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Original Article

Clinical utility of the HALP Index in the classification of schizophrenia: Logistic regression and ROC analysis

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Abstract

Aim: This study compared the Hemoglobin–Albumin–Lymphocyte–Platelet (HALP) index between individuals with schizophrenia and healthy controls and evaluated its discriminative performance in distinguishing schizophrenia.

Materials and Methods: Demographic and laboratory data from 69 patients with schizophrenia and 62 healthy controls were analyzed. A multivariable binary logistic regression model predicting schizophrenia diagnosis included logHALP, age, sex, smoking status, and C-reactive protein (CRP). Model discrimination was evaluated using receiver operating characteristic (ROC) analysis and the corresponding area under the curve (AUC). In the schizophrenia group, associations between the HALP index and cognitive performance or functional outcomes were examined using Spearman's correlation.

Results: Among 131 participants (schizophrenia, n=69; control, n=62), the median HALP index was significantly lower in the schizophrenia group (51.88 [18.89–116.69]) compared with controls (63.47 [31.57–167.54]; p<0.001). In multivariable logistic regression, logHALP demonstrated an independent protective association (B= −3.181; odds ratio [OR]=0.042; 95% confidence interval [CI]: 0.002–0.886; p=0.042), whereas CRP emerged as an independent risk marker (B=1.077; OR=2.936; 95% CI: 1.742–4.947; p<0.001). ROC analysis based on predicted probabilities yielded an AUC of 0.832 (95% CI: 0.763–0.900); as this value is derived from a case–control sample without prevalence information, it reflects discriminative rather than diagnostic performance. Using the Youden index, an optimal cutoff of approximately 0.45 provided 78.3% sensitivity and 74.2% specificity.

Conclusion: Lower HALP index values and elevated CRP levels are independently associated with schizophrenia and may serve as supportive biomarkers to aid in clinical classification and risk stratification.

Keywords: Schizophrenia, hemoglobin–albumin–lymphocyte–platelet, C-reactive protein, biomarker

INTRODUCTION

Schizophrenia is a severe mental disorder that typically emerges in early adulthood (1), follows a chronic and heterogeneous course (2), and substantially impairs overall functioning (3). In addition to hallmark neuropsychiatric symptoms—including delusions, hallucinations, and disorganized thinking—the disorder is associated with widespread systemic consequences such as reduced life expectancy, elevated cardiometabolic burden, altered dietary patterns, sedentary behavior, and medication-related adverse effects (4–6). Although much of the mortality gap is attributable to cardiovascular causes (6), accumulating evidence implicates chronic low-grade inflammation, oxidative stress, and immune dysregulation as key mechanisms underlying this excess risk (7). Prior studies have documented elevations in pro-inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) (8,9); shifts in neutrophil-to-lymphocyte balance (10) and platelet activation (11); and reductions in nutritional biomarkers, including serum albumin (12). Clinically, these biological perturbations intersect with the persistence of negative symptoms, cognitive decline, development of metabolic syndrome, and substantial heterogeneity in treatment response (13,14).

In schizophrenia, the immune–metabolic axis develops against a "multi-hit" background: genetic susceptibility,

neurodevelopmental vulnerability, and environmental stressors interact with nutritional deficiencies, medication side effects, lifestyle factors, and both infectious and sterile inflammatory triggers to drive the immune system toward chronic activation (15–19). This sustained activation influences erythropoiesis, plasma protein synthesis, and adaptive immune function, while also reinforcing the hemostatic–inflammatory interface through altered platelet kinetics and reactivity (8,10–12). Consequently, rather than relying on any single biomarker, composite indices that integrate signals across multiple physiological systems may offer superior clinical predictive value.

The HALP index ([Hemoglobin×Albumin×Lymphocyte] ÷ Platelet) provides a practical, readily obtainable measure that summarizes nutritional, inflammatory, and immune status within a single formula, with higher HALP values generally indicating better nutritional status and preserved immune reserve. (20). In oncology, HALP has been extensively evaluated as a prognostic marker of tumor burden, treatment response, and survival (21–23). In the neurodegenerative context, higher HALP values have been associated with increased familial risk in Parkinson's disease (24). Additionally, the prognostic utility of HALP has been documented in stroke (25) and various cardiovascular conditions (26).

Given the increased prevalence of anemia in schizophrenia (27), susceptibility to hypoalbuminemia (12), alterations in lymphocyte subset dynamics (28), and platelet dysfunction (11), the HALP index could plausibly serve as a biological "fingerprint" in this population. However, despite its growing use in oncology and cardiovascular and neurological disorders, to our knowledge HALP has not yet been systematically investigated in schizophrenia. Specifically, no prior study has evaluated its ability to discriminate patients with schizophrenia from healthy controls or its diagnostic or discriminative capacity, or its associations with clinical symptom severity or treatment characteristics. From a clinical standpoint, an accessible, low-cost, and easily interpretable composite marker could support risk stratification, biopsychosocial care planning, and the identification of adjunctive intervention needs, particularly at initial assessment and throughout follow-up.

Elevated CRP levels have also been consistently reported in schizophrenia (9). Joint evaluation of HALP and CRP may enhance clinical discrimination by simultaneously capturing the burden of systemic inflammation and the integrated status of the nutrition–immune axis. In individuals with persistent negative symptoms or progressive cognitive decline, inflammatory activity and nutritional deficiencies may interact bidirectionally to exacerbate functional deterioration. Accordingly, concurrent interpretation of these biological trajectories may help inform more personalized treatment strategies.

Although related composite ratios—for example, the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR)—have been examined in psychiatric research, a systematic evidence gap remains regarding the discriminative or predictive value of HALP in schizophrenia. This gap presents an opportunity to evaluate the clinical utility of a clinic-friendly index that can be readily measured and calculated within routine outpatient workflows.

Primary aim: To compare HALP levels between patients with schizophrenia and healthy individuals and to evaluate the ability of HALP to discriminate schizophrenia.

Secondary aim: To determine whether the association between logHALP and schizophrenia remains independent after adjustment for clinically relevant covariates, including CRP, age, sex, and smoking status.

Exploratory aim: Within the schizophrenia group, to examine the direction and magnitude of associations between HALP, CRP, cognitive performance, and functional status, thereby elucidating potential links among nutritional–inflammatory signatures, cognition, and clinical functioning. Additionally, we sought to quantify the discriminative performance of HALP-based predicted probabilities using ROC/AUC analysis and to propose a clinically balanced threshold based on the Youden criterion.

MATERIALS AND METHODS

Ethics Approval

This study was approved by the Karabük University Non-Interventional Clinical Research Ethics Committee on 09 January 2025 (Decision No: 2024/2086) and was conducted in accordance with the principles of the Declaration of Helsinki.

Study Design and Sample

This single-center, retrospective case–control study included patients diagnosed with schizophrenia who presented to the psychiatry outpatient clinic between 2020 and 2024. The control group comprised healthy individuals with comparable demographic characteristics whose routine laboratory results were obtained from medical records during the same period. These individuals were evaluated in the psychiatry outpatient clinic for military medical board assessments or pre-employment health examinations.

In our center, complete blood count and biochemistry tests in both groups were requested as part of routine baseline medical evaluation (e.g., before initiating or adjusting psychotropic medication, and during military medical board or pre-employment health assessments), rather than specifically for the investigation of suspected chronic medical disease.

Inclusion Criteria

Schizophrenia group

- Age 18–65 years
- Outpatient visits between January 2020 and November 2024 with a documented diagnosis of schizophrenia

- Availability of complete blood count and biochemistry results

Control group

- Age 18–65 years
- Psychiatry outpatient visits between January 2020 and November 2024 for military medical board evaluations or pre-employment health board reports
- Availability of complete blood count and biochemistry results
- No history of psychiatric, neurological, or chronic systemic disease

Exclusion Criteria

- Missing laboratory data
- History of inflammatory disease, neurological disease, cancer, or diabetes
- Documentation in the electronic medical record of active infection or corticosteroid use within the month preceding laboratory testing

In the control group, the absence of current psychiatric disorders and chronic systemic illnesses was confirmed through detailed review of electronic medical records, including prior diagnoses, medication lists, and consultation notes.

Data Collection

Because of the retrospective design, all data were extracted from electronic hospital records and patient files. Extracted variables included laboratory parameters obtained concurrently with clinical evaluations, sociodemographic characteristics, and standardized assessment scores: the Positive and Negative Syndrome Scale (PANSS), the Montreal Cognitive Assessment (MoCA), and the Global Assessment of Functioning (GAF).

However, data on important potential confounders—such as body mass index (BMI), specific metabolic syndrome parameters (e.g., waist circumference, lipid profile, and fasting glucose), dietary patterns, additional inflammatory markers beyond CRP, and detailed antipsychotic subclasses and doses—were not systematically available in the hospital records and therefore could not be included in the analyses.

Sociodemographic Information Form

Demographic variables—including age, sex, marital status, education level, employment status, and smoking—were extracted using a researcher-designed sociodemographic information form and through review of prior medical records. For the schizophrenia group, additional clinical variables (current medications and doses, age at illness onset, and history of psychiatric hospitalization) were also collected.

Positive and Negative Syndrome Scale (PANSS)

The PANSS is a clinician-administered, 30-item instrument designed to comprehensively assess schizophrenia symptoms across positive, negative, and general psychopathology domains. Each item is rated on a 7-point scale. The scale yields three core subscale scores (Positive, Negative, General Psychopathology) and a total score computed as their sum. Inter-rater reliability is generally high, with coefficients typically in the 0.80s (29,30).

Montreal Cognitive Assessment (MoCA)

The MoCA is a brief cognitive screening tool developed to detect mild cognitive impairment (MCI) and early Alzheimer's disease (31). The 30-point assessment evaluates attention, executive functions, memory, language, visuospatial skills, abstraction, and orientation. A total score of ≥26 is commonly considered within normal limits, with education-based adjustments (e.g., adding 1–2 points for lower educational attainment). Psychometrically, the MoCA demonstrates strong sensitivity (≈87.5–100%) and specificity (≈69.2–74.1%) for detecting MCI or dementia and has been validated in multiple languages, including Turkish (31,32).

Global Assessment of Functioning (GAF)

The GAF is a clinician-rated, single-item measure that summarizes psychological, social, and occupational functioning on a 0–100 scale. Listed under Axis V in the DSM-IV, it has been widely used in clinical and research settings to provide a global overview of symptom severity and functional impairment (33).

Laboratory Analyses and HALP Index

Biochemistry and complete blood count parameters for patients and healthy controls were retrieved from hospital laboratory records. The HALP index was calculated (after unit harmonization) according to the following formula, consistent with prior definitions (34):

$$\mathbf{HALP = (Hemoglobin \times Albumin \times Lymphocyte\ Count) \div Platelet\ Count}$$

Statistical Analysis

Normality of continuous variables was assessed using the Kolmogorov–Smirnov test and distributional plots (histograms and Q–Q plots), and homogeneity of variances was evaluated using Levene's test. Depending on distributional characteristics, between-group comparisons were performed using the independent samples t-test or the Mann–Whitney U-test, while categorical variables were compared using the chi-square test. In the schizophrenia group, associations between HALP or CRP levels and cognitive performance or functioning were examined using Spearman's rank-order correlation. Because HALP showed a right-skewed distribution, a log-transformed variable (logHALP) was used in the regression analyses, whereas CRP, although right-skewed, was entered in its original scale to preserve the clinical interpretability of the odds ratios.

For diagnostic discrimination, a binary logistic regression model was constructed with diagnosis (schizophrenia vs. healthy control) as the dependent variable and logHALP, age, sex, smoking status, and CRP as independent variables. Model

fit and explanatory power were evaluated using Omnibus χ^2, −2 Log Likelihood (−2LL), Cox & Snell R^2, and Nagelkerke R^2; calibration was assessed using the Hosmer–Lemeshow test, with a significant result indicating miscalibration between predicted and observed probabilities.

Classification performance was summarized using accuracy, sensitivity, and specificity. Discrimination was quantified using the area under the ROC curve (AUC, 95% CI), and the optimal cutoff value was identified using the Youden index. A two-sided $p<0.05$ was considered statistically significant. To aid interpretation of clinical significance, effect sizes were calculated for between-group comparisons (Cohen's d for parametric tests and $r=Z/\sqrt{N}$ for non-parametric tests).

RESULTS

Sample Characteristics and Demographic/Laboratory Comparisons

A total of 131 individuals were included in the study (schizophrenia: n=69; healthy controls: n=62). The groups did not differ significantly in age (p=0.203) or sex (p=0.111), whereas marital status (p<0.001) and employment status (p<0.001) showed significant between-group differences.

In laboratory parameters, CRP levels were markedly higher in the schizophrenia group (p<0.001; r=0.56). Conversely, hemoglobin (132 vs. 155 g/L; p<0.001; r=0.49), lymphocyte count (2.10 vs. 2.50×10⁹/L; p=0.002; r=0.27), and total WBC count (7,200 vs. 8,000×10⁹/L; p=0.026; r=0.19) were significantly lower in patients with schizophrenia. Albumin (p=0.233) and platelet counts (p=0.646) did not differ significantly between groups.

The HALP index was substantially lower in the schizophrenia group (51.88 [18.89–116.69]) compared with healthy controls (63.47 [31.57–167.54]; p<0.001; r=0.33). Group-level comparisons are provided in Table 1.

Clinical Characteristics of the Schizophrenia Group

Among individuals with schizophrenia, the median duration since illness onset was 9 years, and the median treatment duration was 8 years. The median antipsychotic dose (chlorpromazine-equivalent) was 600 mg/day (range: 150–1740). Clinical assessment scores were as follows: PANSS total 78 ± 17.6, MoCA 14.9 ± 6.9, and GAF 50 (30–80). Detailed characteristics are presented in Table 2.

Correlation Analyses and Multivariable Modeling

Correlation analyses examining associations between PANSS, MoCA, and GAF scores and CRP and HALP indices in the schizophrenia group revealed no statistically significant relationships (all p>0.05). Full results are summarized in Table 3.

Logistic Regression Analysis

In the multivariable logistic regression model adjusting for age, sex, smoking status, and CRP, logHALP emerged as an independent protective factor (B= −3.181; OR=0.042; 95% CI, 0.002–0.886; p=0.042). CRP was identified as an independent risk factor (B=1.077; OR=2.936; 95% CI, 1.742–4.947; p<0.001). Age (p=0.265), sex (p=0.837), and smoking (p=0.624) were not significant predictors of diagnostic status.

Model diagnostics indicated good overall model performance: Omnibus $\chi^2(5)=54.203$ (p<0.001), −2LL=127.027, Cox & Snell $R^2=0.339$, and Nagelkerke $R^2=0.452$. However, the Hosmer–Lemeshow test indicated poor calibration ($\chi^2(8)=29.881$, p<0.001).

Multicollinearity among the predictors (logHALP, CRP, age, sex, and smoking status) was assessed using variance inflation factors (VIFs); all VIF values were below 2 (range: 1.08–1.85), indicating no relevant multicollinearity, including between CRP and logHALP.

At a 50% probability threshold, the model achieved 74.0% overall classification accuracy (sensitivity 73.9%, specificity 74.2%). Discrimination was strong, with an ROC–AUC of 0.832 (95% CI, 0.763–0.900). Based on the Youden index, an optimal predicted-probability cutoff of approximately 0.45 yielded 78.3% sensitivity and 74.2% specificity. Full regression results are displayed in Table 4, and the ROC curve is presented in Figure 1.

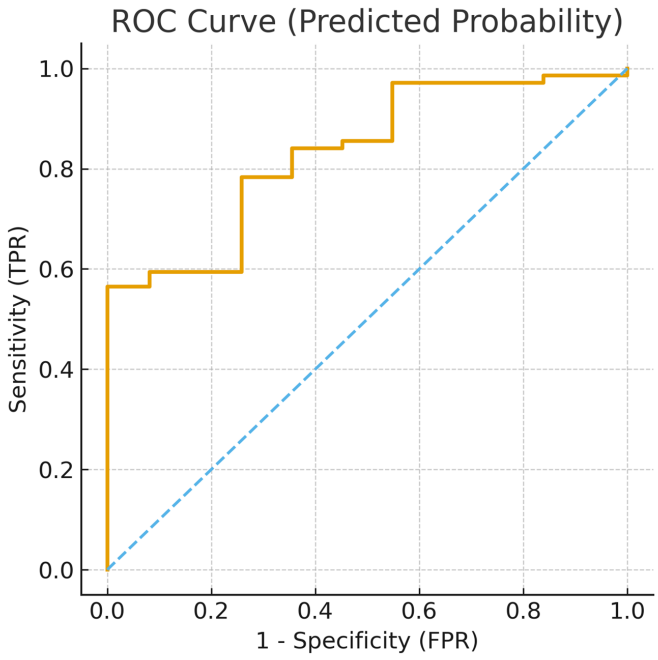

Figure 1. ROC curve based on predicted probabilities from the logistic model (Schizophrenia vs. healthy controls).

Note: The solid line shows the ROC curve of the logistic regression model including logHALP and CRP (adjusted for age, sex, and smoking); the dashed diagonal represents the line of chance. Discrimination is high: AUC=0.832 (SE=0.035; 95% CI:0.763–0.900; p<0.001). The Youden J–derived approximate optimal probability threshold is ≈0.45, yielding 78.3% sensitivity and 74.2% specificity. This threshold is sample-specific and should be re-estimated in other populations.

Table 1. Comparison of demographic and laboratory characteristics between patients with schizophrenia and healthy controls

Variables		Schizophrenia (n=69)	Healthy controls (n=62)	P
Age		40 (20-64)	38 (22-56)	.203[a]
Sex (n)	**Female**	34	22	.111[b]
	Male	35	40	
Marital status (n)	**Married**	17	37	**<.001[b]**
	Single	39	18	
	Widowed	7	3	
	Separated	6	4	
Educational status (n)	**Primary school**	34	23	.326[b]
	High school	28	33	
	University	7	6	
Employment status (n)	**Employed**	12	46	**<.001[b]**
	Unemployed	57	16	
Smoking (n)	**No**	25	29	.221[b]
	Yes	44	33	
WBC (×10³/µL)		7200 (3800-19900)	8000 (6300-12190)	.026[a]
Neutrophils (×10³/µL)		4400 (2100-14400)	4700 (3800-7640)	.066[a]
Hemoglobin (g/L)		132 (92-169)	155 (121-164)	<.001[a]
Lymphocytes (×10³/µL)		2.10 (0.70-4.10)	2.50 (1.90-3.84)	.002[a]
Platelets (×10³/µL)		243.23±71.75	248.11± 48.33	.646[c]
Urea (mg/dL)		23 (10-53)	33 (18-45)	<.001[a]
Creatinine (mg/dL)		0.80 (0.50-2.00)	0.86 (0.50-1.00)	.129[a]
AST (U/L)		19.00 (5.00-56.00)	23.00 (13.00-29.00)	.023[a]
ALT (U/L)		17.00 (6.00-44.00)	21.00 (12.00-37.00)	.043[a]
GGT (U/L)		18.00 (5.00-95.00)	18.00 (14.00-41.00)	.985[a]
Albumin (g/L)		44.00 (36.00-53.00)	45.00 (39.00-53.00)	.233[a]
CRP (mg/L)		2.40 (0.30-17.50)	0.70 (.00-3.00)	<.001[a]
HALP index		51.88 (18.89-116.69)	63.47 (31.57-167.54)	<.001[a]

[a] Mann–Whitney U test; [b] Chi-square test; [c] Student's t-test.
Variables not normally distributed are presented as median (min–max); normally distributed variables as mean ± SD. WBC: white blood cells; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; CRP: C-reactive protein; HALP: Hemoglobin–Albumin–Lymphocyte–Platelet index. $p < 0.05$ considered statistically significant

Table 2. Clinical characteristics and scale scores of the schizophrenia group (n = 69)

Variables	n= 69
Time since illness onset (years)	9 (0-35)
Time since treatment initiation (years)	8 (0-35)
Number of psychiatric hospitalizations (n)	2 (0-20)
Current antipsychotic dose (CPZ-equivalent, mg/day)	600 (150-1740)
PANNS TOTAL	78±17.56
PANNS POZITIVE	20 (10-36)
PANNS NEGATIVE	18 (6- 39)
PANNS GENERAL	36.62±9.57
MoCA	14.92±6.91
GAF	50(30- 80)

Data are presented as median (min–max) for variables not conforming to a normal distribution and as mean ± SD for normally distributed variables. CPZ: chlorpromazine; PANSS: Positive and Negative Syndrome Scale; MoCA: Montreal Cognitive Assessment; GAF: Global Assessment of Functioning

Table 3. Spearman correlations between clinical scales and biomarkers in the schizophrenia group

Variable / Metric	PANSS Total	PANSS positive	PANSS negative	PANSS general	MoCA	GAF	CRP	HALP
PANSS Total — Correlation Coefficient	1.000	.335**	.815**	.900**	.022	-.517**	.072	-.072
PANSS positive — Correlation Coefficient	.335**	1.000	-.061	.207	.137	-.415**	.068	-.073
PANSS negative — Correlation Coefficient	.815**	-.061	1.000	.690**	-.054	-.360**	.036	.043
PANSS general— Correlation Coefficient	.900**	.207	.690**	1.000	.152	-.372**	.048	-.080
MoCA — Correlation Coefficient	.022	.137	-.054	.152	1.000	.266*	.229	-.178
GAF — Correlation Coefficient	-.517**	-.415**	-.360**	-.372**	.266*	1.000	.125	-.002
CRP — Correlation Coefficient	.072	.068	.036	.048	.229	.125	1.000	-.149
HALP — Correlation Coefficient	-.072	-.073	.043	-.080	-.178	-.002	-.149	1.000

Values represent Spearman's rho correlation coefficients using two-tailed significance testing. *p < 0.05; **p < 0.01. PANSS: Positive and Negative Syndrome Scale; MoCA: Montreal Cognitive Assessment; GAF: Global Assessment of Functioning; CRP: C-reactive protein; HALP: Hemoglobin–Albumin–Lymphocyte–Platelet index

Table 4. Adjusted logistic regression and ROC analysis comparing patients with schizophrenia and healthy controls

Section	Metric	Value	p / Statistic	Note
Model (adjusted)	logHALP (B, OR, p)	B= -3.181; OR=0.042	p=.042	95% CI 0.002–0.886
Model (adjusted)	CRP (B, OR, p)	B= 1.077; OR=2.936	p<.001	95% CI 1.742–4.947
Model (adjusted)	Age / Sex / Smoke	—	ns	p=.265/.837/.624
Goodness of fit	Omnibus χ^2 (sd, p)	54.203 (5.<.001)	—	—
Goodness of fit	−2 Log Likelihood	127.027	—	—
Goodness of fit	Cox & Snell R^2 / Nagelkerke R^2	0.339 / 0.452	—	—
Calibration	Hosmer–Lemeshow χ^2 (sd, p)	29.881 (8.<.001)	—	calibration warning
Classification	Accuracy / Sensitivity / Specificity	74.0% / 73.9% / 74.2%	Cut=.50	—
ROC	AUC (SE, %95 CI)	0.832 (0.035; 0.763–0.900)	p<.001	—
ROC	Youden- optimal threshold ($\hat{P}\geq$)	≈0.45	—	Sensitivity; 78.3%; Specificity 74.2%

Dependent variable: diagnosis status (schizophrenia = 1, healthy = 0). Covariates included age, sex, and smoking; primary predictors were logHALP and CRP. B=logistic regression coefficient; OR = exp(B); CI = confidence interval. Goodness-of-fit indices include Omnibus χ^2, –2LL, and Cox & Snell/Nagelkerke R^2. The significant Hosmer–Lemeshow statistic indicates a calibration concern; recalibration and internal/external validation are recommended for probability estimates. Classification metrics reflect a 0.50 threshold; the Youden-optimal threshold (≈0.45) is sample-specific. ROC/AUC describes discriminative performance. CRP: C-reactive protein; HALP: Hemoglobin–Albumin–Lymphocyte–Platelet index

DISCUSSION

To our knowledge, this study is among the first to systematically evaluate the HALP index in schizophrenia and to examine its diagnostic performance alongside established inflammatory markers. We found that HALP values were significantly lower in individuals with schizophrenia compared with healthy controls and that logHALP remained an independent protective factor after adjusting for relevant covariates. As anticipated, CRP levels were higher in the schizophrenia group and emerged as an independent risk factor in multivariable modeling. Taken together, these findings suggest that immune–inflammatory activation and disruptions within the nutrition–hematologic axis may co-occur in schizophrenia, and that composite indices such as HALP could provide a practical, integrative biomarker capable of capturing these multisystem alterations.

The HALP index consolidates readily available biochemical and hematologic parameters to reflect nutritional status (albumin, hemoglobin), immune competence (lymphocytes), and hematologic homeostasis (platelets) (35). In the present study, albumin and platelet counts did not differ significantly between groups; instead, lower hemoglobin and lymphocyte levels in the schizophrenia cohort appeared to be the primary contributors to reduced HALP scores. This pattern is biologically plausible. Anemia is frequently reported in schizophrenia and has been linked to inflammation-mediated iron sequestration, poor dietary intake, and medication effects (27). Similarly, lymphopenia has been associated with chronic stress, systemic inflammation, antipsychotic exposure, and lifestyle-related factors (28). In our study, the presence of patients with chronic schizophrenia, and possibly factors such as inadequate and unbalanced nutrition, also contributed to the decrease in the HALP index. Both mechanisms would be expected to decrease the HALP index.

Within this pathophysiological context, HALP may be

conceptualized as a combined indicator of low-grade chronic inflammation and diminished nutrition–immune reserves, aligning with broader models of immune–metabolic dysregulation in schizophrenia. Its simplicity, low cost, and interpretability further support its feasibility as a biomarker that may supplement existing laboratory and clinical assessments.

In patients with schizophrenia, elevated CRP levels are consistent with prior literature (8). Studies evaluating CRP in relation to cognitive performance have reported associations between higher CRP and poorer cognition (14,36); however, even when statistically significant, the small effect sizes indicate that inflammation alone is unlikely to account for the breadth of cognitive impairment observed in schizophrenia (37).

Although urea levels were higher in the control group, creatinine values were comparable and all measurements remained within the reference range, so this difference was considered a secondary finding outside the main focus on HALP and CRP.

Similarly, in our sample, no significant correlations were detected between HALP or CRP and PANSS, MoCA, or GAF scores within the schizophrenia group. This pattern aligns with previous findings suggesting that cross-sectional linear associations between inflammatory or nutritional biomarkers and concurrent symptom severity, cognitive performance, or overall functioning are generally modest (37).

Several explanations may account for these null correlations.

1. **Cross-sectional limitation:** The study design precludes temporal inference; inflammatory–nutritional markers may function as more trait-like indicators related to long-term disease course, relapse vulnerability, or cumulative metabolic burden, rather than reflecting momentary clinical severity.
2. **Restricted clinical variability:** Most participants were clinically stable outpatients, potentially limiting variability in symptom and functioning scores and thereby reducing the detectable strength of associations.
3. **Residual confounding:** Unmeasured factors—such as BMI, dietary quality, micronutrient deficiencies, medical comorbidities, antipsychotic subclass and dosage, and smoking intensity—may have attenuated relationships between biomarker levels and clinical measures.

Taken together, these findings suggest that HALP may capture an underlying dimension of biological reserve or vulnerability rather than acute psychopathology. This interpretation is consistent with the report by Korkmaz et al. (2024), who showed that several novel inflammation and oxidative stress ratios (MHR, LHR, NHR, PHR, AIP and AC) did not differ between patients with bipolar disorder and schizophrenia during acute episodes, and therefore proposed these indices as peripheral trait biomarkers reflecting enhanced inflammatory signaling across severe mental illnesses (38). The lack of significant correlations may also reflect, in part, the relatively small sample size and the clinical stability of our outpatient cohort, as variability in symptom and functioning scores was limited.Consequently, the index may have greater utility for risk stratification, identification of comorbidity patterns, or monitoring response to adjunctive interventions (e.g., nutritional optimization or anti-inflammatory strategies) during longitudinal follow-up rather than for cross-sectional symptom assessment.

Discriminative performance and modeling findings

After adjustment for all covariates, the persistence of a protective association for logHALP together with an independent risk association for CRP, combined with the model's strong discriminative capacity (AUC=0.832), indicates that using these two parameters jointly can meaningfully enhance schizophrenia–control discrimination. Nonetheless, the Hosmer–Lemeshow calibration warning suggests potential miscalibration of individual probability estimates. Accordingly, although the Youden-optimal threshold (~0.45) yielded a favorable sensitivity–specificity balance in this sample, cut-off values should be re-estimated in external cohorts to ensure generalizability.

Role of CRP and complementarity with HALP

Our results replicate the robust finding that CRP levels are elevated in schizophrenia and retain independent associations in multivariable models. The incremental value of HALP lies in its composite characterization of nutritional and hematologic status in addition to inflammation. Because CRP alone does not reliably differentiate low-grade chronic from acute systemic inflammation (39), and because HALP components reflect more slowly varying biological processes—such as anemia, protein–energy reserves, and lymphocyte dynamics (35)—the two markers likely provide complementary signals. In clinical research, combined modeling of CRP and HALP may therefore yield more informative panels for predicting outcomes such as treatment nonresponse, relapse, hospitalization, or medical comorbidity risk.

Clinical and research implications

- **Screening and stratification:** Owing to its low cost, accessibility, and ease of repetition, HALP represents a practical candidate marker for risk stratification in outpatient settings (35).
- **Intervention target:** Because HALP's components correspond to modifiable physiological states (e.g., anemia, nutritional deficiencies, inflammatory activity) (40), they may support individualized management strategies—such as micronutrient repletion (iron, folate, B12), protein–energy supplementation, enhanced physical activity, and smoking cessation.
- **Biological subtyping:** Joint patterns of CRP and HALP may help delineate inflammatory–metabolic phenotypes, contributing to ongoing efforts to identify biologically informed subtypes of schizophrenia.

Strengths

This study has several strengths. First, it is, to our knowledge, the earliest systematic investigation of the HALP index in schizophrenia. Second, the use of multivariable modeling allowed us to test the independent contribution of HALP alongside

established covariates, increasing the robustness of inference. Third, the incorporation of ROC analysis provided an objective assessment of discriminative performance and highlighted the potential clinical benefit of the HALP + CRP biomarker pair.

Limitations

Several limitations should be acknowledged. The cross-sectional design precludes causal interpretation, and the single-center recruitment with a modest sample size may limit generalizability. The Hosmer–Lemeshow goodness-of-fit test was significant ($p<0.001$), indicating poor model calibration; therefore, absolute predicted probabilities and the proposed cutoff should be interpreted with caution and regarded as exploratory. Future studies should consider resampling-based approaches (e.g., bootstrapped calibration curves) and models incorporating log-transformed CRP (logCRP) to improve model calibration and parameter stability. Moreover, important confounders—such as BMI, metabolic syndrome indicators, dietary quality, use of pro-/anti-inflammatory medications, antipsychotic subclasses and dose, and infection-related markers—were not comprehensively assessed and may have attenuated or obscured associations. In particular, we were unable to adjust our regression models for these metabolic and treatment-related variables, and residual confounding cannot be ruled out.Within the limitations of our study, some degree of selection bias cannot be excluded because only patients and controls with available routine laboratory tests were included. Specifically, the control group consisted of individuals who had undergone military medical board or pre-employment assessments, which may not fully represent the general healthy population, and this laboratory-based sampling frame may further limit the external validity of our findings. Although CRP and HALP indices are inexpensive and clinically accessible markers, overall, these results can be interpreted as a priori, hypothesis-generating evidence that needs to be confirmed in larger, prospective cohorts. Finally, the absence of external validation restricts conclusions regarding the stability and applicability of the identified thresholds across diverse populations.

CONCLUSION

In summary, the significantly lower HALP levels observed in patients with schizophrenia, together with the independent protective association of logHALP in multivariable analysis, suggest that HALP may capture reductions in nutrition–immune reserve characteristic of the disorder. When considered alongside the independent risk signal provided by CRP, the combined HALP + CRP profile emerges as a simple, inexpensive, and complementary biomarker dyad with potential utility in clinical assessment. Future longitudinal and multicenter studies—including external validation cohorts, rigorous control of confounding factors, and interventional trials targeting nutritional and inflammatory pathways—are needed to determine the prognostic and therapeutic relevance of HALP in schizophrenia.

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Conflict of Interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

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Ethical Approval

This study was approved by the Karabük University Non-Interventional Clinical Research Ethics Committee on January 9, 2025 (Decision No: 2024/2086).

REFERENCES

1. Miettunen J, Immonen J, McGrath J, et al. The Age Of Onset Of Schızophrenıa Spectrum Dısorders. Schizophr Bull. 2018;44:270.
2. an der Heiden W, Häfner H. The epidemiology of onset and course of schizophrenia. Eur Arch Psychiatry Clin Neurosci. 2000;250:292-303.
3. Evans SE. When do psychiatric interventions work? An argument for using functional outcomes when evaluating the effectiveness of treating schizophrenia. CNS Spectr. 2025;30:e71.
4. Galletly CA. Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders. Proceedings for Annual Meeting of The Japanese Pharmacological Society. 2018:70-3.
5. Dipasquale S, Pariante CM, Dazzan P, et al. The dietary pattern of patients with schizophrenia: A systematic review. J Psychiatr Res. 2013;47:197-207.
6. Yogaratnam J, Biswas N, Vadivel R, Jacob R. Metabolic complications of schizophrenia and antipsychotic medications--an updated review. East Asian Arch Psychiatry. 2013;23:21-8.
7. Howes O, Pillinger T, Beck K, D'Ambrosio E. Body And Mınd: Cardıo-Metabolıc And Immune Functıon In Fırst Epısode Psychosıs And Comparıson Wıth Central Neurofunctıonal Measures. Schizophr Bull. 2018;44:68.
8. Lestra V, Romeo B, Martelli C, et al. Could CRP be a differential biomarker of illness stages in schizophrenia? A systematic review and meta-analysis. Schizophr Res. 2022;246:175-86.
9. Leonard BE, Schwarz M, Myint AM. The metabolic syndrome in schizophrenia: is inflammation a contributing cause? Journal of Psychopharmacology. 2012;26:33-41.
10. Karageorgiou V, Milas GP, Michopoulos I. Neutrophil-to-lymphocyte ratio in schizophrenia: A systematic review and meta-analysis. Schizophr Res. 2019;206:4-12.
11. Dietrich-Muszalska A, Olas B. The changes of aggregability of blood platelets in schizophrenia. World J Biol Psychiatry. 2009;10:171-6.
12. Yin XY, Cai Y, Zhu ZH, et al. Associations of decreased serum total protein, albumin, and globulin with depressive severity of schizophrenia. Front Psychiatry. 2022;13.
13. Miller BJ, Goldsmith DR. Inflammatory biomarkers in schizophrenia: Implications for heterogeneity and

neurobiology. Biomark Neuropsychiatry. 2019;1:100006.

14. Patlola SR, Donohoe G, McKernan DP. The relationship between inflammatory biomarkers and cognitive dysfunction in patients with schizophrenia: A systematic review and meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2023;121:110668.
15. Comer AL, Carrier M, Tremblay MÈ, Cruz-Martín A. The inflamed brain in schizophrenia: The convergence of genetic and environmental risk factors that lead to uncontrolled neuroinflammation. Front Cell Neurosci. 2020;14.
16. Maynard TM, Sikich L, Lieberman JA, LaMantia AS. Neural Development, Cell-Cell Signaling, and the "Two-Hit" Hypothesis of Schizophrenia. Schizophr Bull. 2001;27:457-76.
17. Davis J, Eyre H, Jacka FN, et al. A review of vulnerability and risks for schizophrenia: Beyond the two hit hypothesis. Neurosci Biobehav Rev. 2016;65:185-94.
18. Rarinca V, Vasile A, Visternicu M, et al. Relevance of diet in schizophrenia: a review focusing on prenatal nutritional deficiency, obesity, oxidative stress and inflammation. Front Nutr. 2024;11.
19. Kelebie M, Kibralew G, Tadesse G, et al. Prevalence and predictors of metabolic syndrome among psychiatric patients receiving antipsychotic treatment in Africa: a systematic review and meta-analysis. BMC Psychiatry. 2025;25:433.
20. Zhang M, Xie C, Liu S, et al. The Prognostic Value of the Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) Score in Lung Cancer: A Systematic Review and Meta-Analysis. J Clin Med. 2025;14:5701.
21. Xu H, Zheng X, Ai J, Yang L. Hemoglobin, albumin, lymphocyte, and platelet (HALP) score and cancer prognosis: A systematic review and meta-analysis of 13,110 patients. Int Immunopharmacol. 2023;114:109496.
22. Yoldaş M, Karabacakoğlu B, Yücel C, et al. Effect of HALP Rate to Pathological Stage with Bladder Tumor Patients. The Journal of Tepecik Education and Research Hospital. 2022;32:323-7.
23. Gao S, Huang Q, Wei S, et al. Prognostic nomogram based on pre-treatment HALP score for patients with advanced non-small cell lung cancer. Clinics. 2024;79:100371.
24. Zhou W, Xia Q, Liu D, et al. The HALP score differs among sporadic and familial Parkinson's disease. Parkinsonism Relat Disord. 2025;133:107305.
25. Wazır J, Khan W, Shumaıla, et al. Utılıty Of Halp Score In Predıctıng Mortalıty In Acute Ischemıc Stroke. Biological and Clinical Sciences Research Journal. 2024:1069.
26. Karakayali M, Omar T, Artac I, et al. The prognostic value of HALP score in predicting in-hospital mortality in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. Coron Artery Dis. 2023;34:483-8.
27. Ali I, Abu Taha A, Zahran H. Prevalence of Anemia among Schizophrenic Patients in Palestine. Palestinian Medical and Pharmaceutical Journal. 2017;2:70-4.
28. Zhou L, Ma X, Wang W. Immune dysregulation is associated with symptom dimensions and cognitive deficits in schizophrenia: accessible evidence from complete blood count. BMC Psychiatry. 2024;24:48.
29. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. Schizophr Bull. 1987;13:261-76.
30. Kay SR, Opler LA, Lindenmayer JP. Reliability and validity of the positive and negative syndrome scale for schizophrenics. Psychiatry Res. 1988;23:99-110.
31. Chertkow H, Nasreddine Z, Johns E, et al. The Montreal cognitive assessment (MoCA): Validation of alternate forms and new recommendations for education corrections. Alzheimer's & Dementia. 2011;7:1-143.
32. Kaya Y, Aki OE, Can UA, et al. Validation of Montreal Cognitive Assessment and Discriminant Power of Montreal Cognitive Assessment Subtests in Patients With Mild Cognitive Impairment and Alzheimer Dementia in Turkish Population. J Geriatr Psychiatry Neurol. 2014;27:103-9.
33. Aas IM. Global Assessment of Functioning (GAF): properties and frontier of current knowledge. Ann Gen Psychiatry. 2010;9:20.
34. Yalav O, Topal U, Unal AG, Eray IC. Prognostic significance of preoperative hemoglobin and albumin levels and lymphocyte and platelet counts (HALP) in patients undergoing curative resection for colorectal cancer. Ann Ital Chir. 2021;92:283-92.
35. Zhang F, Li L, Shi T, et al. The hemoglobin, albumin, lymphocyte, and platelet (HALP) is a potent indicator for the prognosis in hemodialysis patients. Medicine. 2023;102:e33650.
36. Dal Santo F, González-Blanco L, García-Álvarez L, et al. Cognitive impairment and C-reactive protein in clinically stable schizophrenia outpatients: a focus on sex differences. Sci Rep. 2020;10:15963.
37. Bora E. Peripheral inflammatory and neurotrophic biomarkers of cognitive impairment in schizophrenia: a meta-analysis. Psychol Med. 2019;49:1971-9.
38. Korkmaz, Ş. A. Comparison of novel oxidative stress and systemic inflammation marker levels in patients with bipolar disorder and schizophrenia. Ankyra Medical Journal. n2024;3:54-5.
39. Koenig W, Pepys MB. C-Reactive Protein Risk Prediction: Low Specificity, High Sensitivity. Ann Intern Med. 2002;136:550-2.
40. Tortum F, Tekin E, Gur A. Predictive value of the Hemoglobin, Albumin, Lymphocyte and Platelet score for mortality in geriatric patients presenting to the emergency department. Geriatr Gerontol Int. 2025;25:387-91.