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Original Article

Serum Copper, Zinc, Iron, and Superoxide Dismutase Levels as Biomarkers in Depression

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ABSTRACT

Objective: To assess levels of hemoglobin, serum copper (Cu), zinc (Zn), iron (Fe), and superoxide dismutase (SOD) levels in individuals with depressive disorder and to evaluate their diagnostic utility as biomarkers using receiver operating characteristic (ROC) curve analysis.

Methodology: This cross-sectional comparative study was conducted at the University of Health Sciences, Lahore from September 2025 to March 2026 and serum samples were collected from Combined Military Hospital, Muzaffarabad. After obtaining institutional ethical approval, 30 healthy controls and 60 patients with depressive disorder diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria were included. Study participants were recruited using non-probability consecutive sampling technique. After obtaining informed written consent, blood samples were analyzed for hemoglobin, copper, zinc, iron, and SOD levels using standard laboratory methods. Statistical Package for the Social Sciences (SPSS) version 25.0 was used for data analysis and a p-value <0.05 was considered statistically significant.

Results: Patients with depression had significantly higher serum copper levels (129.31±45.81 vs. 101.32±14.14 µg/dL, p=0.001) and Cu/Zn ratio (1.71±1.05 vs. 1.15±0.44, p=0.001), but lower hemoglobin levels (10.89±0.92 vs. 11.35±1.01 g/dL, p=0.040) and SOD activity (54.14±44.66 vs. 84.02±28.72 U/mL, p=0.001) compared to healthy controls. In the depression group, serum copper showed significant inverse correlations with zinc (r=-0.38, p=0.004) and SOD activity (r=-0.41, p=0.002). Regarding diagnostic performance, serum copper demonstrated fair discriminatory ability [area under the curve (AUC)=0.70, 95% confidence interval (CI):0.58-0.82], while a combined model of serum copper and Cu/Zn ratio showed improved performance (AUC=0.82, 95% CI:0.71-0.90), indicating good discriminatory ability.

Conclusion: The depression group showed significantly elevated serum copper, increased Cu/Zn ratio, reduced SOD activity, and lower hemoglobin levels as compared to healthy controls. Serum copper was inversely correlated with zinc and SOD in the depression group. Serum copper and the Cu/Zn ratio combined showed good diagnostic performance on ROC analysis. Serum zinc and iron levels were not significantly different between groups.

Keywords: *Depressive disorder. Copper. Zinc. Superoxide dismutase. Oxidative stress.*

INTRODUCTION

Depression is a complex and multifactorial psychiatric disorder influenced by the interaction of genetic, environmental, and biochemical factors. Over the past years, more attention has been given to the role of oxidative and trace element imbalances in its etiology.[1] Trace elements, particularly Cu, Zn, and Fe, play essential roles in normal brain function; however, their imbalance may contribute to disease processes. Copper functions as an important enzymatic cofactor but may act as a pro-oxidant in excess, promoting the generation of reactive oxygen species and neuronal damage.[2] In contrast, zinc is critical for synaptic plasticity, neurogenesis, and regulation of glutamatergic neurotransmission, and its deficiency has been associated with depressive symptoms.[3] The copper-to-zinc (Cu/Zn) ratio is considered a significant marker of oxidative stress and trace element imbalance. A raised Cu/Zn ratio has been linked with mood disorders and may better reflect the biological changes underlying depression than individual copper or zinc levels alone.[4] Hemoglobin reflects oxygen carrying capacity and overall iron status. Reduced hemoglobin levels may impair cerebral oxygen delivery and neurotransmitter metabolism, contributing to depressive symptoms and cognitive dysfunction. Previous evidence has shown that iron deficiency and related hematological abnormalities are associated with a higher burden of depressive and internalizing symptoms.[5] Iron is essential for monoamine neurotransmitter synthesis and cellular energy metabolism, and its dysregulation has been linked to mood disturbances and cognitive dysfunction.[5,6]

The antioxidant defense system also plays a vital role in maintaining neuronal integrity.[7] Emerging evidence suggests that disruption of redox homeostasis contributes to neuronal dysfunction through mechanisms including neuroinflammation, mitochondrial impairment, and altered neurotransmission.[1] Superoxide dismutase (SOD), a key antioxidant enzyme, neutralizes reactive oxygen species and helps preserve cellular redox balance. Reduced SOD activity has been reported in depressive disorders, suggesting impaired antioxidant defense and increased oxidative stress.[7]

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Although previous studies have explored the association of trace elements and oxidative stress with depression, the findings remain inconsistent across different populations, with some studies reporting significant alterations in serum copper, zinc, iron, and antioxidant enzyme levels, while others have found non-significant associations. Moreover, limited data are available regarding the simultaneous assessment of these biomarkers within the same clinical setting. Considering the opposing biological effects of copper and zinc, the copper-to-zinc ratio may provide a more reliable indicator of redox imbalance than individual measurements alone. Our study aimed to compare hemoglobin, serum copper, zinc, iron, and SOD levels in patients diagnosed with depressive disorder and healthy controls, and to determine their individual and combined diagnostic potential.

METHODOLOGY

This cross-sectional comparative study was conducted in the University of Health Sciences, Lahore from September 2025 to March 2026. Serum samples were collected from Combined Military Hospital, Muzaffarabad after taking the ethical approval from the Institutional Review Board (Letter No. UHS/DPS-25/1198, 12-08-2025). All study subjects provided written informed consent. The sample size was determined using OpenEpi software as 53 cases and 27 controls (total n=80), based on a 95% confidence level, 80% power, and mean serum copper levels in depressed patients as 0.88±0.13 mg/L and in healthy controls as 1.02±0.24 mg/L, with a control-to-case ratio of 0.5.[4] The sample size was increased to 90 participants (60 cases and 30 controls) to enhance statistical power and account for missing data. A non-probability consecutive sampling was used to enroll the study subjects.

The study included adult subjects aged ≥18 years. Cases were diagnosed with depressive disorder by a consultant psychiatrist following the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).[8] The severity of depressive disorder was calculated by Beck Depression Inventory-II (BDI-II) and categorized as minimal, mild, moderate, and severe according to standard scoring criteria.[9] Healthy hospital controls were age & gender-matched individuals with no history of psychiatric illness, confirmed through psychiatric evaluation. Participants in both groups were excluded if they had pregnancy or lactation, acute or chronic inflammatory conditions, hepatic, renal, or endocrine disorders, malignancy, recent surgery or blood transfusion, alcohol or substance dependence, or were currently using mineral supplements, antioxidant therapy, or immunomodulatory drugs.

Sociodemographic data were recorded on a preformed proforma. A venous blood sample of 10 ml was collected aseptically from each participant. Blood samples were distributed into ethylenediaminetetraacetic acid (EDTA) tubes for hemoglobin level estimation and serum separator tubes for detection of the trace elements (copper, iron, and zinc) and SOD. Serum was separated by centrifugation at 3000 rpm for 10 minutes, aliquoted, and stored according to assay requirements.

Hemoglobin was measured using an automated hematology analyzer (Sysmex XT-1000i, Sysmex Corporation, Kobe, Japan). Serum trace elements (copper, zinc, and iron) were analyzed using atomic absorption spectrophotometry (Hitachi U-2800/2900, Hitachi High-Technologies, Tokyo, Japan) at wavelengths of 324 nm (Cu), 248 nm (Fe), and 214 nm (Zn), following standard procedures. The activity of superoxide dismutase was measured using an enzyme-linked immunosorbent assay (ELISA) based 96-well assay kit (SOD Kit, Catalog No. EIASODC, Glory Scientific, China) available commercially. The assay was performed following the manufacturer's protocol (Pub. No. MAN0019052, Rev. A.0). The assessment of absorbance was done at 405 nm using a Bio-Rad ELISA microplate reader.

For laboratory interpretation, the reference serum concentrations in adults are approximately as follows: hemoglobin 12-16 g/dL (females) and 14-18 g/dL (males); copper 100-200 µg/dL; zinc 75-140 µg/dL; and iron 50-150 µg/dL.[10] The reference range for serum SOD is approximately 80-120 U/mL (according to kit literature), and it may vary depending on assay methodology and manufacturer specifications.

STATISTICAL ANALYSIS

Data was analyzed using the Statistical Package for the Social Sciences (SPSS) version 25.0. Mean±standard deviation (SD) was used for presentation of continuous variables. The qualitative (categorical) variables were reported as frequencies & percentages. The Chi-square test was applied for the comparison of categorical variables. Independent t-test and one-way analysis of variance (ANOVA) were used for the comparative analysis of means between two groups and more than two groups, respectively.

Correlation analysis of biochemical parameters within groups was performed using Pearson's correlation coefficients. Diagnostic performance was

evaluated using ROC curve analysis, and AUC was calculated with 95% CI. An AUC equal to or greater than 0.6 is considered meaningful. Values between ≥0.6 and <0.7 show poor diagnostic accuracy, ≥0.7 to <0.8 as fair accuracy, ≥0.8 to <0.9 as good accuracy, while values ≥0.9 represent excellent diagnostic accuracy.[11] A p-value less than 0.05 was used to establish statistical significance.

RESULTS

The frequency of females was slightly higher in both groups (63.33% in depression vs. 76.67% in controls). Participants in both groups had statistically similar distribution of age, gender, educational level, and occupational status (p >0.05).

Patients with depression showed significantly higher serum copper levels of 129.31±45.81 µg/dL compared to 101.32±14.14 µg/dL in healthy controls, along with a higher Cu/Zn ratio of 1.71±1.05 versus 1.15±0.44 (p=0.001). Furthermore, the depression group showed lower hemoglobin levels of 10.89±0.92 g/dL compared to 11.35±1.01 g/dL (p=0.040), along with markedly decreased SOD activity of 54.14±44.66 U/mL versus 84.02±28.72 U/mL (p=0.001). Levels of serum zinc and iron between the groups were not different significantly (Table 1).

Among the 60 cases, 26(43.3%) had mild depression, 22(36.7%) had moderate depression, and 12(20.0%) had severe depression, while none of the participants had minimal depression. Serum copper levels increased significantly (p=0.001) with increasing severity of depression, while zinc levels showed a significant reduction (p=0.005). In addition, Cu/Zn ratio exhibited a highly significant rise (p=0.001), indicating a marked disturbance in trace element balance with disease severity. In contrast, hemoglobin, serum iron, and SOD levels did not show statistically significant differences across categories of depression severity (p >0.05) (Table 2).

A significant inverse relationship was observed between serum copper and zinc (r=-0.38, p=0.004) and copper and SOD activity (r=-0.41, p=0.002) in the depression group on correlation analysis. These findings indicate that higher copper levels were associated with lower zinc concentrations and reduced antioxidant activity. The control group showed no significant correlations (Figure 1).

Assessment of diagnostic performance showed that serum copper demonstrated fair discriminatory ability (AUC=0.70, 95% CI:0.58-0.82). In contrast, zinc, Cu/Zn ratio, iron, and SOD exhibited poor diagnostic performance (Figure 2). A combined model incorporating serum copper and the Cu/Zn ratio demonstrated improved diagnostic effectiveness, with an AUC of 0.82 (95% CI:0.71-0.90), depicting good discriminatory ability (Figure 3).

DISCUSSION

Alterations in essential micronutrients and disruption of redox homeostasis have been implicated in the processes leading to depression. The depression group showed significantly higher serum copper levels in the present study (129.31±45.81 µg/dL) compared with controls (101.32±14.14 µg/dL). Similarly, Huang et al. reported significantly high levels of serum copper concentrations (123.88±26.05 µg/dL) in adults with depressive symptoms as compared to healthy controls (116.99±29.00 µg/dL) (p <0.001).[12] Another study reported that patients with depression exhibit significantly elevated serum copper levels compared with healthy individuals.[13] Another meta-analysis included 24 studies and identified significantly higher serum copper levels in major depressive disorder patients as compared to controls (p=0.001).[14] A systematic review was conducted on Wilson's disease, where copper hemostasis becomes disturbed, and free copper accumulates in various organs, including the brain. Patients with this disease demonstrated a high prevalence (up to 47%) of depression.[15]

The serum zinc levels were not significantly different in the group with depression (86.11±24.60 µg/dL) as compared with controls (95.05±23.05 µg/dL) (p=0.095). In contrast, a meta-analysis revealed significantly decreased serum zinc levels in cases of major depressive disorder when compared to controls.[13] Yosaee et al. also reported in their meta-analysis that individuals with increased intake of zinc had a 28% lower risk of depression compared to those with lower intake [Relative Risk (RR):0.66; 95% CI: 0.50-0.82]. Moreover, their analysis of randomized controlled studies demonstrated that zinc supplementation significantly improved depressive symptoms in patients with depression (p <0.01).[16] The lack of statistical significance in our study may reflect sample size limitations, dietary variability, and the multifactorial nature of depression.

Table 1: Comparative Analysis of Biomarkers between Patients with Depression and Healthy Controls

Biochemical Markers	Depression Group	Control Group	p-value
	(Mean±SD)		
Hemoglobin (g/dL)	10.89±0.92	11.35±1.01	0.040*
Copper (µg/dL)	129.31±45.81	101.32±14.14	0.001*
Zinc (µg/dL)	86.11±24.60	95.05±23.05	0.095
Iron (µg/dL)	122.72±62.73	138.91±62.43	0.252
SOD (U/mL)	54.14±44.66	84.02±28.72	0.001*
Cu/Zn ratio	1.71±1.05	1.15±0.44	0.001*

**Significant p-value*

Table 2: Association of Biochemical Markers with the Severity of Disease

Biochemical Markers	Depression Severity			p-value
	Mild Depression	Moderate Depression	Severe Depression	
	(Mean±SD)			
Hemoglobin (g/dL)	11.0±0.7	10.8±1.0	10.7±0.8	0.652
Copper (µg/dL)	104.8±25.1	132.3±43.4	176.7±48.2	0.001*
Zinc (µg/dL)	95.6±21.8	84.1±25.1	69.0±20.2	0.005*
Iron (µg/dL)	117.7±61.8	140.0±65.7	101.8±54.9	0.208
SOD (U/mL)	68.5±53.4	48.4±37.4	33.3±22.1	0.056
Cu/Zn ratio	1.18±0.4	1.70±0.7	2.80±1.4	0.001*

**Significant p-value*

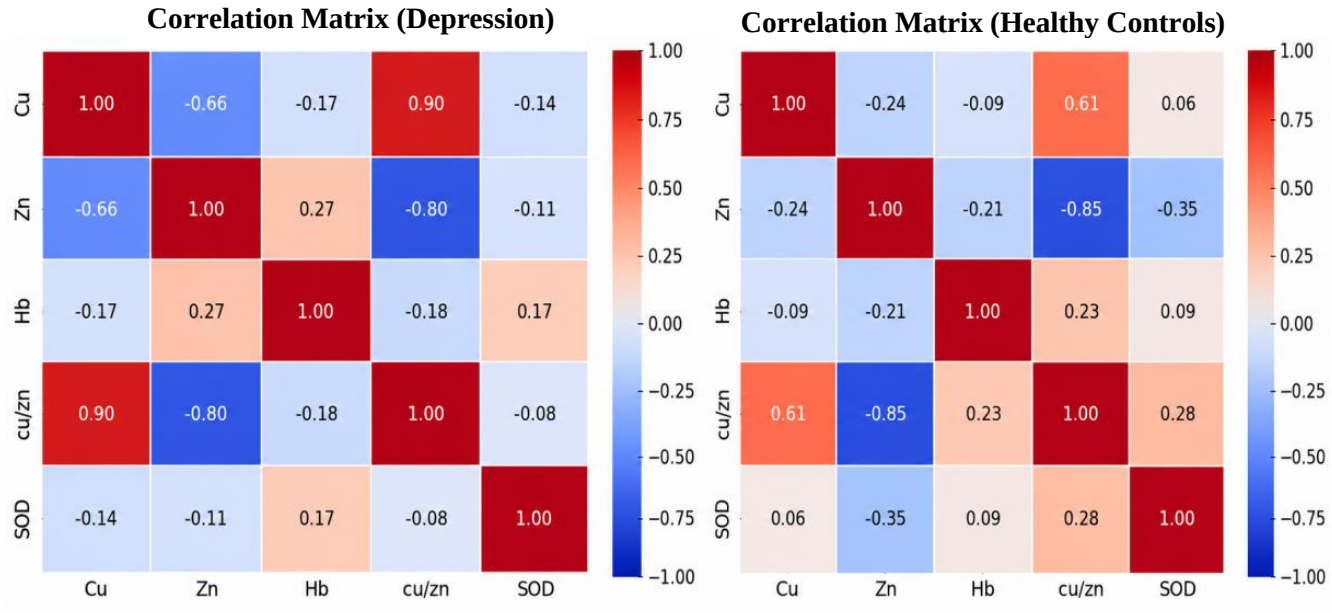

Figure 1: Correlation Matrices showing Relationships among Serum Copper, Zinc, Hemoglobin, Cu/Zn ratio, and SOD Levels in Depressive Patients and Healthy Controls

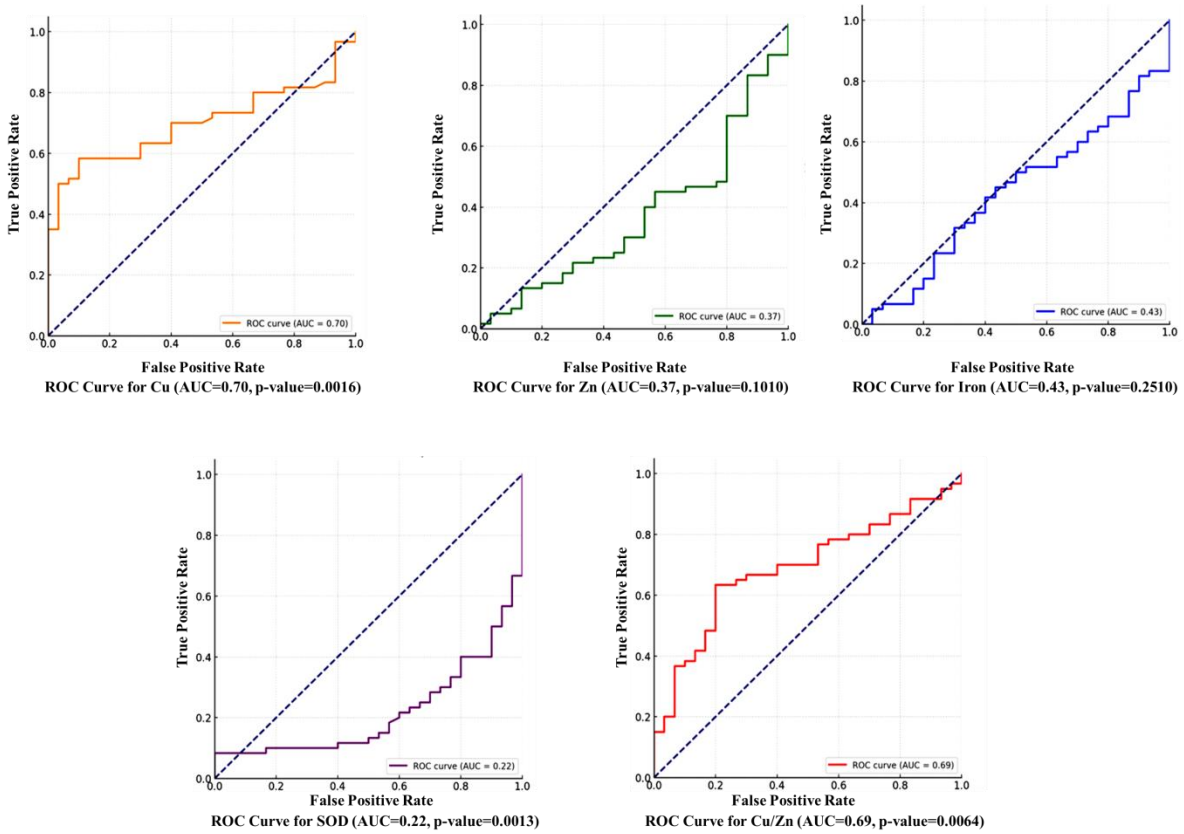

Figure 2: ROC Curves of Individual Biochemical Markers for Distinguishing Patients with Depression from Healthy Controls

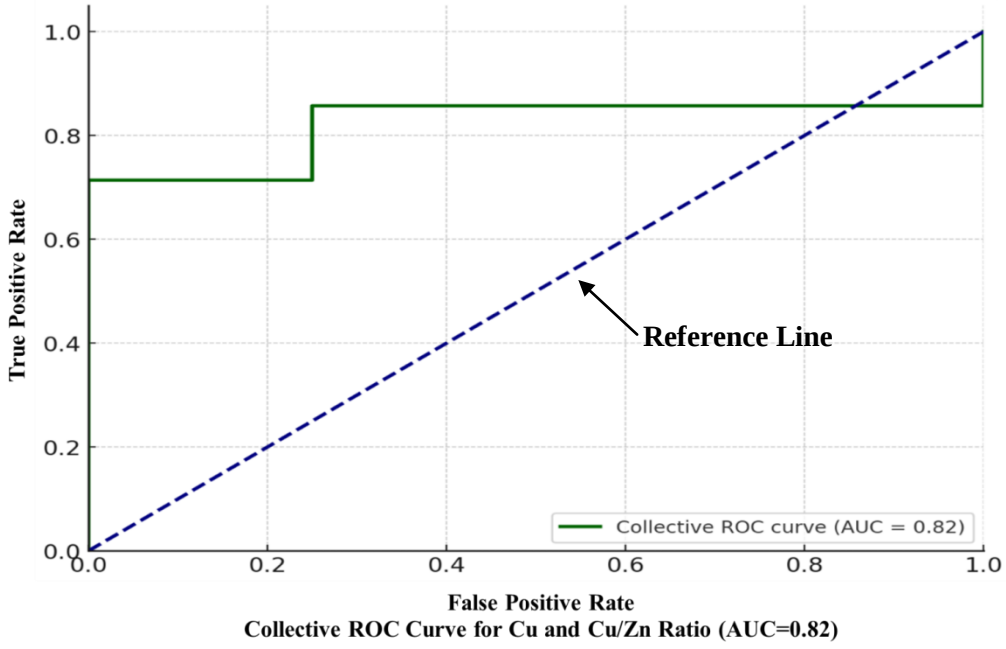

Figure 3: ROC Analysis of the Combined Model using Serum Copper and Cu/Zn ratio for Distinguishing Patients with Depression from Healthy Controls

A notable finding of the present study was the significantly elevated Cu/Zn ratio in patients with depression compared to controls (1.71±1.05 vs. 1.15±0.44). Correlation analysis further showed a significant inverse relationship between serum copper and zinc levels (r=-0.38, p=0.004). Another study highlighted that patients with depressive disorders exhibited an increased Cu/Zn ratio, demonstrating a possible association between trace element imbalance and mood disorders.[4] Lopez-Alonso et al. observed that increased Cu/Zn ratio reflects oxidative imbalance that contributes substantially to depressive pathology.[17] In contrast, another study conducted in 2020 reported that the Cu/Zn ratio did not significantly differ between patients with depression and healthy controls (2.24±2.09 vs. 1.77±1.32, p ≥0.05). They also observed positive correlations of both serum copper levels and the Cu/Zn ratio with interleukin-6 in depressive patients.[18] These findings suggest that disturbances in copper-zinc homeostasis may be linked to inflammatory pathways in depression.

In the current study, patients with depression had significantly reduced hemoglobin levels than healthy controls (10.89±0.92 vs. 11.35±1.01 g/dL, p=0.040). Similar observations have been reported in the literature, where iron deficiency and associated hematological disturbances were linked with depressive symptoms and impaired emotional well-being.[5,6] Reduced hemoglobin levels may represent a biological factor contributing to the development of depressive disorders.

Iron levels were lower in patients with depression in this study; however, the result was not statistically significant (p=0.208). Leung et al also revealed that more (25.7%) depressed patients had serum iron deficiency as compared to controls (20%), but the results were not significant (p=0.774).[19] Contrary to our findings, a meta-analysis revealed that cases of major depressive disorder had significantly lower serum iron levels (SMD=-0.36; 95% CI: -0.52 to -0.20).[13] This pattern indicates that iron may not follow a uniform trend across all depressive populations, limiting its reliability as an independent marker in cross-sectional assessments.[5]

The present study also demonstrated significantly reduced SOD activity in patients with depression (54.14±44.66 U/mL) when compared with healthy controls (84.02±28.72 U/mL). Similar reductions in antioxidant enzyme activity have been consistently reported in depressive disorders. It was reported in a study that Chinese patients with depression exhibited increased oxidative stress, evidenced by significantly altered oxidative stress markers, including reduced catalase activity compared with healthy controls.[20] Abd Elmoneim et al. also found significantly lower SOD levels in depressive patients (5.8±2.4) as compared to healthy controls (19.4±10.5) (p<0.001).[21] A significant inverse relationship between copper SOD activity was found in patients with depression (r=-0.41, p=0.002). These findings suggest that elevated copper levels may contribute to oxidative stress through depletion of antioxidant defenses and disruption of trace element balance.[22]

From a diagnostic perspective, the present study demonstrated that serum copper (AUC=0.70, 95% CI: 0.58-0.82) showed fair discriminatory ability. The combined model incorporating serum copper and the Cu/Zn ratio showed improved performance (AUC=0.82, 95% CI: 0.71-0.90), indicating good discrimination between patients and controls. Swiadro et al. highlighted the diagnostic relevance of copper and zinc imbalance in mood disorders, supporting the possible use of the Cu/Zn ratio as a biomarker.[4] Zinc, iron, and SOD demonstrated poor individual diagnostic performance (AUC <0.50) in this study, suggesting limited value as standalone markers. Another study highlighted the notorious heterogeneity and inconsistency of peripheral oxidative stress biomarkers in depressive disorders. This may be explained by their susceptibility to multiple external and physiological influences, resulting in overlap between patient and control groups.[23]

CONCLUSION

Oxidative stress and trace element imbalance appear to contribute to depressive disorder, as evidenced by significantly elevated serum copper levels, an increased Cu/Zn ratio, reduced SOD activity, and lower hemoglobin levels in patients with depression. There was no significant difference observed in serum zinc or iron levels between cases and controls. Serum copper showed significant inverse correlations with both zinc and SOD in the depression group. Moreover, serum copper and the Cu/Zn ratio combined demonstrated good diagnostic performance on ROC curve analysis.

LIMITATIONS & RECOMMENDATIONS

The study is limited by its single-centered, cross-sectional design, which restricts generalizability and causal inference. Potential confounders, including diet, socioeconomic status, inflammation, and medication history, were not fully assessed. Although serum copper showed fair diagnostic

performance, larger multicenter longitudinal studies are needed to confirm its clinical utility in depression.

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Authors' Contributions:

Authors approved the draft and are accountable in ensuring that questions related to accuracy or integrity of the work are duly investigated and resolved.

A.T: Conceptualization, data collection, laboratory analysis, statistical analysis, manuscript writing.
U.A: Study design, data interpretation, manuscript revision.
A.S: Data collection, literature review, manuscript drafting.
Y.L: Data collection, data entry, manuscript drafting.
U.S: Statistical analysis, data interpretation, manuscript revision.
S.H: Supervision, conceptual guidance, critical review of the manuscript.

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