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The Impact of Chemotherapy on Oxidant and Antioxidant Status in Acute Lymphoblastic Leukemia

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ABSTRACT:

Acute lymphoblastic leukemia (ALL) is a malignant disorder of lymphoid lineage. Chemotherapy remains the mainstay of treatment, yet it induces systemic damage partly through oxidative stress, which may worsen prognosis, increase relapse risk, and impair responsiveness to therapy.

A total of 64 individuals participated in the study: 21 newly diagnosed ALL (ND-ALL) patients with a median age of 10 years (IQR 3-27.5), 23 patients receiving maintenance chemotherapy with a median age of 13 years (IQR 5-23), and 20 healthy controls with a median age of 11.5 years (IQR 5-23), (cross-sectional study). Following remission induction treatment, ND-ALL patients were also reassessed (longitudinal study). ELISA kits were used to detect superoxide dismutase (SOD), glutathione peroxidase (GSH-PX), total antioxidant capacity (T-AOC), malondialdehyde (MDA), 8-hydroxy-2′-deoxyguanosine(8-OHdG), and protein carbonyl (PC).

In the cross-sectional study, MDA ($p = 0.05$) and 8-OHdG ($p = 0.001$) were significantly higher in ND-ALL patients. SOD demonstrated a considerable decline ($p = 0.001$), the antioxidants GSH-PX and T-AOC also decreased significantly ($p = 0.01$). There were no significant differences between the maintenance group and the controls. Significant increases in MDA, 8-OHdG, and PC ($p = 0.05, 0.01, 0.01$, respectively), and decreases in GSH-PX, SOD, and T-AOC ($p = 0.01, 0.05, 0.01$, respectively) were observed following treatment.

Chemotherapy significantly alters the oxidant-antioxidant balance in patients with ALL. Treatment was associated with an increase in oxidative stress markers, accompanied by a marked reduction in antioxidant defense capacity.

Keywords: Acute lymphoblastic leukemia, Antioxidant, Chemotherapy, Oxidative stress, Reactive oxygen species.

1 INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a type of malignancy that is distinguished by the aberrant growth of immature lymphoid cells. [1]. Twenty-five percent of all newly diagnosed children's malignancies are ALL. In the US, there are between 3.7 and 4.9 instances for every 100,000 children annually. The incidence of ALL peaks between the ages of 2 and 5 years, and males are slightly more likely than females to develop it. Leukemogenesis can be caused by prior exposure to radiation therapy, chemotherapy, or ionizing radiation; Down syndrome; ataxia-telangiectasia; Fanconi anemia; Li-Fraumeni syndrome; neurofibromatosis 1; or other hereditary conditions[2].

Reactive oxygen species (ROS) are molecules with high oxidative activity[3]. ROS are made up of oxygen free radicals ($O2^{\cdot -}$, $OH^{\cdot}$) and nonradical oxidants (H_2O_2 and $1O_2$). NADPH oxidases (NOX) and mitochondria are the two primary producers of endogenous ROS in tumor cells. In cells, ROS serve a paradoxical purpose. ROS have a crucial role in maintaining cell differentiation, proliferation, and homeostasis in vivo. To combat oxidative stress (OS), cells mainly depend on antioxidants such as glutathione peroxidase (GSH-PX), superoxide dismutase (SOD), catalase (CAT), and DNA repair proteins. An imbalance between ROS and antioxidants can lead to OS, which can harm proteins, lipids,

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and DNA and promote the growth of tumor cells. Ironically, pro-oxidative stress has also proven successful in eradicating tumor cells with specificity. Unlike normal cells, tumor cells need more ROS to proliferate. However, because of their antioxidant ability, they must work to eliminate excess ROS while preserving antitumor cell apoptosis and pro-tumor signaling. Therefore, tumor cells will undergo apoptosis once ROS overproduction reaches a threshold or the antioxidant system is compromised [4].

Extensive experimental data suggest that oxidative damage permanently damages proteins, DNA, and lipids found in cellular membranes. Since 8-hydroxy-2' -deoxyguanosine (8-OHdG) or 8-oxo-7,8-dihydro-2' -deoxyguanosine (8-oxodG) is one of the most common types of oxidative lesions caused by free radicals, it is frequently employed as a biomarker for oxidative stress and carcinogenesis in nuclear and mitochondrial DNA[5-7]. Even though organisms have many non-enzymatic antioxidant defenses and DNA enzymatic repair mechanisms to preserve genomic integrity G-C to T-A transversions in daughter DNA strands may result from the synthesis of 8-OHdG from 2′-deoxyguanosine due to oxidative damage to DNA bases[8]

One of the most prevalent oxidative changes in proteins is carbonylation. Since protein oxidation causes aggregation, polymerization, unfolding, or conformational changes that may result in a loss of structural or functional activity, it is especially concerning. Cell dysfunction results from the formation of oxidized protein aggregates, which are difficult for the cell to break down. Protein carbonyls (aldehydes and ketones) are involved in the majority of protein oxidative changes, while there are many more conceivable. Oxidative stress can cause protein carbonylation directly, or subsequent byproduct processes can cause it indirectly[9].

To achieve complete remission or response, ALL patients must undergo chemotherapy induction to remove immature white blood cells from their blood and bone marrow. A month is allotted for the induction phase of treatment. The three stages of chemotherapy are the induction, consolidation, and maintenance phases. A reduction of less than 5% of blast cells in the bone marrow is typically referred to as remission, and this is the aim of treatment. [10]. By analyzing alterations in antioxidant defenses (SOD, GSH-PX) and oxidative indicators (MDA, 8-OHdG, PC), this study aims to understand how chemotherapy affects oxidative stress in ALL patients and offer insights into the consequences of treatment and patient outcomes.

2 MATERIALS AND METHOD

2.1 STUDY DESIGN AND PARTICIPANTS

This study is an observational study, included a total of 64 individuals with B-cell ALL and T-cell ALL. Samples were collected at Nanakali Hospital for Hematology and Oncology in Erbil, and Hiwa Hospital in Sulaymaniyah.

Samples were collected from 21 ALL patients before the initiation of chemotherapy (newly diagnosed group ND), with a median age of 10 years (IQR 3-27.5), including 12 males (57.14%) and 9 females (42.86%), and from the same individuals after 29 days of induction remission therapy (RI group) for a longitudinal comparison.

Additionally, serum samples were obtained from 23 ALL patients on maintenance chemotherapy (maintenance group M), with a median age of 13 years (IQR 5-23), including thirteen males (56.5%) and ten females (43.5%).

To provide a basis of comparison, twenty healthy people who were matched for age and gender made up the control group with a median age of 11.5 years (IQR 5.25-23), including 12 males (60%) and 8 females (40%). Excluding those with any chronic diseases.

Patients with chronic diseases, bacterial or fungal infections, mixed phenotype ALL, Philadelphia chromosome positive ALL, relapsed ALL, and those with Central Nervous System (CNS) involvement, were excluded from the study.

2.2 ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Human Ethics Study Committee at the College of Science, Salahaddin University-Erbil, has approved the ethical and regulatory concerns surrounding the collection of human specimens for study in accordance with the Declaration of Helsinki (reference number:45/283). Patients provided their written informed consent.

2.2 SAMPLE COLLECTION AND STORAGE

Five milliliters of venous blood were extracted from each participant and put into a gel-filled serum tube. To enable a clot to form, the blood was left undisturbed at room temperature for 15 to 20 minutes. The samples were centrifuged at 5000 rpm for 10 minutes after the clot formed in order to extract the serum. It was separated into three sterile Eppendorf tubes and stored at -80°C to prevent repeated freeze-thaw cycles.

2.3 MEDICATIONS AND CHEMOTHERAPY REGIMENS ADMINISTERED TO THE STUDY COHORT

Chemotherapy for study participants was administered based on three different regimens such as; The United Kingdom Acute Lymphoblastic Leukemia (UKALL) protocol[11], Hyper-fractionated Cyclophosphamide, Vincristine, Doxorubicin, and Dexamethasone (Hyper-CVAD) protocol[12], or the modified/dose-reduced version (Mini-CVAD)[13], (see Table 1).

Table 1. Distribution of ALL patients by treatment regimen and phase.

Regimen	Treatment phase	Number of patients (n)	Percentage %
UKALL	Induction	14	31.81
Hyper-CVAD	Induction	5	11.36
Mini Hyper-CVAD	Induction	2	4.54
UKALL	Maintenance	20	45.45
Hyper-CVAD	Maintenance	3	6.81
Total	_____	44	100

2.4 MEASURMENT OF OXIDATIVE STRESS MARKERS AND ANTIOXIDANTS

Throughout the investigation, ELISA kits supplied by Sunlong Biotech Co., Ltd.,Hangzhou, China, were used to assess serum levels of antioxidants and oxidative stress indicators (MDA, 8OHdg, PC, GSH-PX, SOD, and T-AOC) [14]. The ELISA method was employed because of its proven sensitivity, specificity, and accuracy in assessing biomarkers associated with oxidative stress and antioxidant defense. Absorbance was read at 450 nm using a microplate reader and concentrations were calculated according to the manufacturer's instructions.

2.5 STATISTICAL ANALYSES

To analyze the data, GraphPad Prism 9.0.0 was used[15]. The Anderson-Darling, D'Agostino & Pearson, Shapiro-Wilk, and Kolmogorov-Smirnov tests were used to evaluate the data's normality, and all datasets were found to be non-parametric. Accordingly, data are presented as median (IQR). Group comparisons were performed using Kruskal-Wallis test followed by Dunn's multiple comparison test. Paired comparisons between ND-ALL and RI groups were conducted using the Wilcoxon signed-rank test. A p-value ≤ 0.05 was considered statistically significant.

3 RESULTS

The results of oxidative stress levels in 21 ND-ALL patients, 23 ALL patients who are on maintenance chemotherapy, and 20 control healthy individuals were compared (cross-sectional study), the data were analyzed by One-way ANOVA followed by the multiple comparison tests. The present study also compared oxidative stress biomarkers and antioxidant status between ND-ALL patients and ALL patients after induction remission chemotherapy (longitudinal study), the data were analyzed using paired t-test and Wilcoxon test. The results summarized in Tables 2, 3, 4. And Figures 1,2,3, and 4.

Table 2 and **Figures 1 and 2** present the results of MDA,8-OHdG, PC, SOD, GSH-PX, and T-AOC. Post hoc analysis revealed that the median MDA level increased significantly in ND-ALL patients compared to the control group from 32.93(IQR 30.02-42.51) to 42.31(IQR 33.93-50.54). The level of MDA in the M group was non-significantly higher than the control group.

8OHdG levels increased significantly in ND-ALL patients, with a p-value (0.001), compared to the control group, and decreased significantly in the maintenance group compared to ND-ALL patients, with a p-value (0.001).

Table 2. Comparison of antioxidant status and oxidative stress levels among the control group (C, n=20), newly diagnosed acute lymphoblastic leukemia patients (ND-ALL patients n=21), and ALL patients under maintenance chemotherapy (M, n=23). Data were analyzed using Kruskal-Wallis test (post hoc Dunn's test). Data are presented as Median (IQR 25-75).

Parameters	Control (n=20)	ND-ALL patients(n=21)	M(n=23)	C vs ND p-value	ND vs M p-value	C vs M p-value
MDA ng/ml	32.93 (30.02-42.51)	42.31 (33.93-50.54)	34.70 (32.47-44.77)	(0.05)	ns	ns
8-OHdG pg/ml	349.6 (320.1-395.5)	408.1 (369.8-452.0)	359.5 (333.1-382.6)	(0.001)	(0.001)	ns
PC ng/ml	8.277 (6.188-10.74)	9.709 (8.165-13.02)	7.542 (5.679-9.567)	ns	ns	ns
GSH-PX ng/ml	9.967 (7.119-12.06)	6.870 (4.537-9.433)	7.412 (5.574-10.53)	(0.01)	ns	ns
SOD ng/ml	4.140 (3.237-5.475)	2.518 (2.173-3.304)	3.635 (2.630-4.560)	(0.001)	(0.05)	ns
T-AOC U/ml	5.556 (3.815-9.182)	3.418 (2.436-4.216)	4.024 (2.901-5.910)	(0.01)	ns	ns

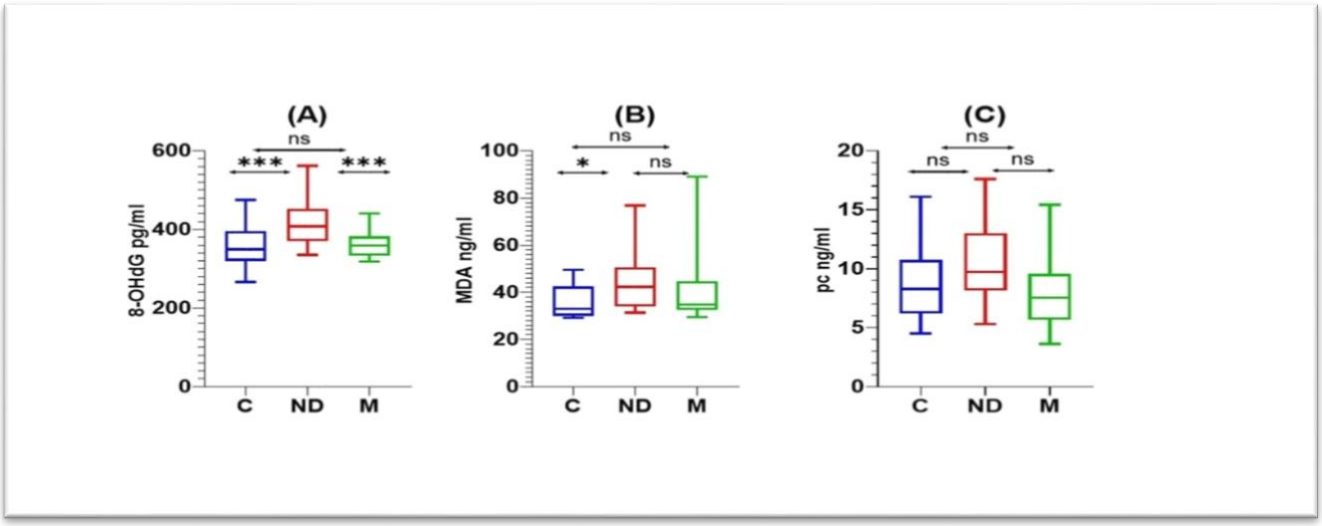

FIGURE 1. Comparison of oxidative stress biomarkers, including 8-hydroxy-2'-deoxyguanosine (8-OHdG (A)), malondialdehyde (MDA (B)), and protein carbonyl (PC (C)). * Shows the level of significance, ns=non-significance. Statistical comparisons were performed using the Kruskal–Wallis test followed by Dunn's multiple comparisons test.

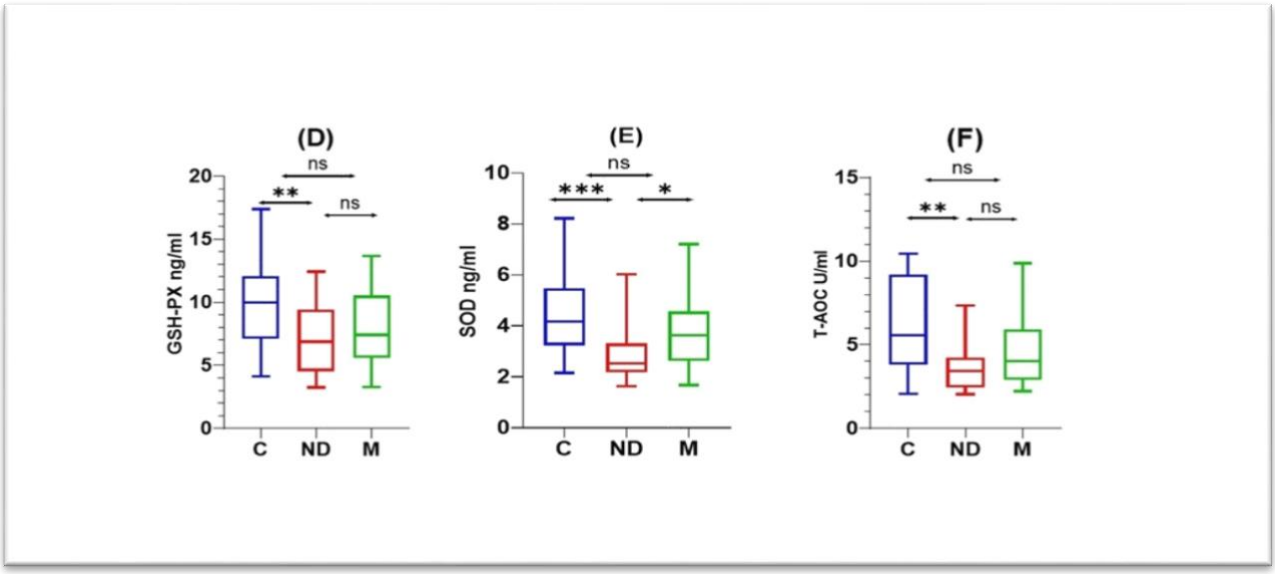

FIGURE 2. Comparison of Antioxidant status, including glutathione peroxidase (GSH-PX(D)), superoxide dismutase (SOD(E)), and total antioxidant capacity (T-AOC(F)), among the control (C) group, newly diagnosed ALL patients (ND), and patients on maintenance chemotherapy (M) group. * Shows the level of significance, ns=non-significance. Statistical comparisons were performed using the Kruskal–Wallis test followed by Dunn's multiple comparisons test.

The T-AOC level 3.418(IQR 2.436-4.216) and GSH-PX level 6.870 (IQR 4.537-9.433) demonstrated a significant decrease in ND-ALL patients when compared to the control group, whereas the decrease observed in the maintenance group was not statistically significant.

here was a highly significant decrease in SOD levels in ND-ALL patients compared to the control group, with a p value (0.001), and a significant difference was also observed between ND-ALL patients and the maintenance group (p-value = 0.05).

Table 3 and **Figures 3 and 4** present the results of MDA,8-OHdG, PC, SOD, GSH-PX, and T-AOC between ND-ALL patients and the same group after remission induction chemotherapy. The levels of MDA, 8-OHdG, and PC increased significantly in the RI group, with (p = 0.05, p = 0.01, and p = 0.01, respectively), indicating enhanced oxidative stress, while the levels of GSH-PX, SOD, and T-AOC decreased significantly.

Table 3. Comparison of antioxidant status and oxidative stress levels between newly diagnosed ALL-patient (ND), and ALL patients after induction remission chemotherapy (RI). (Median IQR 25-75). Paired comparisons were analyzed using the Wilcoxon signed-rank test.

Parameters	ND-ALL patients (n=21)	RI (n=21)	*p-value*
MDA ng/ml	42.31 (33.93-50.54)	54.46 (42.91-65.90)	0.05
8-OHdG pg/ml	408.1 (369.8-452.0)	451.6 (392.5-490.8)	0.01
PC ng/ml	9.709 (8.165-13.02)	13.18 (9.048-14.94)	0.01
GSH-PX ng/ml	6.870 (4.537-9.433)	5.434 (4.066-6.744)	0.01
SOD ng/ml	2.719 (2.226-3.304)	2.363 (1.963-2.472)	0.05
T-AOC U/ml	3.488 (2.622-4.738)	3.098 (2.385-3.558)	0.01

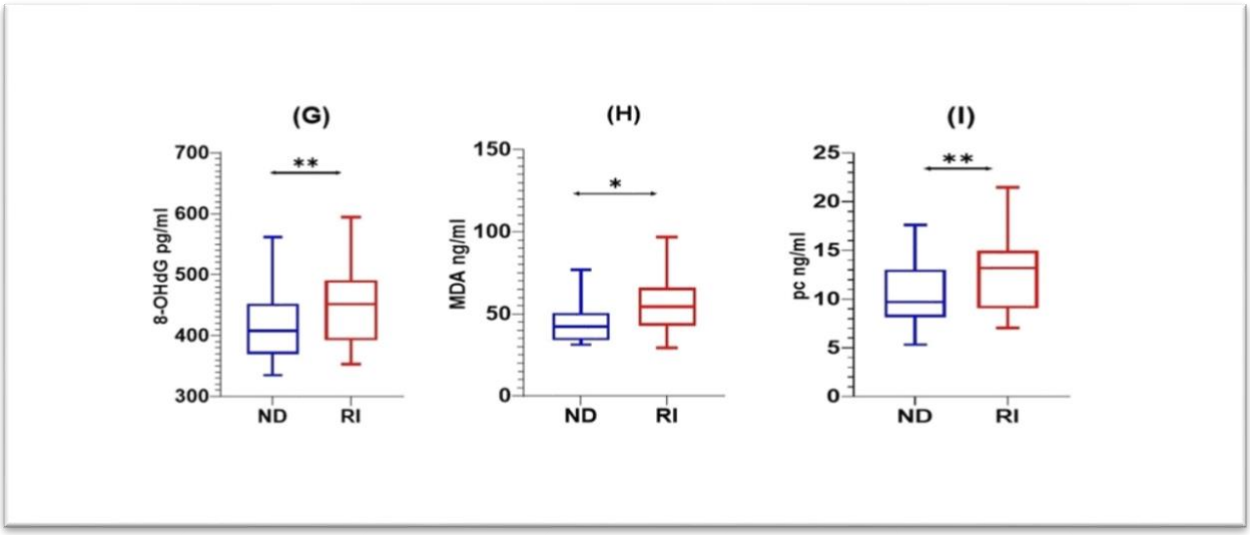

FIGURE 3. Comparison of oxidative stress biomarkers 8-OHdG(G), MDA(H), and PC(I), between newly diagnosed ALL patients (ND), and remission induction (RI) groups. * Shows the level of significance, ns=non-significance. Paired comparisons were analyzed using the Wilcoxon signed-rank test.

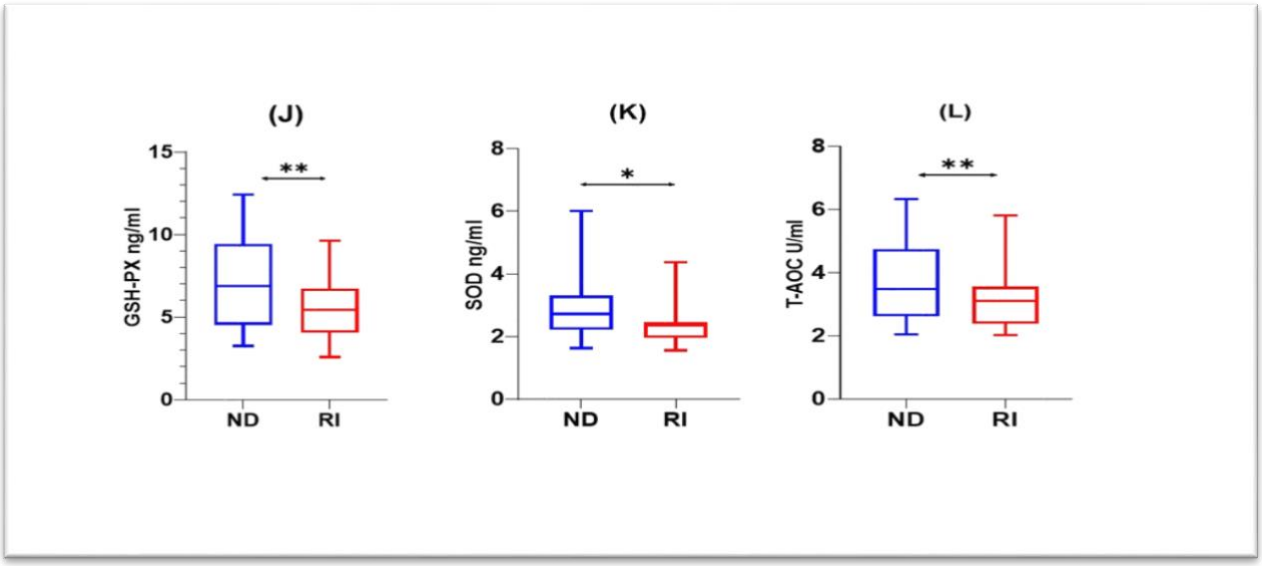

FIGURE 4. Comparison of Antioxidant status GSH-PX(J), SOD(K), and T-AOC(L), between the ND and RI groups. * Shows the level of significance, ns=non-significance. Paired comparisons were analyzed using the Wilcoxon signed-rank test.

4 DISCUSSION

The results of the study indicate that chemotherapy has an important effect on the redox balance in ALL patients. Chemotherapy promotes the formation of ROS, which leads to OS, and targets abnormal cells. Elevated levels of biomarkers such as MDA, 8OHdG, and PC showed an increase in OS.

ALL patients who receive the best available treatment currently have an overall survival of over 90%, due to significant advancements in recent decades [16].

The body remains in homeostasis and permits appropriate cell differentiation when ROS generation and antioxidant activity are in balance. However, because of the hypermetabolic state of the neoplastic cells, this equilibrium is changed

in leukemia toward increased ROS generation and a decrease in antioxidant activity. Leukemogenesis is accelerated by mutagenesis and DNA damage caused by elevated OS in the bone marrow microenvironment [17].

In the current research, antioxidant levels and oxidative stress indicators were assessed in ALL patients at various treatment stages in comparison to healthy controls. When compared to healthy individuals, we discovered that OS biomarker production was higher and antioxidant defense was lower in ALL patients. The idea that there is a connection between ROS activity and malignancy and that cancer or malignant cells generate a lot of ROS is supported by this finding [18, 19]. Numerous studies have demonstrated that low antioxidant levels in children with ALL at initial diagnosis are a sign of underlying leukemia, which in turn leads to higher OS. Curiously, it has also been demonstrated that chemotherapy causes oxidative damage, which triggers the death of malignant cells and so enhances the therapeutic impact [17].

According to our research, MDA levels were considerably higher in ND-ALL patients than in the control group. These findings are consistent with the rise in MDA levels in acute leukemia patients' serum [20]. OS has been implicated in the pathogenesis of acute leukemia patients. The mechanism of raised MDA may be due to lymphocyte cells are the source of superoxide and other oxygen metabolites, which lead to lipid peroxidation, and disrupt the OS/antioxidant balance in leukemia [21].

Most chemotherapeutics generate ROS in cancer cells. It is hypothesized that chemotherapeutic amplification of ROS levels pushes the already increased cancer cells over a threshold to induce cell death[22]. Anthracycline antibiotics, such as doxorubicin (DOX), and pirarubicin, are widely used as broad-spectrum chemotherapy drugs in the treatment of various types of cancer, including leukemia they lead to excessive production of ROS[23].By reducing antioxidant defenses, glucocorticoids like dexamethasone and prednisone also enhance oxidative stress. They achieve this by attaching to their receptors and suppressing the expression of genes that encode antioxidant enzymes[24].

In this study, 8-OHdG level was also significantly higher in ND-ALL patients compared to the control group. The elevated levels of 8-OHdG prior to chemotherapy indicate increased DNA oxidation and a heightened state of oxidative stress. Notably, 8-OHdG levels increased even further following chemotherapy, suggesting that treatment may exacerbate oxidative damage rather than alleviate it. In contrast, the 8-OHdG levels in the maintenance group were closer to those of the control group. This result is in harmony with [25], demonstrating a partial restoration of oxidative equilibrium in the latter stages of therapy. In multiple studies, 8-OHdG has been implicated in carcinogenesis and is a valuable indicator for evaluating oxidative DNA damage [26].

PC, a form of protein oxidation that reactive oxygen species can encourage, This study found that newly diagnosed ALL patients had a non-significantly greater level of PC than the control group; this finding is consistent with [27, 28], which reported higher plasmatic concentrations of MDA and PC in ALL patients. [29]also showed a higher level of MDA in ND-ALL patients compared to the control group which indicates the presence of heightened OS at diagnosis, likely reflecting the increased production of reactive oxygen species. The levels of 8-OHdG, MDA, and PC were also compared. In the maintenance group, the levels of these markers were higher than those in the control group but lower than patients undergoing induction remission chemotherapy, which aligns with the reduced chemotherapy dosage during the maintenance phase. These findings suggest that oxidative stress increases during induction chemotherapy but partially recovers during maintenance therapy. This reduction may reflect an improvement in the patients' condition and a partial recovery from chemotherapy-induced oxidative stress that was in harmony with [28]results that measured MDA levels in ALL patients in the maintenance group, which were higher when compared with the control group. Lipid peroxidation products rise after treatment, but antioxidant plasma levels sharply decline [30, 31] Lower levels of anti-oxidants are associated with increases in the adverse side effects of chemotherapy [31],other studies showed that MDA levels increased significantly following remission induction chemotherapy, which may be attributed to the high dosage of chemotherapeutic agents administered during this phase [32].

The current study supports earlier research showing that SOD levels are lower in leukemias, including ALL, than in healthy individuals. The main factor contributing to the buildup of ROS in disease is a weakened antioxidant system. Numerous growth and proliferation pathways are also impacted by the increased ROS levels. Among the most important enzymatic scavengers during physiological cellular respiration are SOD and GSH-PX. GSH-PX scavenges the H_2O_2 that SOD creates from superoxide radical ($O2\ ^{\cdot -}$) to stop the buildup of the more hazardous Hydroxyl radical ($^{\cdot}OH$).[33]. In the present study the results indicated that SOD and GSH-PX levels decreased significantly when we compared newly diagnosed ALL patients with the control group. [34] ,likewise demonstrated that the level of these enzymes was lower in the control group than in ND ALL patients. Studies on other malignancies, such as breast cancer, have revealed a large rise in SOD levels in contrast to these findings, indicating that antioxidant responses are regulated differently depending on the kind of cancer[35]. This is still a controversial topic, though, because depending on the circumstances, leukemia cells' antioxidant activity may be enhanced or diminished. For instance, it has been discovered that several leukemia types have either up- or down-regulated SOD levels. In actuality, SOD activities are up-regulated in AML but down-

regulated in ALL[36]. Variations in tumor type, disease stage, therapy phase, and underlying amount of oxidative stress can all affect how antioxidant enzymes are regulated, which could account for this disparity.

Comparing the control group to the maintenance group indicated no discernible drop in the levels of these enzymes which is consistent with [28]SOD and GSH-PX levels in newly diagnosed ALL patients and the same group following induction remission treatment were also studied. Following chemotherapy, there was a significant decrease in GSH-PX levels and SOD levels. [37], who reported that leukemia significantly decreases vitamin E and A levels as well as SOD, CAT, and GSH-PX. According to these findings, the biological system is protected from ROS by antioxidant enzymes as well as vitamins E and A. Vitamin E levels are lower in ALL patients than in healthy controls. Furthermore, as free radicals are known to cause apoptosis in human leukemic cells since antileukemic regimens suppress GSH-PX and SOD, lower GSH-PX and SOD levels in treated ALL patients may be the cause of increased free radical formation and, consequently, leukemic cell apoptosis. SOD enzymes reduce the potential toxicity of various ROS and reactive nitrogen species (RNS) by regulating their levels. Their signaling activities also control a wide range of cellular functions [38].

The T-AOC level was measured and compared in the current study between ND- ALL patients, the maintenance group, and the control group. The T-AOC level was not considerably lower in the maintenance group, but it was significantly lower in ND ALL patients when compared to the control group. [39], who reported that complete remission status in leukemia was linked to persistently low T-AOC. In the current study T-AOC level after remission induction chemotherapy decreased significantly when compared to ND-ALL patients, with a p-value (0.01). OS should be observed during successive treatment cycles and during the maintenance period as well, since a rise in OS was noted following the first month of treatment.

The study suggests that tracking oxidative stress indicators can provide valuable insights for managing ALL, predicting toxicity and guiding care strategies. However, it did not directly assess prognosis or treatment outcomes.

CONCLUSION

The current study demonstrated that both the disease and chemotherapy induce increased OS in. MDA, 8-OHdG, and, PC levels were elevated in ND-ALL patients, and continued to rise during remission induction, suggesting that therapy exacerbates OS. Antioxidant defenses (GSH-PX, SOD, and T-AOC) were also markedly reduced in ND-ALL and continued to diminish after induction. Oxidative and antioxidant indicators partially returned to normal during the maintenance phase, indicating a slow restoration of redox equilibrium as chemotherapy intensity drops. This study offers valuable insights into oxidative stress and antioxidant enzymes activity in ND-ALL patient, spanning not only the newly diagnosed stage but also after remission induction and during maintenance therapy despite the limitations, like small sample size and limited longitudinal follow-up. To enhance therapy tolerance and improve patient outcomes, future approaches should focus on targeted modulation of redox balance.

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