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Research Article

Assessment of peripheral biomarkers and their correlation with oxidative stress index in schizophrenia: an integrated strategy

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Abstract

The innovative search for in vivo biomarkers in schizophrenia today offers a new perspective on improving diagnosis and understanding the disease process. Currently, effective diagnostic methods for schizophrenia are extremely limited, despite the fact that it is a multifactorial health problem affecting less than 0.4% of the world's population. The challenges to mental health in Pakistan are compounded by an over-reliance on traditional diagnostic techniques that yield mostly unsatisfactory results. Diagnostic difficulties can arise as a consequence of factors such as irregular and varied patient history, overlapping and unstable elements, and the number of inexperienced professionals, and diagnosis is frequently inexact. The target of the recent investigation is to investigation to estimate the results of tangential biomarkers like oxidants, antioxidants, and inflammatory markers and their association to the oxidative stress index (OSI) in schizophrenia. Standard approach were employed to gauge reactive protein (CRP), inflammatory markers, serum lipid levels, leukocyte indices, (PON1) Paraoxonase 1, total oxidant/antioxidant status (TAS and TOS), and (OSI) oxidative stress index in two groups: The study cohort comprised 50 patients with schizophrenia (Sz) and 50 healthy controls**,** with data analyzed using appropriate statistical methods. Findings confirmed the role of oxidative stress in schizophrenia and suggested that OSI could be used as a marker which in conjunction with other parameters might yield more accurate diagnoses. In schizophrenia, inflammation and oxidative stress appear to work together, and while OSI represents a useful quantitative index for more valuable diagnosis, additional evaluation, particularly in larger prospective trials, is warranted.

Keywords: Schizophrenia, Oxidative Stress, Oxidative Stress Index (OSI), Inflammatory Markers, Antioxidant Status, Paraoxonase-1 (PON1).

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Introduction

Psychiatric issues have attained alarming levels in Pakistan, exacerbated by numerous factors that worsen the overall situation. The healthcare system may be insufficient to address these mounting challenges, especially concerning mental health. Finding accurate biomarkers for the detection and prognosis of neuropsychiatric illnesses, especially in individuals with schizophrenia, is a major challenge.

Oxidative stress is believed to play a significant role in the development of several psychiatric conditions and may contribute to the pathophysiology of schizophrenia [1]. Inflammation and oxidative stress are closely interconnected; however, while these radicals are involved in normal physiological processes, antioxidant enzyme systems work to neutralize them [2]. Oxidative stress, which can harm cell membranes and ultimately cause neurodegeneration, can be brought on by the generation of free radicals like hydroxyl ions, superoxide, and nitric oxide during regular aerobic metabolism [3]. Multiple factors associated with oxidative stress-induced inflammation, such as C-reactive protein (CRP) and circulating lymphocytes, have been linked to schizophrenia [4].

In patients with schizophrenia, different interrelated mechanisms create positive signals to produce reactive oxygen species, or negatively signal the production of anti-oxidative capacity [5]. Thus, oxidative stress has been explored indirectly either through measuring enzyme activity for various antioxidant enzymes but the actual oxidants stress markers still remain murky. Good levels of HDL are an important part of the antioxidant systems built into plasma. The anti-atherogenic properties conferred by the protective function of HDL may be compromised in schizophrenia patients by high cholesterol/HDL ratios. The aryl-esterase enzyme serum Paraoxonase 1 (PON1) which is fundamental in preventing oxidative consequences of LDL is chiefly accountable for HDL's antioxidant qualities [6]. HDL also has demonstration that it has anti-inflammatory activity inhibiting LDL oxidation and cytotoxicity curtailing cytokine induced activation of endothelial cell adhesion molecules [7].

The pathophysiology of schizophrenia has been linked to immune markers, such as the pentraxin protein [8] and specific cytokine-mediated markers such as interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), IL-6, IL-2, and others, in addition to the nonspecific inflammatory marker C-reactive protein (CRP) [9]. The primary source of CRP, a unique marker in schizophrenia, is the liver cells' reaction to acute-phase inflammation. Increased CRP levels imply that immune system dysregulation, which can result in comorbidities and poor health outcomes, may be connected to psychotic disorders, aggravating negative symptoms [10]. Leukocytes, lymphocytes, and macrophages release mediators like cytokines during inflammatory responses in order to promote intercellular communication by attaching to particular receptors and changing cellular functions. Schizophrenia-related structural and functional abnormalities may arise from this process [11]. The precise processes that cause the immune system to become activated in schizophrenia are still being studied [11]. However, the exact mechanisms triggering immune system activation in schizophrenia remain under investigation.

The immune system is a potential target for positive symptom improvement in schizophrenia and antipsychotic drugs are known as an immuno-modulatory therapeutic option. These medications are useful for controlling psychotic symptoms

and decreasing the risk of recurrence [12]. Some of the atypical and typical antipsychotics may anti-inflammatory through inactivating microglia, activated microglia promote inflammation and suppress neurogenesis [13]. In addition, the free radicals may contribute to the neuroleptic-induced tardive dyskinesia. It has been shown that the adjunctive administration of antioxidant agents, such as N-acetylcysteine (NAC), can reduce oxidative stress and substantially ameliorate psychopathological symptoms in schizophrenia patients.

Determination of serum oxidant and antioxidant status can be difficult to measure and may not always adequately represent an individual's oxidative condition even when highly sophisticated analyses are used. This is due to fact that serum may harbor unknown oxidants and antioxidant molecules as well as various forms of these substances could be combined synergistically, making interpretation very hard. The measurement of a few oxidants and antioxidants alone is unable to fully prove the relationship between oxidative stress and correlated pathologies. Thus, the OSI is often used as an index of overall oxidative balance in the body, and it is determined by measuring total oxidant status to total antioxidant status ratio.

Our primary aim was to evaluate oxidative status using TOS, TAS, OSI, and PON1 while assessing peripheral systemic inflammation through markers such as hs-C Reactive Protein, IFN-g, TNF-a, IL-1a, and GM-CSF. By comparing this information with (OSI) oxidative stress index in people with schizophrenia, we sought to determine how these variables might drive the progression of the illness.

Materials and Methods

Research design and participants

This study used a variety of approaches to look into the peripheral role of oxidative stress and inflammatory markers in schizophrenia. 50 schizophrenic patients, both male and female, with ages ranging from 21 to 65, were recruited to provide blood samples from different behavioral healthcare facilities located throughout Karachi, Pakistan. In line with standard clinical practice, all patients had been on antipsychotic medication for more than 12 weeks and met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) benchmark for the diagnosis of schizophrenia. 50 healthy people who were matched by age and gender and who were chosen at random and had no prior history of mental illnesses, common diseases, or drug use, made up the control group.

Self-reported status

A structured questionnaire was used to get the patients' or their guardians' informed consent before a blood sample was taken. The consent form was filled out by hospital staff or the patients' family members or guardians for inpatients or seriously ill patients who were unable to give their own consent. Age, gender, age at onset, length of illness, type and daily dosage of antipsychotic medications, and other pertinent information were also documented for the schizophrenic patients.

Procedures

Serum lipid profiles, including total lipids, cholesterol, triglycerides, and both high- and low-density lipoprotein cholesterol (HDL-C and LDL-C), were assessed utilizing standardized reagent kits on a STAT Lab 300 Plus analyzer. Leukocyte parameters were determined using the ABX-Micros-60 hematology system. Additionally, serum or plasma concentrations of (PON1) paraoxonase, (TOS) total oxidant status, and total antioxidant status (TAS and TAOC) were

quantified with Bioassay ELISA kits and read via an (ELISA Reader DIA-2000). The percentage proportion of TOS to TAS and TAOC levels was used to compute the Oxidative Stress Index (OSI), using the standard formula. To measure key inflammatory markers specifically (GM-CSF), granulocyte-macrophage colony-stimulating factor, interleukin-1 alpha (IL-1α), (TNF-α) tumor necrosis factor-alpha, (IFN-γ) interferon-gamma, and (hs-CRP) high-sensitivity C-reactive protein, the study utilized commercialized ELISA kits from Bioassay Technology Laboratory (Shanghai, China).

Assay protocol

The oxidative stress and inflammatory markers were quantitatively detected by using sandwich ELISA kits (Bioassay Technology Laboratory, Shanghai, China) following the prescribed protocol by the manufacturer. The target of specific human antibodies which were precoated on the plates targeted each marker. Sample was added to the wells in order to allow the target analytes to bind to the coated antibodies. After the addition of biotinylated human antibodies specific to each of the markers, the analyte in the samples attached to the antibodies. The streptavidin-HRP conjugate was next conjugated to the biotinylated antibodies. A washing step was used after incubation to remove Unbound Streptavidin-HRP. The color was proportional to the concentration of a target marker to be measured, and it changed after the addition of a substrate solution. The ELISA Reader DIA-2000 was used to measure the reaction using the acidic stop solution and the absorbance was taken at 450 nm.

Ethical considerations

This study was authorized by Jinnah University of Women's (JUW) Institutional Ethical Review Board (IERB).

Statistical analysis

A number of statistical analyses was administered utilizing standard software (SPSS version 25.0). The data are analyzed using a level of significance of $p = 0.05$ and is presented in the form of mean standard deviation (SD). In the proper course of action, the Mann-Whitney U test was used to evaluate medians and interquartile ranges (IQR). The diagnostic value of the parameters including PON, TAS, TOS and OSI were assessed by the c-statistic that was applied to determine the optimal cutoff points and cost-effectiveness of the diagnostic standards in terms of the area under the receiver operating characteristic (ROC) curve (AUC). Python was used to create the correlation heatmap and correlation network model to depict the direction and degree to which biomarkers are related.

Results

Routine biochemical indices

Table 1 gives a summary of different biochemical indices. It shows that the WBC count of the patients changed insignificantly whereas their percentage of lymphocytes and granulocytes changed significantly ($p<0.001$ and $p<0.05$, respectively) contrast to the control group. Low HDL cholesterol levels ($P>0.033$), high levels of plasma total lipid ($P<0.048$), total cholesterol ($P<0.046$) and triglyceride levels ($P>0.033$) are evidence of dyslipidemia in the patients of schizophrenia.

Inflammatory markers

Serum inflammatory markers (IFN-γ, TNF-α, IL-1α, GM-CSF, and hs-CRP) measured by ELISA show that schizophrenic patients had significantly lower levels of IFN-γ ($P<0.003$) and TNF-α ($P<0.017$) than controls, but no remarkable differences

were seen in GM-CSF and IL-1α levels. Furthermore, it was found that the patient's hs-CRP level was significantly (P>0.033) higher than that of the control group.

Table 1: Comparative profile of biochemical indices in schizophrenia patients as compared to healthy controls.

Indices/ Profiles	Biochemical Parameters	Control (n=50) Mean ±SD	Schizophrenic Patients(n=50) Mean ±SD	P-Value
WBCs Profile	WBC (10^3/mL)	7.45 ± 1.73	7.88 ± 2.68	NS
	% Lymphocytes	30.30 ± 6.18	33.24 ±4.70**	<0.002 **
	% Granulocytes	58.18 ± 7.99	62.04 ± 7.04*	<0.033 *
	% Monocytes	4.98 ± 2.12	4.73 ± 0.86	NS
Lipid Profile	Total Lipid(mg/dl)	287.3±44.03	324.3±86.1	0.048*
	Total Cholesterol (mg/dl)	129.6±24.18	140.4±42.15	0.046*
	Triglyceride (mg/dl)	105.7±26.61	124.6±55.52	<0.033 *
	HDL-Cholesterol (mg/dl)	61.81±19.22	48.33±36.01	<0.033 *
	LDL-Cholesterol (mg/dl)	87.31±34.06	90.34±36.85	NS
Hs-CRP	Hs-CRP	1.67±0.256	1.83±0.223	<0.033 *
Inflammatory Markers	IL 1α	6.851±4.72	6.24±7.00	NS
	IFN γ	33.00±7.076	22.29±6.574	0.002**
	TNF	29.70±25.55	15.84±10.60	0.033*
	GMCSF	5.385±2.27	5.381±3.116	NS

Level of significance ***p<0.0001, **p<0.01, *p<0.05 as compared with control (t-test).

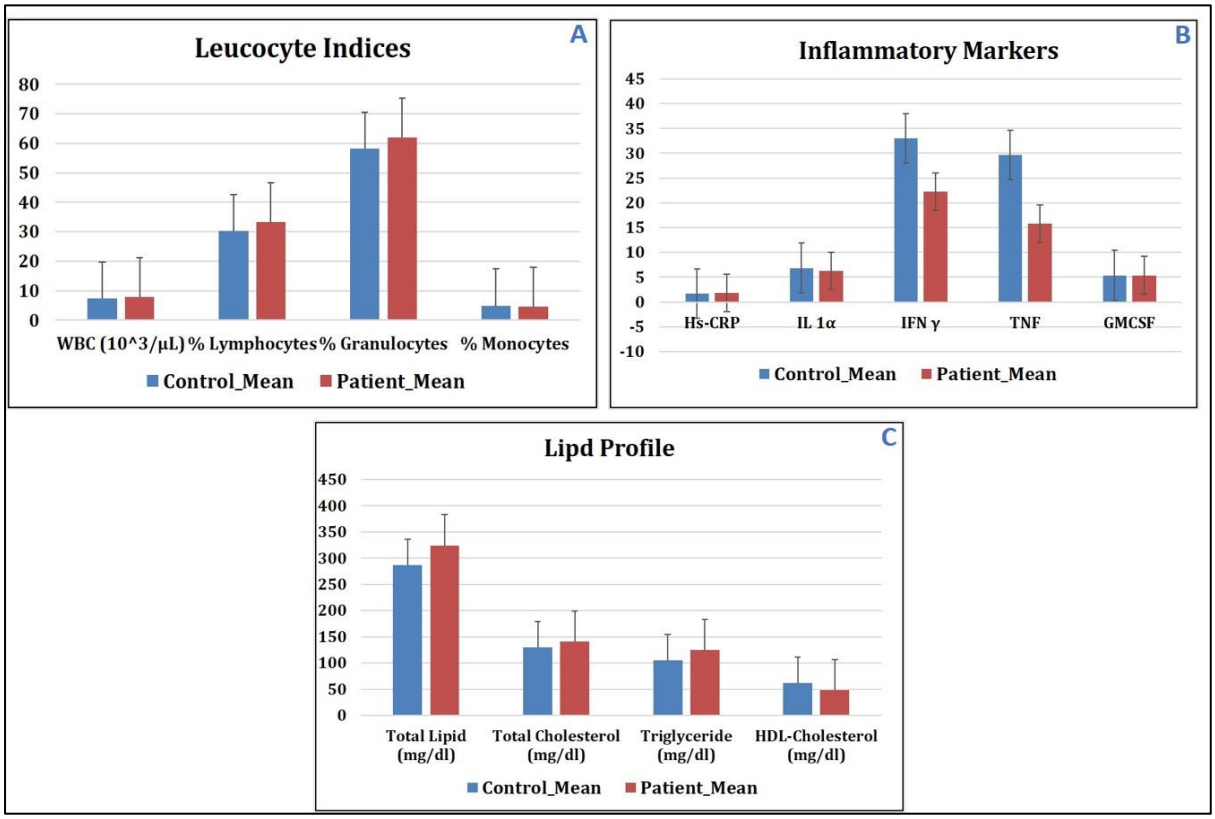

Figure 1: Comparison of a) Leucocyte indices & b) Inflammatory markers c) Lipid profile in Schizophrenic patients and healthy controls.

Oxidative stress markers

PON1, TOS, and TAS values had significantly low mean ±S.D. values, according to the C-C-statistics analysis (Figure 2).

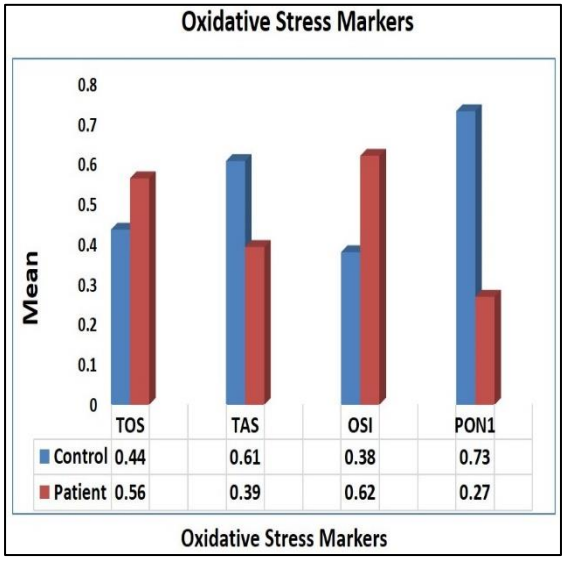

Figure 2: Comparison of a) oxidative stress markers & b) oxidative stress index (OSI) in schizophrenic patients and healthy controls.

However, when compared to the control group, schizophrenia patients' OSI values were noticeably higher. According to ROC analysis, the ideal cut-off levels and related indicative execution (sensitivity, specificity) of PON1, TOS, TAS, and OSI. while OSI values were significantly high in schizophrenic patients compared to the control group as shown in Figure 3.

As indicated by the analysis, patients with schizophrenia had high diagnostic values for both OSI and TOS, with corresponding AUCs of 0.620 and 0. 564.Conversely, the control group showed greater diagnostic performance for TAS and PON1, with corresponding AUCs of 0.607 and 0.731 **(**Table 2). The two paired variables were statistically evaluated using a paired t-test, while differences between group means were assessed through ANOVA. The results revealed no remarkable associations between these stress markers. Levene's test was used to test for equality of variances; like ANOVA, the dependent variable is represented by the absolute value, which is the difference between a score and the associated group mean. The F-statistic generated through ANOVA ($p > 0.05$) corresponds to the test statistic W. Since the p-value exceeds 0.05, the null hypothesis which proposes that all groups possess the equivalent variability, except for TOS ($p < 0.001$), demonstrating a statistically major distinction in variance.

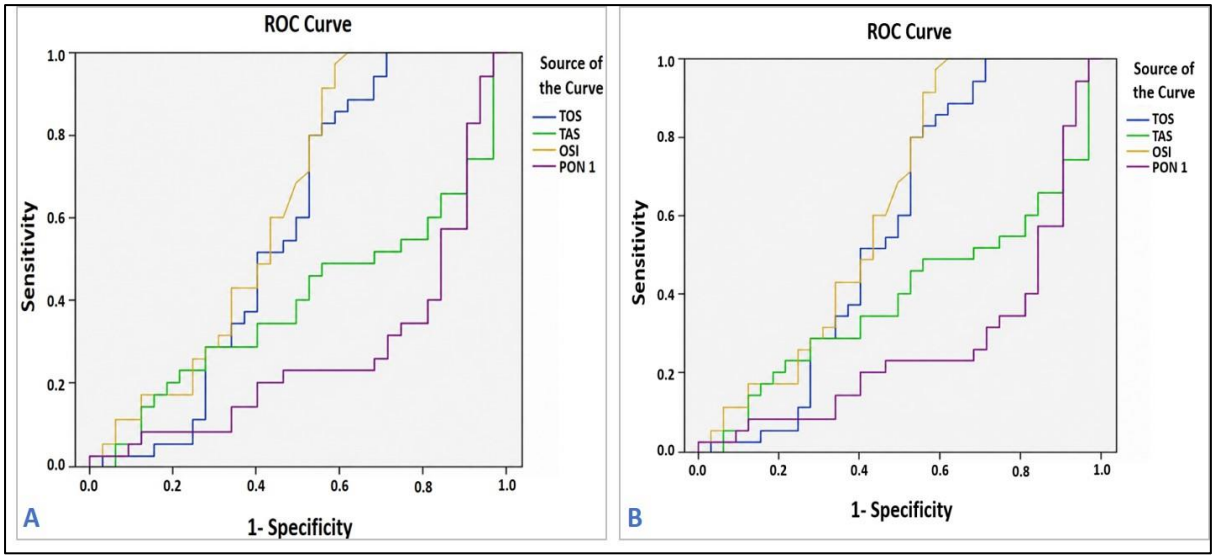

Figure 3: Diagnostic performances (Sensitivity and Specificity) of TOS, TAS, OSI and PON1 based on ROC analysis in a) Healthy Controls & b) Schizophrenic Patients

Table 2: AUC values of different Oxidative Stress markers in schizophrenic patients and Healthy Controls.

Markers	Control	Patients	ANOVA (Combined)	F	Significance	Levene's Test for Equality of Variances	F	Significance
TOS	0.436	0.564	Between Groups	0.481	.490	Equal variances assumed	12.602	.001*
			Within Groups					
			Total			Equal variances not assumed		
TAS	0.607	0.393	Between Groups	1.777	.187	Equal variances assumed	.468	.496
			Within Groups					
			Total			Equal variances not assumed		
OSI	0.38	0.62	Between Groups	0.496	.484	Equal variances assumed	.998	.321
			Within Groups					
			Total			Equal variances not assumed		
PON1	0.731	0.269	Between Groups	1.692	.197	Equal variances assumed	.209	.648
			Within Groups					
			Total			Equal variances not assumed		

* The independent sample test yields no significant findings, with the exception of TOS.

Levene's test confirmed that all samples' variances were equal (homogeneity of variance) (p>.05). The null hypothesis, which states that all groups have equal variance, is correct because the p-value is greater than 0.05. However, TOS* indicates that there is a substantial difference between the variances.

Pearson's correlation analysis

Table 3 used Pearson's correlation analysis to show different levels of correlation between various data sets. Oxidative stress index (OSI) and total antioxidant status (TAOC/TAS) showed a significant negative correlation (r = -0.325**, p>0.01) and a significant positive correlation (r = 0.825**, p>0.01). Nevertheless, no significant correlations were observed between these markers and other indices, including the lipid profile, S-100B, PON1, CRP, inflammatory markers, and WBC indices.

Total lipid has a positive correlation with LDL (r=0.448**), total cholesterol (r=0.549**), and triglycerides (r=0.835**). Additionally, there was a significant correlation between LDL and triglycerides and total cholesterol. Other than lymphocytes, which show an intense negative interaction with granulocytes and a favorable relationship with monocytes.

Table 3: Pearson correlation of different biomarkers in schizophrenic patients and healthy control.

Variables	TOS	TAS	OSI	PON1	TL	TG	TC	HDL	LDL	WBCS	LYM	MON	GRA	CRP	IL-1	IFN	TNF	GMCSF
TOS	–	.832**																
TAS		–	-.325**															
OSI	.832**	-.325**	–															
PON1				–														
TL				–	.835**	.549**												
TG				.835**	–				.203*									
TC				.549**		–			.507**									
HDL							–											.206*
LDL				.448**	.203*	.507**	–											
WBCS								–										
LYM									–		.299**	-.684**						
MON										.299**	–	-.491**						
GRA										-.684**	-.491**	–						
CRP													–					
IL-1														–				.244*
IFN				-.264**	-.199*										–		.276**	
TNF															.276**	–		.215*
GMCSF									.206*					.244*			.215*	–

* $p < 0.05$ ** $p < 0.01$

** Correlation is significant at the 0.01 level (2-tailed),

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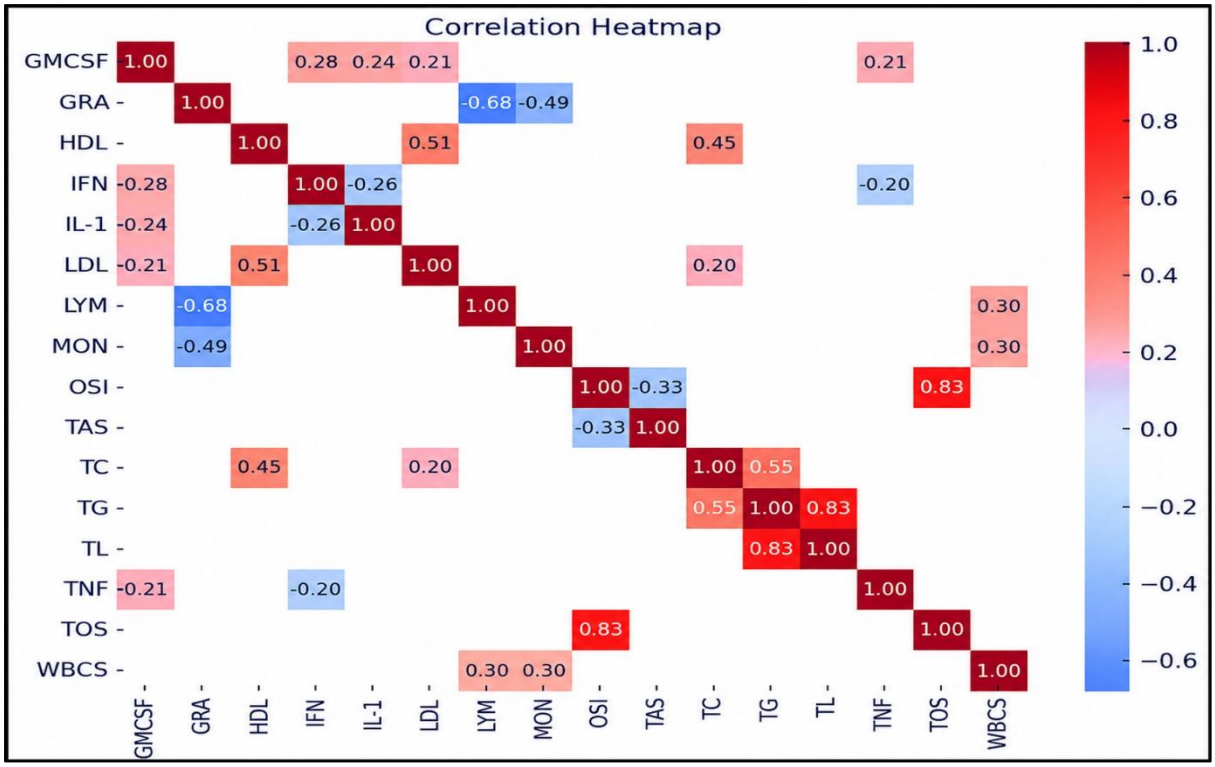

Figure 4: Correlation analysis between oxidative stress and lipid profile biomarkers.

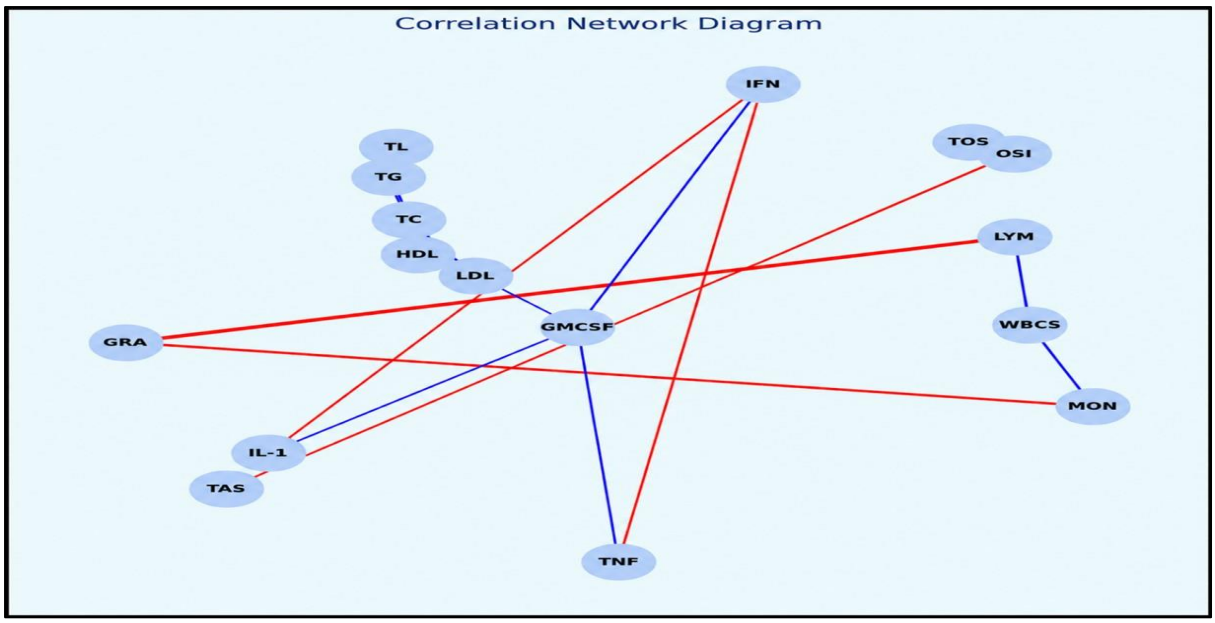

Figure 5: Interconnected network of biochemical and hematological biomarkers.

OSI Correlation Interactive graph

In automatic linear modeling, the thickness values are displayed in a responsive chart that links the predictor's predictability score with its predictive strength for the dependent variable. The histogram shows the results along with their best-fit Gaussian curve [14]. Conversely, the study found an inverse or negative correlation between the OSI and Total Antioxidant Status (TAOC/TAS), as shown by the correlation coefficient ($r = -0.325^{**}$, $p>0.01$) [1]. This suggests that individuals with higher levels of antioxidants (TAOC/TAS) tend to have a lower OSI. Despite that, Figure 6 indicates that oxidative stress could be connected to schizophrenia, given its minimal interaction regarding the inflammatory marker TNF, granulocytes, and lymphocytes.

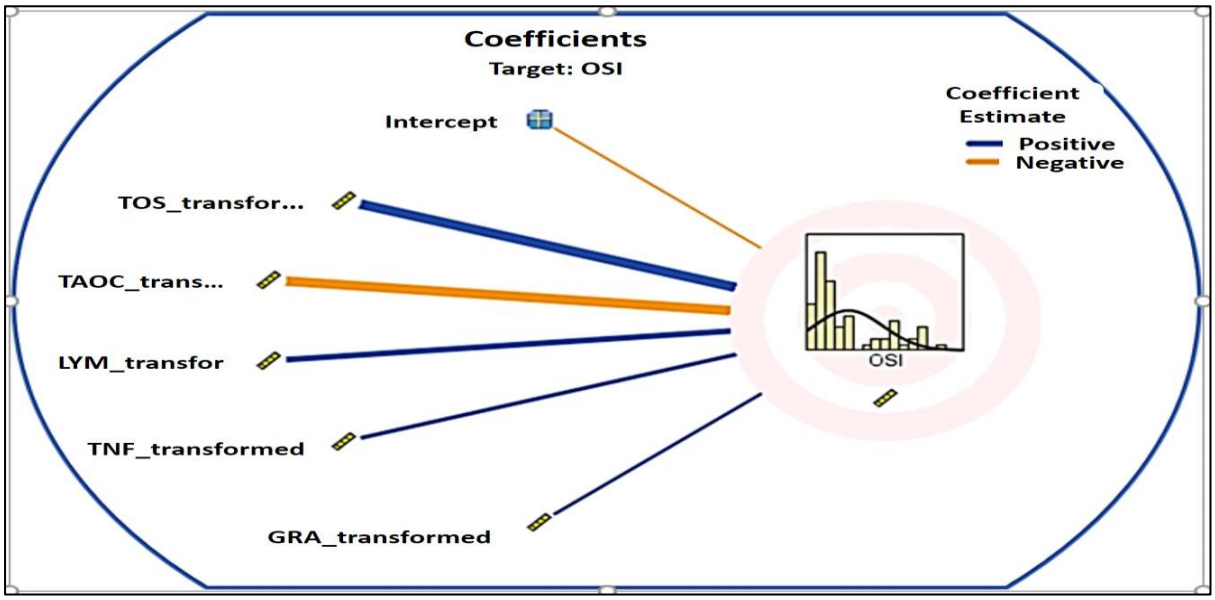

Figure 6: Automatic linear modeling targeting OSI-oxidative stress index representing correlation analysis of estimated means targeting OSI with TOS, TAS, LYM, TNF & GRA.

Discussion

Numerous human health conditions are particularly vulnerable to the negative impacts of oxidative stress and free radicals, which are especially prevalent in neuropsychiatric disorders. Schizophrenia [15]. The presence of oxidative stress in schizophrenia patients is demonstrated by a wide variety of biomarkers, which may be categorized as metabolic, inflammatory, or oxidative biomarkers, among others. Numerous indicators, which can be categorized as oxidative, inflammatory, metabolic, etc., demonstrate the presence of oxidative stress in schizophrenia patients. Peripheral or central biomarkers may offer a comprehensive understanding of disease pathogenesis and diagnostic/therapeutic approaches. The relationship between schizophrenia and possible hematological side effects including leukocytosis, anemia, iron deficiency anemia (IDA), and neutrophil cytotoxicity in reaction to certain antipsychotic medications has been reported previously [16 - 17].

Similarly, changes in blood inflammatory markers, such as WBC count and cytokines, have long been linked to schizophrenia. Compared to healthy controls, schizophrenic patients have significantly higher ($p<0.001$ and $p<0.05$, respectively) WBC profiles, the primary indicator of inflammation, which include lymphocytes and granulocytes (Table 1). Our findings are in line with earlier research that found that schizophrenia is associated with higher total and differential WBC counts. We also looked at WBC indices and cytokines as indicators of low-grade inflammation that are linked to the disease's pathophysiology and treatment.

Numerous reports in the literature have documented the prevalence of dyslipidemia in individuals with schizophrenia [18]. Our findings also supported the existence of dyslipidemia (Table 1), which may raise the risk of comorbidities like diabetes and coronary heart disease in schizophrenic patients due to high levels of plasma total lipid ($P<0.048$), total cholesterol ($P<0.046$), and triglycerides ($P>0.033$) and low levels of HDL cholesterol ($P>0.033$) in comparison to the healthy controls. Significantly, higher triglycerides and lower HDL cholesterol have been reported in schizophrenic patients compared to the control group [19]. These findings could support our findings and suggest that patients receiving antipsychotic treatment have their lipid profiles regularly monitored because the severity of their symptoms may indicate dyslipidemia as the disease progresses [20]. Along with other anomalies like altered glucose metabolism and/or metabolic syndromes, dyslipidemia is also seen in patients who are not receiving treatment, indicating that it may be related to the illness itself rather than the effects of antipsychotic drugs [21]. Neuronal cell death results from lipid peroxidation and cholesterol oxidation, which supports the idea that inflammation and oxidative stress play a role in the development of schizophrenia at various stages [22]. In schizophrenia, inflammation is probably caused by dysregulated cytokines in addition to other elements like mental and physical stress. However, antipsychotic medication treatment has an anti-inflammatory effect, which lowers pro-inflammatory cytokine levels. ELISA-based analysis revealed no significant differences in IL-1α and GM-CSF levels between schizophrenia patients and controls.

TNF alpha and INF gamma were considered as common signs of schizophrenia. INF-g, a secretion of T-lymphocytes, the primary mediator of immunity, initiates the activation of macrophages to generate the TNF- a, a cytokine that performs two functions: it suppresses the synthesis of the anti-inflammatory cytokines and promotes the

synthesis of the pro-inflammatory cytokines [23]. Its dissociation by activated microglia can thus pass through the blood-brain barrier and result in the peripheral blood passing through into the brain tissue [24]. This is why the treatment of schizophrenia with antipsychotics can change the blood-brain barrier through the blockage of microglia which would result in the significant reduction of the level of INF-7 and TNF- 7. They discovered that the concentration of these inflammatory markers greatly reduced and this was yet another confirmation of our results.

The possible involvement of GM-CSF and IL-1α, another cytokine which encourages inflammation Since our results revealed no apparent variations in the intensity of these markers, it is unclear what is created by the activated macrophages and lymphocytes in this investigation. Hematopoiesis regulator IL-1α may also maintain GM-CSF, a cytokine and hematopoietic growth factor that promotes myeloid precursor cell development and maturation [25].

Raised inflammatory markers in neuropsychiatric disorders also result in the release of CRP by the hepatocytes, which causes continually high levels of hs-CRP. This explains why inflammation is important in schizophrenia and justifies our results that the hs-CRP levels of schizophrenic patients were significantly ($P>0.033$) elevated equated to those of the healthy control group [26]. This is an indication that the levels of hs-CRP in schizophrenia are still high even with antipsychotic therapy.

The shift of balance towards the oxidative side is a sign of oxidative stress, whereas the change towards the antioxidant side is a sign of an imbalance between the antioxidants. The ROC analysis suggested that the oxidative stress markers OSI and TOS had high diagnostic value in patients with schizophrenia, with specificity and sensitivity values reflected by AUCs of 0.620 and 0.564, correspondingly. On the other hand, TAS and PON1 had higher diagnostic values obtained with the controls of 0.607 and 0.731, respectively (Table 2). Table 3 of Pearson correlation has been used to demonstrate in an interactive graph of automatic linear modeling (Figure 6) that there is significant positive correlation of OSI and TOS ($r = 0.825$, then significant) and significant negative correlation ($r = -0.325$, then significant) between OSI and TOS/TAS. Despite, no associations were observed with other parameters, including lipid profile, PON1, CRP, inflammatory markers, and WBC indices, and the weakest correlations were found with lymphocytes, granulocytes, and the inflammatory cytokine TNF.

The literature has long examined the relevance of oxidative and antioxidative systems in the pathophysiology of schizophrenia, with varying degrees of success [27]. No discernible difference in TAS, TOS, and OSI values was observed between 50 samples of schizophrenia patients and the control group [28]. Another study found that schizophrenia patients (64 samples) had considerably greater TAS and TOS levels than controls, but there was no significant association with PON1 levels. Moreover, patients with remission of schizophrenia (64 samples) were observed to have substantially higher levels of TOS and OSI than healthy controls, exhibiting no relationship with TAS levels [29]. In a similar vein, additional evidence has validated these results, further confirming the connection between enhanced oxidative stress and schizophrenia [30].

The correlation heatmap indicates positive and negative relationships between the biomarkers of interest and presents the pair-wise correlation between the biomarkers. There were strong positive correlations between TOS and OSI, between TG and TL, and LDL and HDL, which can indicate

that these parameters can be strongly correlated in either biological or metabolic terms. The intensity of these associations is in the gradient of the color intensity which indicates the coordinated changes in the indicators of oxidative stress and lipid metabolism in the research population indicated in Figure 4. The correlation network diagram also provides a visual summary of the relationships between hematological and biochemical biomarkers. Correlations have their direction and strength indicated by edges of every node which indicates a variable. Blue margins reflect positive relationship between two variables, red edges refer to negative relationship whereas thicker edges signify stronger association. Interestingly, GRA demonstrated a significant negative correlation with LYM and MON, which suggests that the condition of pathophysiology being examined is associated with immune cell activity or with the inverted regulatory effects depicted in Figure 5.

Conclusions

To sum up, inflammation and oxidative stress are complimentary in most disorders, particularly degenerative ones like schizophrenia, where the redox balance suppresses inflammation while oxidative stress causes it. Since there are now no trustworthy biomarkers that can anticipate mental illnesses, the continued use of the oxidative stress index as a biomarker may indicate that the psychiatric diagnostic should be introduced cautiously. It is also necessary to look into how an antioxidant treatment might affect oxidative stress markers and neuropsychiatric disease symptoms.

Author contributions

The conceptualization of the study was done with the help of A.Z.W, F.J, and S.R. A.Z.W. and F.J. developed the methodology and formal analysis was done by A.Z.W., F.J., N.B., D.K., Z.Z., N.S., and S.R. A.Z.W., and A.R. prepared the original version and critically reviewed it, respectively. Visualization was undertaken by A.Z.W., and supervising was done by A.Z.W. Funding acquisition was done under the leadership of A.Z.W. The final version of the manuscript has been read by all the authors and approved.

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