement, providing adequate statistical power for the planned analyses.

3 Results

3.1 Baseline Demographic and Clinical Characteristics

The demographic and clinical characteristics of the 131 adolescents are summarized in Table 1. The two groups were comparable in sex distribution (female: 79.4% vs. 80.9%; $\chi^2=0.05$, $p=0.830$), age (18.03 ± 4.40 vs. 16.84 ± 4.68 years; $t=1.662$, $p=0.099$), BMI, and education (all $p>0.05$). No significant differences were observed in age at onset, illness duration, or family history of mental disorders (all $p>0.05$). However, the MDD-Psy group had a higher proportion of recurrent episodes (55.9% vs. 39.7%; $\chi^2=4.56$, $p=0.033$) and

greater antipsychotic use (38.2% vs. 9.5%; $\chi^2=14.89$, $p<0.001$), while fewer were unmedicated (29.4% vs. 52.4%; $\chi^2=7.11$, $p=0.008$). Regarding clinical severity, the MDD-Psy group exhibited significantly higher KDAS total scores (16.21 ± 2.44 vs. 14.86 ± 1.93 ; $t=-3.488$, $p=0.001$), driven by elevated lack of drive ($p=0.003$) and restlessness ($p=0.010$) subscale scores. They also showed higher BPRS total scores (34.56 ± 2.90 vs. 29.19 ± 1.54 ; $t=-13.081$, $p<0.001$), with significantly greater thought disturbance, activation, and hostility (all $p<0.01$). In contrast, anxiety-depression and emotional withdrawal subscales did not differ between groups (both $p>0.05$).

3.2 Comparison of Laboratory Parameters Between Groups

The comparisons of hematological, biochemical, and thyroid function parameters between the MDD-NonPsy and MDD-Psy groups are presented in Table 2. Overall, no statistically significant differences were observed in any laboratory parameter after applying the Benjamini–Hochberg FDR correction for multiple comparisons (all $q > 0.05$).

In unadjusted analyses, several parameters showed nominal significance. The MDD-NonPsy group exhibited a higher neutrophil percentage ($61.72\% \pm 12.27\%$ vs. $56.67\% \pm 13.01\%$; $t = 2.273$, $p = 0.025$) and a lower lymphocyte percentage ($29.58\% \pm 11.28\%$ vs. $33.94\% \pm 11.82\%$; $t = -2.152$, $p = 0.033$) compared to the MDD-Psy group. The albumin/globulin ratio was lower in the MDD-NonPsy group (1.63 ± 0.24 vs. 1.71 ± 0.22 ; $t = -2.090$, $p = 0.039$), while triiodothyronine levels were higher in the MDD-Psy group (1.18 ± 0.17 nmol/L vs. 1.11 ± 0.16 nmol/L; $t = -2.368$, $p = 0.019$). Globulin levels tended to be higher in the MDD-NonPsy group, approaching significance (28.25 ± 4.48 g/L vs. 26.87 ± 3.64 g/L; $t = 1.939$, $p = 0.055$). However, none of these differences survived FDR correction (all $q > 0.05$). All other measured parameters, including white blood cell and differential counts, lipid profiles, thyroid hormones (thyroxine, free triiodothyronine, free thyroxine, thyroid-stimulating hormone), and cortisol, were comparable between the two groups (all uncorrected $p > 0.05$).

3.3 Correlations between Clinical Severity and Peripheral Biomarkers

The correlations between clinical severity scales and peripheral biomarkers are presented in Table 3. In unadjusted analyses, several modest but statistically significant correlations were observed. The albumin/globulin ratio was positively correlated with BPRS total score ($r = 0.238$, $p = 0.006$), thought disturbance ($r = 0.236$, $p = 0.007$), and hostility ($r = 0.272$, $p = 0.002$). Triiodothyronine showed positive correlations with BPRS total ($r = 0.174$, $p = 0.048$) and thought disturbance ($r = 0.201$, $p = 0.022$). Neutrophil percentage was negatively correlated with thought disturbance ($r = -0.172$, $p = 0.050$). No significant correlations were found between any biomarker and KDAS total, lack of drive, or activation (all $p > 0.05$).

After applying the Benjamini–Hochberg FDR correction for 24 comparisons, only the correlation between hostility and albumin/globulin ratio remained statistically significant ($q = 0.048$). The scatter plot depicting this relationship is presented in Figure 1. All other correlations did not survive FDR correction ($q > 0.05$).

3.4 Binary Logistic Regression Analysis for Predicting Psychotic Symptoms

A binary logistic regression analysis was performed to identify independent predictors of psychotic symptoms (MDD-Psy vs. MDD-NonPsy), with all clinical scale scores and peripheral biomarkers entered as covariates. The results are presented in Table 4. The Hosmer–Lemeshow test indicated adequate model fit ($\chi^2 = 7.386$, $df = 8$, $p = 0.496$).

Among all variables examined, only thought disturbance emerged as a significant independent predictor of psychotic symptoms. Higher scores on the thought disturbance subscale were associated with a markedly increased likelihood of belonging to the MDD-Psy group ($B = 2.644$, $SE = 0.809$, Wald $\chi^2 = 10.670$, $p = 0.001$, $OR = 14.066$, 95% CI: 2.879–68.718). Specifically, each one-point increase in thought disturbance score increased the odds of psychotic symptoms by approximately 13-fold.

None of the other clinical scale scores—including KDAS total, lack of drive, BPRS total, activation, or hostility—demonstrated significant predictive value (all $p > 0.05$). Similarly, no peripheral biomarkers, including neutrophil percentage, lymphocyte percentage, albumin/globulin ratio, or triiodothyronine, were significantly associated with psychotic symptoms in the multivariable model (all $p > 0.05$).

3.5 Receiver Operating Characteristic Analysis for Differentiating Psychotic Symptoms

To evaluate the discriminative ability of clinical severity scales in distinguishing adolescents with MDD-Psy from those with MDD-NonPsy, ROC analyses were performed. The area under the curve (AUC) values for each scale are presented in Figure 2.

Among the scales examined, thought disturbance demonstrated excellent discriminative performance, with an AUC of 0.975 ($p < 0.001$). The BPRS total score also showed high accuracy (AUC = 0.951, $p < 0.001$), followed by hostility (AUC = 0.834, $p < 0.001$). Moderate discriminative ability was observed for KDAS total score (AUC = 0.679, $p < 0.001$), activation (AUC = 0.647, $p = 0.004$), lack of drive (AUC = 0.642, $p = 0.005$), and restlessness (AUC = 0.634, $p = 0.008$). All scales achieved statistically significant separation between the two groups.

4 Discussion

The present study investigated clinical characteristics and peripheral blood biomarkers in a well-characterized sample of 131 adolescents with major depressive episode, comparing those with and without psychotic features. Our major findings can be summarized as follows: First, adolescents with MDD-Psy exhibited significantly greater clinical severity across multiple domains, including higher KDAS total scores, elevated BPRS total scores, and specifically increased scores on thought disturbance, activation, and hostility subscales compared to the MDD-NonPsy group. Second, although several peripheral biomarkers showed nominal differences between groups in unadjusted analyses—including neutrophil percentage, lymphocyte percentage, albumin/globulin ratio, and triiodothyronine—none of these differences remained statistically significant after applying rigorous FDR correction for multiple

comparisons. Third, correlation analyses revealed that after FDR correction, only the positive association between hostility and albumin/globulin ratio remained significant ($r = 0.272$, $q = 0.048$), suggesting a potential relationship between this specific symptom dimension and inflammatory/nutritional status. Fourth, binary logistic regression identified thought disturbance as the sole independent predictor of psychotic symptoms, with each one-point increase in this subscale conferring a 14-fold increase in the odds of belonging to the MDD-Psy group (OR = 14.07, 95% CI: 2.88–68.72, $p = 0.001$). Finally, receiver operating characteristic analysis demonstrated excellent discriminative performance for thought disturbance (AUC = 0.975) and BPRS total score (AUC = 0.951), while the KDAS and its subscales showed only modest discriminative ability. Collectively, these findings indicate that clinical severity scales—particularly those assessing thought disturbance—effectively differentiate adolescents with psychotic depression from their non-psychotic counterparts, whereas routine peripheral blood biomarkers have limited discriminative value in this population after appropriate statistical correction.

Our finding that adolescents with MDD-Psy exhibit more severe psychopathology aligns with previous studies documenting greater symptom burden in psychotic depression^{3,6}. The marked elevation in thought disturbance, activation, and hostility subscales parallels the work of Crebbin and colleagues, who reported that first-episode psychotic depression patients display severe symptomatology comparable to schizophrenia⁸. The specificity of thought disturbance as a predictor in our logistic regression model (OR = 14.07) underscores the centrality of formal thought pathology in differentiating psychotic from non-psychotic depression, consistent with diagnostic guidelines emphasizing delusions and hallucinations as core distinguishing features³. The similar levels of anxiety-depression across groups support the conceptualization of psychotic depression as a distinct subtype characterized by psychotic features superimposed on a depressive diathesis, rather than simply more severe depression.

The significantly higher rate of recurrent episodes in our MDD-Psy group (55.9% vs. 39.7%) is consistent with previous literature documenting a more chronic course in psychotic depression. Barbuti and colleagues found that high-recurrence MDD was associated with psychotic features⁴⁸, and Mazzarini and colleagues reported that recurrent MDD showed higher rates of psychotic features compared to non-recurrent depression⁴⁹. The marked difference in antipsychotic use between groups (38.2% vs. 9.5%) reflects appropriate clinical practice^{3,5} and aligns with findings from Gaudiano and colleagues showing higher antipsychotic prescription rates in hospitalized psychotic depression patients.

The absence of significant biomarker differences after FDR correction warrants careful consideration. Our negative findings are consistent with Li and colleagues, who found that while calcium, white blood cell count, and neutrophil count showed some association with psychotic symptoms in adolescents, the predictive model demonstrated poor discriminative performance (AUC = 0.598)⁴⁰. Similarly, Morrens and colleagues, in their meta-analysis of immune-cognitive relationships in mood and psychotic disorders, found only very weak associations between blood-based immune markers and clinical outcomes, with evidence of significant publication bias inflating positive findings³⁵. The contrast with some adult studies reporting elevated platelet-to-lymphocyte ratios³⁰ or altered neutrophil-to-lymphocyte ratios²⁸ in

psychotic populations may reflect developmental differences in immune function between adolescents and adults³⁹, medication effects⁵⁰, or the importance of rigorous multiple comparison correction.

The correlation between hostility and albumin/globulin ratio that survived FDR correction ($r = 0.272$) is intriguing, though the modest effect size indicates it explains only approximately 7% of variance. The albumin/globulin ratio reflects both nutritional status and inflammatory activity²³. Previous research has linked hostility and aggression to immune dysfunction^{19,20}, and Mongan and colleagues found associations between psychotic disorder and elevated inflammatory markers²¹. The persistence of this correlation after correction suggests it may represent a true signal worthy of further investigation, though the clinical significance remains uncertain.

The excellent discriminative performance of thought disturbance (AUC = 0.975) and BPRS total score (AUC = 0.951) compared to the modest performance of KDAS (AUC = 0.679) highlights the importance of using instruments that explicitly assess psychotic symptoms when evaluating depressed adolescents^{11,41}. The KDAS, designed to assess depressive symptoms broadly, lacks items specifically probing psychotic features⁴³, whereas the BPRS thought disturbance subscale directly assesses core psychotic phenomena. This finding supports DSM-5's approach of specifying psychotic features as a separate specifier rather than incorporating psychosis into the severity dimension⁶.

The focus on adolescents in this study addresses a significant gap in the literature, as most biomarker research in psychotic depression has been conducted in adult populations^{38,39}. Developmental differences in immune function, neuroendocrine regulation, and brain maturation may influence the relationship between peripheral biomarkers and psychopathology in ways that are not yet well understood. Our findings suggest that routine peripheral biomarkers may have even less utility in adolescents than in adults, though direct age-comparative studies are needed to confirm this impression. The correlation between hostility and albumin/globulin ratio that survived correction, while modest, provides a potential clue for future research exploring developmental trajectories of inflammation-psychopathology relationships. Longitudinal studies tracking both clinical symptoms and biomarkers across the transition from adolescence to adulthood would be particularly valuable.

In summary, the methodological strengths of this study—including rigorous FDR correction, multi-modal statistical analysis, comprehensive clinical assessment, and focus on an understudied adolescent population—provide confidence in our primary conclusion: structured clinical assessment, particularly using instruments that explicitly evaluate psychotic symptoms, effectively differentiates adolescents with psychotic depression from those without psychotic features. Routine peripheral blood biomarkers, in contrast, demonstrate limited discriminative value after appropriate statistical correction, with the possible exception of the hostility-albumin/globulin ratio association, which warrants further investigation. These findings support the continued centrality of careful phenomenological assessment in psychiatric diagnosis and highlight the challenges of biomarker discovery in this population.

Several limitations of the present study should be acknowledged when interpreting our findings. First, the cross-sectional design precludes examination of causal relationships between clinical symptoms, biomarkers, and psychotic features; longitudinal studies are needed to determine whether the observed differences predict illness course, treatment response, and long-term outcomes^{9,13}. Second, the significant difference in antipsychotic use between groups (38.2% vs. 9.5%) represents a major potential confounder, as antipsychotic medications can influence inflammatory markers, metabolic parameters, and thyroid function^{50,51}. Studies of medication-naïve first-episode patients would be valuable to determine whether biomarker patterns differ in the absence of treatment effects^{28,29}. Third, while our sample size was adequate to detect medium-to-large effect sizes, it may have been insufficient to identify smaller biomarker differences after FDR correction; larger multi-center studies are needed to definitively establish whether any peripheral biomarkers have clinically meaningful associations with psychotic features in adolescent depression^{37,44}. Fourth, our focus on routine clinical laboratory parameters may not capture the most relevant biological processes underlying psychotic depression; more sophisticated biomarkers—including inflammatory cytokines^{21,22}, proteomic profiles^{16,37}, and neuroimaging measures¹⁷—may demonstrate stronger associations. Fifth, recruitment from a single center in China may limit generalizability, and multi-center international collaborations are needed to establish robustness across diverse populations^{5,52}. Sixth, unmeasured confounders such as childhood trauma⁵³, socioeconomic status⁵⁴, and physical activity⁵⁵ may influence both clinical presentation and biomarker levels. Finally, the absence of a healthy control group limits our ability to determine whether biomarker values in either patient group deviate from population norms^{31,32}. Future research should employ longitudinal designs, expand to novel biomarker platforms, investigate the hostility-albumin/globulin ratio association in independent cohorts, examine medication-naïve patients, integrate multi-modal markers using machine learning approaches, and conduct cross-cultural studies to validate and extend our findings.

5 Conclusions

This study demonstrates that clinical severity scales, particularly the thought disturbance subscale of the Brief Psychiatric Rating Scale and the BPRS total score, effectively differentiate adolescents with major depressive disorder with psychotic features from those without psychosis. The excellent discriminative performance of these clinical instruments (AUC = 0.975 and 0.951, respectively) supports their continued use as frontline tools for identifying psychotic features in adolescent depression, a task of critical clinical importance given the poorer outcomes and elevated suicide risk associated with this subtype. In contrast, routine peripheral blood biomarkers—including complete blood count parameters, biochemical indices, and thyroid function tests—show limited discriminative value after rigorous statistical correction for multiple comparisons, suggesting that these measures are not useful as standalone diagnostic biomarkers in this population. The modest but significant correlation between hostility and albumin/globulin ratio that survived false discovery rate correction provides a tentative clue for future research exploring the biological underpinnings of specific symptom dimensions, though

replication in independent cohorts is essential before drawing firm conclusions. Future studies should employ longitudinal designs to examine whether baseline clinical characteristics predict illness course and treatment outcomes, expand biomarker discovery efforts to include more sophisticated measures such as inflammatory cytokines, proteomic profiles, and neuroimaging markers, and investigate the potential for integrating clinical and biological data using machine learning approaches to develop personalized treatment strategies for this vulnerable adolescent population.

Abbreviations

AUC

Area under the curve

BMI

Body mass index

BPRS

Brief Psychiatric Rating Scale

CI

Confidence interval

CRP

C-reactive protein

DSM-5

Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

FDR

False discovery rate

FT3

Free triiodothyronine

FT4

Free thyroxine

IL-6

Interleukin-6

IQR

Interquartile range

KDAS

Kutcher Adolescent Depression Scale

MDD

Major depressive disorder

MDD-NonPsy

Major depressive disorder without psychotic symptoms

MDD-Psy

Major depressive disorder with psychotic symptoms

NLR

Neutrophil-to-lymphocyte ratio
OR
Odds ratio
PLR
Platelet-to-lymphocyte ratio
ROC
Receiver operating characteristic
SCID-5
Structured Clinical Interview for DSM-5
T3
Triiodothyronine
T4
Thyroxine
TNF- α
Tumor necrosis factor-alpha
TSH
Thyroid-stimulating hormone
WBC
White blood cell

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki (2013 revision) and its later amendments. The research protocol was approved by the Ethics Committee of the Zigong Mental Health Center (Approval No. 2023021). All participants and their legal guardians received detailed information about the study objectives, procedures, potential risks, and benefits. Written informed consent was obtained from all legal guardians, and written assent was obtained from all adolescent participants prior to enrollment. Participants were assured of their right to withdraw from the study at any time without consequences for their clinical care.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available due to patient confidentiality and ethical restrictions but are available from the corresponding author on reasonable request, subject to approval by the institutional ethics committee of Zigong Mental Health Center.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author Contributions

Dexin Liao, Jin Peng, and Ming Liu contributed equally to this work and share first authorship.

Dexin Liao: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft. Jin Peng: Methodology, Investigation, Data curation, Writing – original draft. Ming Liu: Methodology, Investigation, Data curation, Writing – original draft. Yudiao Liang: Investigation, Formal analysis, Writing – original draft. Lei Wang: Investigation, Data curation. Sha Zhang: Investigation, Resources. Kezhi Liu: Conceptualization, Supervision, Project administration, Funding acquisition, Writing – review & editing. Youguo Tan: Conceptualization, Supervision, Writing – review & editing. All authors have read and agreed to the published version of the manuscript.

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Tables

Table 1. Demographic and Clinical Characteristics of Adolescents with Major Depressive Episode, Stratified by Psychotic Symptoms

Characteristic	MDD-NonPsy (n = 63)	MDD-Psy (n = 68)	Statistic	P value
Demographics				
Female, n (%)	50 (79.4)	55 (80.9)	$\chi^2 = 0.05$	0.830
Age (years), mean $\pm$ SD	18.03 $\pm$ 4.40	16.84 $\pm$ 4.68	t = 1.662	0.099
BMI (kg/m ²), mean $\pm$ SD	21.5 $\pm$ 3.2	21.8 $\pm$ 3.5	t = -0.52	0.604
Education (years), mean $\pm$ SD	11.2 $\pm$ 2.1	11.5 $\pm$ 2.3	t = -0.78	0.437
Clinical History				
Age at onset (years), mean $\pm$ SD	20.1 $\pm$ 7.0	18.3 $\pm$ 7.2	t = 1.45	0.149
Illness duration (months), median (IQR)	8.5 (4.0–14.0)	9.0 (5.0–16.0)	Z = -1.24	0.215
Episode status, n (%)			$\chi^2 = 4.56$	0.033
First episode	38 (60.3)	30 (44.1)		
Recurrent episode	25 (39.7)	38 (55.9)		
Family history of mental disorders, n (%)	12 (19.0)	16 (23.5)	$\chi^2 = 0.39$	0.532
Medication Status, n (%)				
Antidepressant use	24 (38.1)	29 (42.6)	$\chi^2 = 0.28$	0.598
Antipsychotic use	6 (9.5)	26 (38.2)	$\chi^2 = 14.89$	<0.001
Mood stabilizer use	3 (4.8)	7 (10.3)	$\chi^2 = 1.44$	0.230
Unmedicated	33 (52.4)	20 (29.4)	$\chi^2 = 7.11$	0.008
Clinical Severity (at enrollment)				
KDAS total score, mean $\pm$ SD	14.86 $\pm$ 1.93	16.21 $\pm$ 2.44	t = -3.488	0.001
Lack of drive, mean $\pm$ SD	6.75 $\pm$ 1.14	7.49 $\pm$ 1.60	t = -3.031	0.003
Restlessness, mean $\pm$ SD	8.11 $\pm$ 1.30	8.72 $\pm$ 1.38	t = -2.599	0.010
BPRS total score, mean $\pm$ SD	29.19 $\pm$ 1.54	34.56 $\pm$ 2.90	t = -13.081	<0.001
Anxiety–depression, mean $\pm$ SD	14.35 $\pm$ 0.83	14.19 $\pm$ 0.94	t = 1.022	0.309
Emotional withdrawal, mean $\pm$ SD	4.05 $\pm$ 0.22	4.12 $\pm$ 0.47	t = -1.075	0.285
Thought disturbance, mean $\pm$ SD	4.30 $\pm$ 0.78	7.56 $\pm$ 1.43	t = -16.037	<0.001

Activation, mean ± SD	3.22 ± 0.46	3.56 ± 0.63	t = -3.472	0.001
Hostility, mean ± SD	3.27 ± 0.60	5.13 ± 1.42	t = -9.617	<0.001

Abbreviations: MDD-NonPsy, major depressive episode without psychotic symptoms; MDD-Psy, major depressive episode with psychotic symptoms; KDAS, Kutcher Adolescent Depression Scale; BPRS, Brief Psychiatric Rating Scale; IQR, interquartile range.

Table 2. Comparison of Laboratory Parameters Between MDD-NonPsy and MDD-Psy Groups

Parameter	MDD-NonPsy (n = 63)	MDD-Psy (n = 68)	t	p (uncorrected)	q value (FDR corrected)
Hematological parameters					
White blood cell count ($\times 10^9/L$)	6.88 $\pm$ 2.39	6.49 $\pm$ 1.95	1.037	0.302	0.534
Neutrophil count ($\times 10^9/L$)	4.38 $\pm$ 2.09	3.83 $\pm$ 1.95	1.551	0.123	0.354
Lymphocyte count ($\times 10^9/L$)	1.91 $\pm$ 0.79	2.07 $\pm$ 0.66	– 1.229	0.221	0.462
Monocyte count ($\times 10^9/L$)	0.41 $\pm$ 0.18	0.42 $\pm$ 0.15	– 0.216	0.829	0.867
Eosinophil count ($\times 10^9/L$)	0.14 $\pm$ 0.14	0.14 $\pm$ 0.11	– 0.045	0.964	0.964
Basophil count ($\times 10^9/L$)	0.03 $\pm$ 0.02	0.03 $\pm$ 0.02	– 0.486	0.628	0.803
Neutrophil percentage (%)	61.72 $\pm$ 12.27	56.67 $\pm$ 13.01	2.273	0.025	0.288
Lymphocyte percentage (%)	29.58 $\pm$ 11.28	33.94 $\pm$ 11.82	– 2.152	0.033	0.253
Monocyte percentage (%)	6.18 $\pm$ 1.98	6.68 $\pm$ 2.28	– 1.315	0.191	0.439
Eosinophil percentage (%)	2.14 $\pm$ 1.93	2.28 $\pm$ 1.75	– 0.443	0.659	0.758
Basophil percentage (%)	0.39 $\pm$ 0.25	0.44 $\pm$ 0.30	– 0.995	0.322	0.494
Biochemical parameters					
Total protein (g/L)	73.34 $\pm$ 6.67	72.20 $\pm$ 5.91	1.036	0.302	0.496
Albumin (g/L)	45.09 $\pm$ 3.43	45.33 $\pm$ 3.21	– 0.413	0.680	0.745
Globulin (g/L)	28.25 $\pm$ 4.48	26.87 $\pm$ 3.64	1.939	0.055	0.253
Albumin/globulin ratio	1.63 $\pm$ 0.24	1.71 $\pm$ 0.22	– 2.090	0.039	0.224
High-density lipoprotein (mmol/L)	1.52 $\pm$ 0.36	1.46 $\pm$ 0.36	0.989	0.324	0.466
Low-density lipoprotein (mmol/L)	2.63 $\pm$ 0.75	2.48 $\pm$ 0.84	1.074	0.285	0.546

Thyroid function					
Triiodothyronine (nmol/L)	1.11 ± 0.16	1.18±0.17	– 2.368	0.019	0.437
Thyroxine (nmol/L)	12.77±5.28	11.35±5.15	1.561	0.121	0.398
Free triiodothyronine (pmol/L)	5.36±0.60	5.54±0.61	– 1.766	0.080	0.307
Free thyroxine (pmol/L)	17.04±2.38	16.83±2.39	0.509	0.612	0.828
Thyroid-stimulating hormone (mIU/L)	2.69±1.58	2.34±1.14	1.420 [†]	0.158	0.404
Other					
Cortisol (nmol/L)	12.30±5.58	11.79±6.91	0.461	0.645	0.781

Note: Data are presented as mean ± standard deviation. Sample sizes: MDD-NonPsy group n = 63 for all parameters; MDD-Psy group n = 68 for most parameters. The q values were calculated using the Benjamini–Hochberg FDR method for 23 comparisons. No parameter remained statistically significant after FDR correction (all q > 0.05).

Table 3. Correlations between Clinical Severity Scales and Peripheral Biomarkers

Scale	Neutrophil %	Lymphocyte %	Albumin/Globulin ratio	Triiodothyronine
KDAS total	–0.068	0.097	0.047	0.034
Lack of drive	0.032	–0.003	0.037	0.005
BPRS total	–0.075	0.073	0.238**	0.174*
Thought disturbance	–0.172*	0.172	0.236**	0.201*
Activation	0.020	–0.006	0.027	0.122
Hostility	–0.082	0.060	0.272**	0.157

Note: Values are Pearson correlation coefficients (r).p < 0.05, ** p < 0.01 (two-tailed, uncorrected). After applying the Benjamini–Hochberg FDR correction for 24 comparisons, only the correlation between Hostility and Albumin/Globulin ratio remained significant (q = 0.048). All other correlations were no longer significant after FDR correction (q > 0.05).

Abbreviations: KDAS, Kutcher Adolescent Depression Scale; BPRS, Brief Psychiatric Rating Scale.

Table 4. Binary Logistic Regression Analysis for Predicting Psychotic Symptoms

Variable	B	SE	Wald χ^2	p	OR	95% CI for OR
KDAS total score	−0.107	0.440	0.059	0.808	0.899	0.379–2.130
Lack of drive	0.725	0.714	1.030	0.310	2.065	0.509–8.377
BPRS total score	−0.173	0.599	0.084	0.772	0.841	0.260–2.719
Thought disturbance	2.644	0.809	10.670	0.001	14.066	2.879–68.718
Activation	0.715	0.814	0.772	0.380	2.045	0.415–10.087
Hostility	0.123	0.724	0.029	0.865	1.131	0.274–4.671
Neutrophil %	−0.043	0.142	0.093	0.761	0.958	0.725–1.265
Lymphocyte %	−0.008	0.158	0.003	0.958	0.992	0.728–1.351
Albumin/globulin ratio	−2.240	1.866	1.442	0.230	0.106	0.003–4.123
Triiodothyronine	0.895	2.652	0.114	0.736	2.448	0.014–442.969
Constant	−10.238	18.025	0.323	0.570	0.000	–

Note: Hosmer–Lemeshow goodness-of-fit test: $\chi^2 = 7.386$, $df = 8$, $p = 0.496$, indicating adequate model fit. Abbreviations: KDAS, Kutcher Adolescent Depression Scale; BPRS, Brief Psychiatric Rating Scale; OR, odds ratio; CI, confidence interval.

Figures

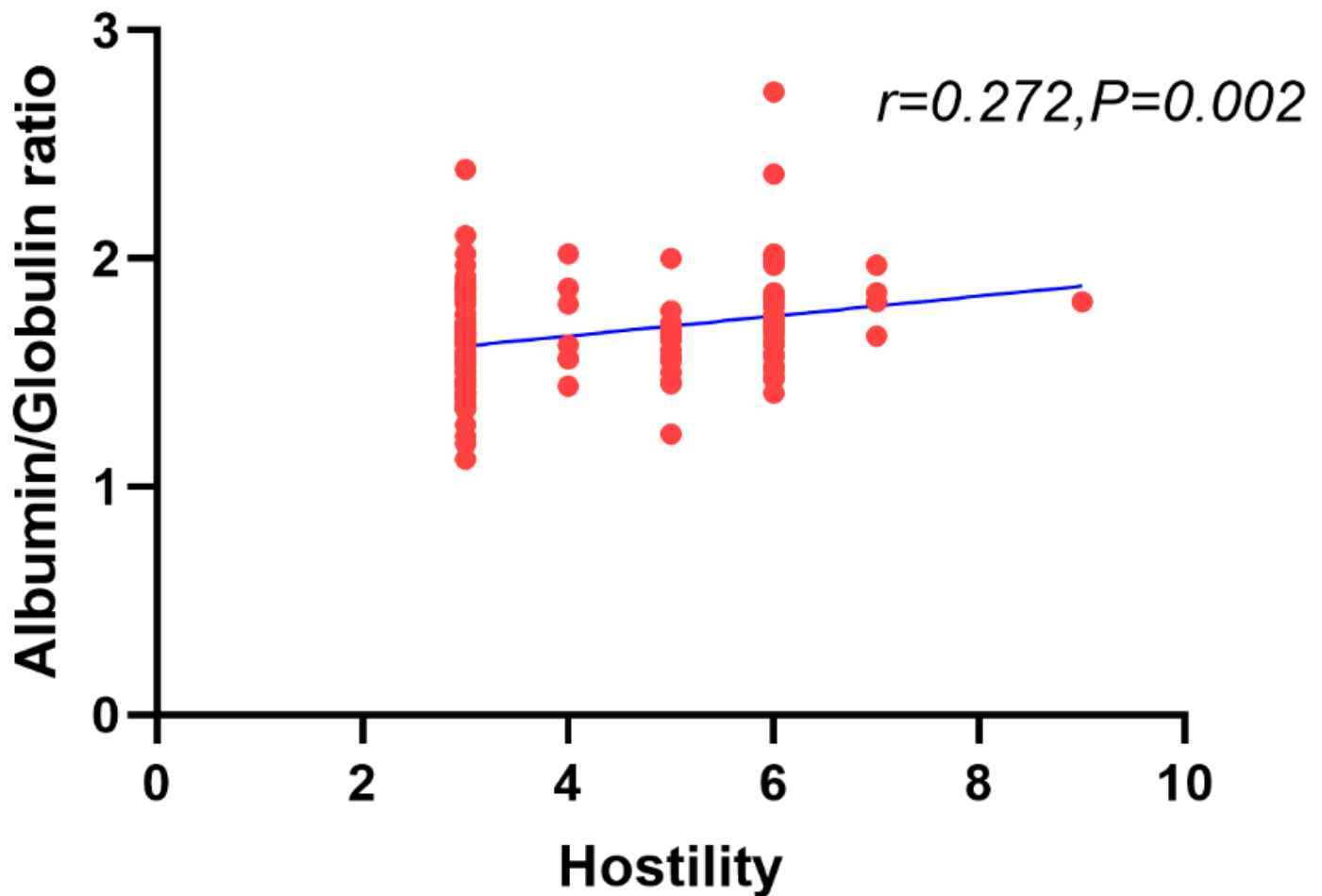


Figure 1

Scatter Plot Showing the Correlation between Hostility Scores and Albumin/Globulin Ratio

The scatter plot illustrates the relationship between hostility subscale scores from the BPRS and albumin/globulin ratio in the combined sample of adolescents with major depressive episode. Each data point represents an individual participant. The regression line indicates a positive correlation, with higher hostility scores associated with increased albumin/globulin ratios. Pearson correlation analysis revealed a modest but statistically significant positive correlation ($r = 0.272$, $p = 0.002$, uncorrected). After applying the Benjamini–Hochberg FDR correction for multiple comparisons, this correlation remained significant ($q = 0.048$).

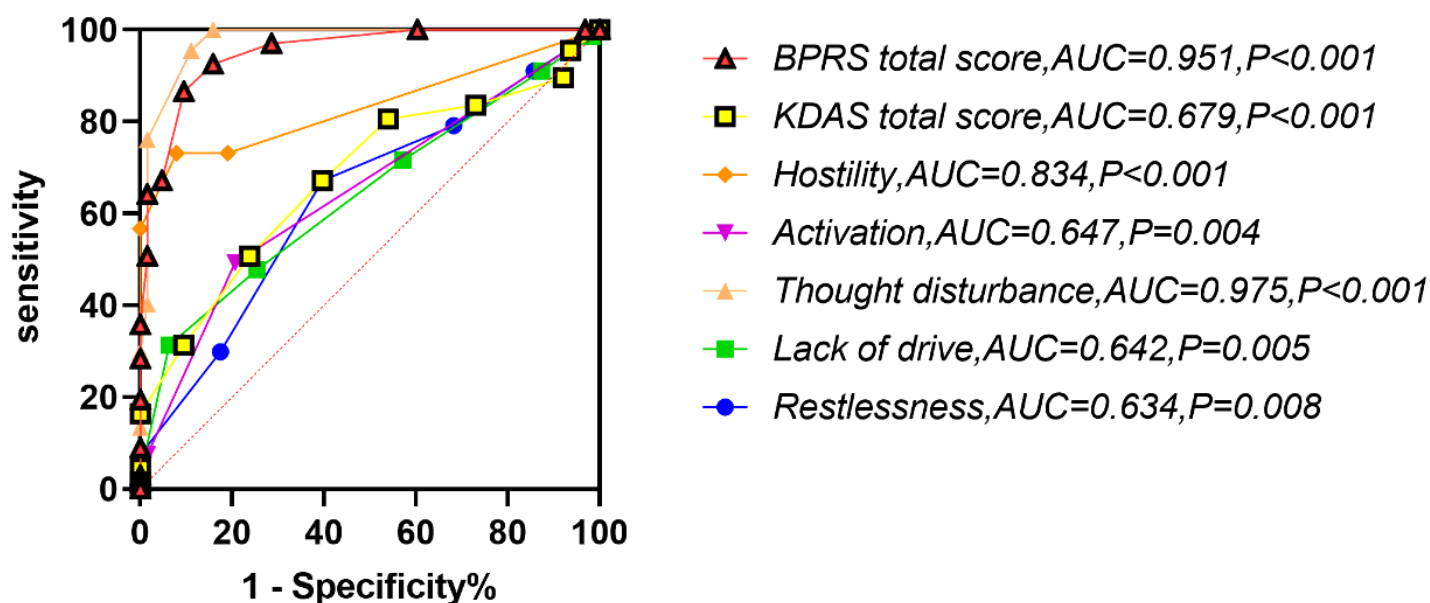


Figure 2

Receiver Operating Characteristic Curves for Clinical Severity Scales in Differentiating MDD-Psy from MDD-NonPsy

ROC curves illustrate the discriminative ability of individual clinical severity scales to distinguish adolescents with major depressive episode with psychotic symptoms (MDD-Psy) from those without psychotic symptoms (MDD-NonPsy). Among the scales examined, thought disturbance demonstrated the highest discriminative performance (AUC = 0.975, $p < 0.001$), followed by BPRS total score (AUC = 0.951, $p < 0.001$) and hostility (AUC = 0.834, $p < 0.001$). Moderate discriminative ability was observed for KDAS total score (AUC = 0.679, $p < 0.001$), activation (AUC = 0.647, $p = 0.004$), lack of drive (AUC = 0.642, $p = 0.005$), and restlessness (AUC = 0.634, $p = 0.008$). All scales achieved statistically significant separation between the two groups.