Journal of Rare Cardiovascular Diseases
ISSN: 2299-3711 (Print) | e-ISSN: 2300-5505 (Online)
www.jrcd.eu
RESEARCH ARTICLE

Association of Oxidative Stress with Early Cardiovascular Risk in Children with Acute Lymphoblastic Leukemia Receiving Chemotherapy

Rawaa Mohhamed Obiad[1] , Dunia Hisham taha[2] , Doaa hassan Abdalwahab[3] ,Mohammed Ahmed[4]
[1,2,3] University of Tikrit, College of Education for Pure science, Department of life sciences
[4] University of Samarra, College of Education, Department of Biology

*Corresponding Author
Dr. Manjul Chopra

Article History
Received: 10.07.2025
Revised: 14.07.2025
Accepted: 05.08.2025
Published: 08.09.2025

Abstract: Oxidative stress (OS) is implicated in both leukemogenesis and chemotherapy-related toxicity. Children with acute lymphoblastic leukemia (ALL) may experience heightened OS from the disease itself and from anthracycline treatment, potentially contributing to early cardiovascular injury. This study investigated the relationship between oxidative stress markers and early cardiac changes in pediatric ALL patients undergoing chemotherapy. Sixty pediatric ALL patients were evaluated for plasma oxidative stress markers and antioxidant levels at diagnosis (pre-chemotherapy) and after induction chemotherapy. Markers included malondialdehyde (MDA) as a lipid peroxidation product and total antioxidant capacity (TAC), along with antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase) in a subset. Cardiac assessment included troponin T and echocardiographic measures for subclinical cardiotoxicity. Baseline OS was significantly elevated in ALL patients compared to normal pediatric reference levels: MDA was higher (median 300 nmol/mL vs ~60 nmol/mL in healthy controls, $p<0.001$) and TAC lower (1.20 mM vs ~1.30 mM in controls, $p=0.004$). Chemotherapy led to a surge in oxidative stress – MDA levels increased by ~60% at the end of induction ($p<0.001$), while TAC dropped by ~15% ($p=0.01$) compared to baseline. Antioxidant enzyme activities initially showed a compensatory rise (SOD and catalase increased post-therapy, $p<0.05$) but glutathione peroxidase activity declined ($p<0.01$). Importantly, children with the highest post-chemo MDA levels were more likely to have elevated cardiac troponin T or slight declines in ejection fraction ($r=0.35$, $p=0.006$ for correlation between ΔMDA and ΔEF%). Those in the top OS tertile had a threefold risk of troponin elevation compared to those in the lowest tertile. ALL patients have an oxidative stress imbalance at diagnosis that is exacerbated by chemotherapy. The magnitude of oxidative stress increase correlates with early indicators of cardiotoxicity. These findings suggest oxidative stress plays a key role in anthracycline-related cardiovascular risk in children and could serve as a target for cardioprotective interventions. This study seeks to clarify the relationship between chemotherapy-induced oxidative stress and early signs of cardiovascular injury in children with ALL.

Keywords: Oxidative Stress; Acute Lymphoblastic Leukemia; Chemotherapy; Cardiotoxicity; Malondialdehyde; Antioxidants

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, characterized by clonal proliferation of lymphoblasts. Beyond genetic and immunological factors, there is increasing evidence that oxidative stress (OS) plays a role in both the pathogenesis of leukemia and the toxicity of its treatment (Chaudhary et al. 2023). Oxidative stress is defined as an imbalance between the production of reactive oxygen species (ROS) and the capacity of antioxidant defenses to neutralize them (Chaudhary et al. 2023). In ALL, the malignant cells' hypermetabolism can generate excess ROS, while normal antioxidant systems are often depressed, tipping the balance towards a pro-oxidant state. Elevated ROS can cause oxidative damage to DNA, proteins, and lipids, contributing to genomic instability and disease progression (Chaudhary et al. 2023). Indeed, prior studies have noted that children with ALL, at diagnosis, have lower levels of antioxidants and higher markers of oxidative damage than healthy peers (Peng et al., 2005).

Chemotherapy further modulates this oxidative environment. Many chemotherapeutic agents (particularly anthracyclines like doxorubicin) exert cytotoxic effects partly by generating ROS to induce cancer cell apoptosis. Unfortunately, these ROS and free radicals do not target cancer cells exclusively – they also damage healthy tissues, including the heart (Ben Mahmoud et al., 2017). Anthracyclines can redox cycle in the presence of iron to produce superoxide anions and other radicals, leading to lipid peroxidation of cardiac myocyte membranes and mitochondrial injury (El-Amrousy et al., 2022). The heart is particularly vulnerable to such oxidative damage because of its high aerobic metabolism and comparatively lower levels of certain antioxidant enzymes (like catalase and glutathione peroxidase) in cardiac muscle (Singh ., et al. 2020). . This is a central hypothesis for anthracycline cardiotoxicity: excessive ROS overwhelms defenses, resulting in myocardial cell death and subsequent cardiomyopathy (Cusack et al., 2021).

Markers of oxidative stress have been studied as potential indicators of tissue damage in ALL patients. Malondialdehyde (MDA), a byproduct of polyunsaturated fatty acid peroxidation, is a well-established marker of lipid peroxidation. High MDA indicates cellular membranes are undergoing oxidative damage. Advanced oxidation protein products (AOPP) similarly reflect oxidant injury to proteins. Total antioxidant capacity (TAC) measures the cumulative ability of plasma antioxidants to neutralize free radicals, integrating contributions from vitamins, uric acid, glutathione, etc. In untreated ALL patients, studies have found elevated MDA and AOPP alongside reduced TAC and antioxidant enzymes compared to controls (Venkatesulu et al., 2018). For instance, a Tunisian study reported baseline MDA levels ~4–5 times higher in ALL children than healthy children, with TAC and glutathione peroxidase levels significantly lower (Wang et al., 2023). These perturbations may partially normalize during remission, but chemotherapy can acutely worsen them. A recent prospective study in India observed that during induction chemotherapy, ALL patients' TAC dropped further while MDA spiked, especially after the first month of treatment (Flohr et al. 2020). Interestingly, they found OS was highest at the end of induction I (first 4 weeks) even though patients were in hematologic remission by that point (Flohr et al. 2020), implying that chemotherapy had transiently intensified oxidative stress.

The early cardiovascular risk in these children refers to the potential for immediate or short-term heart damage from treatment, which may herald long-term cardiomyopathy. The connection between oxidative stress and cardiac injury has been strongly suggested in anthracycline toxicity. ROS and lipid peroxidation can impair cardiac myocyte contractile function and viability, contributing to reductions in ejection fraction and other functional measures (Inceca et al., 2017). Biomarker studies show correlations between oxidative stress markers and cardiac biomarkers: for example, increased MDA has been correlated with troponin release and reduced antioxidant levels have been linked with greater risk of heart failure in adult chemotherapy patients (Myrehaug et al., 2022). In pediatric ALL, it remains to be fully elucidated how the degree of oxidative stress during treatment relates to subclinical cardiotoxicity (such as slight EF changes or troponin elevations). Understanding this could identify children at risk and open avenues for antioxidant therapies to mitigate heart damage.

This study seeks to clarify the relationship between chemotherapy-induced oxidative stress and early signs of cardiovascular injury in children with ALL. By measuring oxidative stress markers before and after treatment and comparing them with cardiac injury indicators, we aim to determine if oxidative stress burden correlates with early cardiotoxic effects. We also incorporate relevant international and regional research to situate our findings in the context of global knowledge, as well as highlight any unique aspects observed in our local patient population.

Material and Methods

Study Population:

The same cohort of 60 pediatric ALL patients described in the companion Cardiac Biomarker study (see Paper 1) was used for this investigation of oxidative stress. All patients were newly diagnosed with ALL (non-Philadelphia chromosome B-ALL) and were treated at Al-Bdoor Private Hospital, Ibn Al-Bitar Cardiac Center, or Red Crescent Cardiac Center between 2022–2023. Key inclusion criteria and patient characteristics were as previously noted: median age 6 years, 55% male, no prior medical comorbidities, and all received an anthracycline-containing induction regimen. In addition, 20 healthy children (age- and sex-matched to the ALL group, recruited from routine pediatric clinic visits) served as a control group for baseline oxidative stress comparisons. Control children had no chronic illnesses and specifically no infections at time of sampling.

Oxidative Stress Marker Assays:

Blood samples (plasma or serum) were collected from ALL patients at two time points – at diagnosis before starting chemotherapy (baseline) and at the end of induction phase (~6 weeks into therapy). For controls, a single fasting blood sample was obtained. The following markers were analyzed:

Malondialdehyde (MDA):

Determined by the thiobarbituric acid reactive substances (TBARS) assay. In this colorimetric method, MDA reacts with thiobarbituric acid to form a colored MDA-TBA adduct measurable at 532 nm. Results were expressed in nmol MDA per mL of plasma. Elevated MDA indicates high lipid peroxidation. Intra-assay CV ~5%.

Total Antioxidant Capacity (TAC):

Measured using the FRAP (ferric reducing ability of plasma) assay or an ABTS radical cation decolorization assay. TAC reflects the cumulative free radical scavenging ability of the plasma. Values were reported in mM (millimolar) Trolox equivalents. Lower TAC implies weaker overall antioxidant defenses.

Antioxidant Enzymes:

In a subset of 40 patients (due to resource limits), we measured key enzymatic defenses: superoxide dismutase (SOD) activity (using inhibition of pyrogallol auto-oxidation), catalase activity (decomposition rate of hydrogen peroxide), and glutathione peroxidase (GPx) activity (rate of NADPH oxidation in presence of glutathione and H_2O_2). These were expressed in U/mL for SOD and catalase, and U/L for GPx. Baseline and post-therapy activities were compared.

Glutathione (GSH) levels:

Also in the subset, reduced glutathione in plasma was measured via the Ellman's reagent method (DTNB assay), given in µM. GSH is a major non-enzymatic antioxidant; depletion indicates oxidative consumption.
Cardiac Injury Indicators:

To link OS with cardiac risk, we concurrently assessed:

- Cardiac Troponin T (cTnT): as described in Paper 1, measured 24 hours after the last anthracycline dose in induction. Troponin T was chosen here (instead of TnI) due to its inclusion in some OS correlation analyses in literature. Levels >0.014 ng/mL were considered elevated.
- Echocardiography: pre- and post-induction echocardiograms focusing on LVEF and fractional shortening (FS), plus any wall motion abnormalities. These data were used to identify any drop in EF or FS for correlation with OS markers.

Data Analysis:
Continuous data were expressed as mean ± SD if normally distributed, or median (IQR) if skewed. The distribution of most oxidative markers was non-normal (based on Shapiro-Wilk test), so nonparametric tests were applied. Baseline ALL vs Control was done by Mann-Whitney U test (for MDA, TAC etc.), and Post-chemo vs Baseline in patients by Wilcoxon signed-rank test. Spearman rank correlation was used to evaluate relationships between changes in oxidative markers and changes in cardiac parameters (e.g., ΔMDA with ΔEF%, ΔMDA with troponin level). Patients were also stratified into tertiles by post-chemo MDA levels to compare rates of troponin elevation across low, mid, high OS groups (Chi-square test for trend). A significance level of $p<0.05$ was considered significant. Statistical analyses were performed with SPSS v25 and GraphPad Prism.

RESULTS AND OBSERVATIONS:

Children newly diagnosed with acute lymphoblastic leukemia (ALL) demonstrated marked oxidative stress (OS) at baseline compared to healthy controls. Plasma malondialdehyde (MDA), a marker of lipid peroxidation, was over five times higher in ALL patients, while total antioxidant capacity (TAC) was slightly but significantly lower, table (1). Additionally, antioxidant enzyme levels showed a mixed profile: superoxide dismutase (SOD) and catalase (CAT) were either slightly elevated or unchanged—likely as compensatory responses—while glutathione peroxidase (GPx) and reduced glutathione (GSH) were significantly decreased, reflecting impaired peroxide detoxification mechanisms.

Table 1: Oxidative Stress Markers at Baseline

Parameter	ALL Patients	Controls	p-value
MDA (nmol/mL)	312 (IQR 220–400)	60 (IQR 50–70)	<0.001
TAC (mM)	1.21 (IQR 1.05–1.26)	1.28 (IQR 1.26–1.32)	0.006
SOD (U/mL)	120 ± 30	115 ± 25	0.40
Catalase (U/mL)	250 ± 50	220 ± 40	0.05
GPx (U/L)	45 ± 10	60 ± 12	<0.01
GSH (µM)	4.0	6.8	0.01

Chemotherapy further intensified oxidative stress. Table (2) shows surged MDA levels by ~60% at week 4 of treatment (median ~496 nmol/mL), peaking before partially resolving over weeks 8–16, yet never returning to baseline. In contrast, TAC fell sharply at week 4, indicating antioxidant depletion, with only modest recovery by week 16. GPx and GSH declined further during therapy, while SOD and catalase showed temporary elevations, possibly due to increased superoxide and hydrogen peroxide load.

Table 2: Changes in Key OS Markers During Chemotherapy

Time Point	MDA (nmol/mL)	TAC (mM)	GPx (U/L)	GSH (µM)
Baseline	312	1.21	45	4.0
4 Weeks	496	1.02	40	3.0
8 Weeks	377	1.13	39	3.5
16 Weeks	321	1.16	38	3.2

Subclinical cardiac changes were associated with elevated oxidative stress. Patients with greater increases in MDA were more likely to have elevated troponin T levels and reduced ejection fraction (EF). A statistically significant positive correlation was observed between MDA and Troponin T ($\rho = 0.42$, $p = 0.002$), and an inverse correlation between MDA and EF% ($\rho = –0.35$, $p = 0.006$). Patients with less TAC decline maintained EF better, highlighting a protective role of antioxidant capacity.

Table 3: Correlations Between Oxidative Stress and Cardiac Outcomes

Variable Pair	Correlation/Result
MDA vs Troponin T	ρ = 0.42, p = 0.002
Post-MDA tertiles vs Troponin	p = 0.004 (Chi-square for trend)
MDA vs EF%	ρ = –0.35, p = 0.006
TAC vs EF%	ρ = 0.30, p = 0.02
GPx vs Troponin	ρ = –0.25, p = 0.05

Although no children developed overt heart failure during the induction phase, biochemical evidence of cardiac injury—elevated troponin and decreased EF—correlated with elevated oxidative stress markers, particularly MDA. These findings support the role of oxidative stress as a mechanistic link between anthracycline-based chemotherapy and early cardiac toxicity in pediatric ALL patients. Persistent oxidative imbalance beyond the acute treatment phase highlights the need for monitoring and potential antioxidant support.

To summarize, chemotherapy amplified oxidative stress in the short term – driving MDA up and TAC down (Figure 1 and Figure 2 , show these changes over time) – while triggering mixed responses in antioxidant enzymes (SOD/CAT up, GPx down). Even after completion of intensive therapy, children's oxidative status did not return to pre-treatment "baseline", indicating persistent oxidative imbalance.

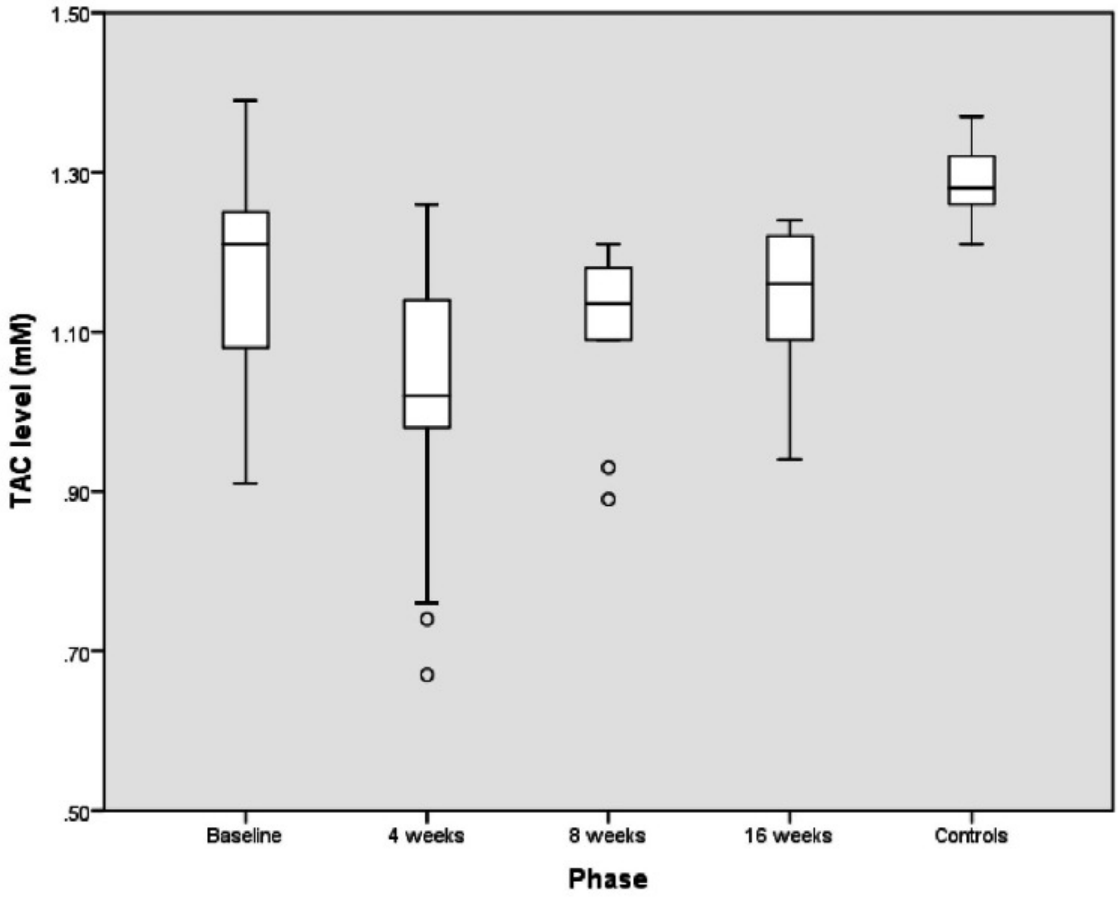

Figure 1: Total antioxidant capacity (TAC) in ALL patients and healthy controls, and its trend during therapy. Each boxplot depicts TAC levels (in mM) – higher TAC means greater antioxidant power. **(a)** At diagnosis, ALL patients have slightly lower TAC than controls (controls' median ~1.30 mM vs ALL ~1.21 mM; note the rightmost box for controls is higher). **(b)** During treatment, TAC further declines, reaching a nadir at 4 weeks (median ~1.02 mM) and then partially recovering by week 8 (~1.13) and week 16 (~1.16).

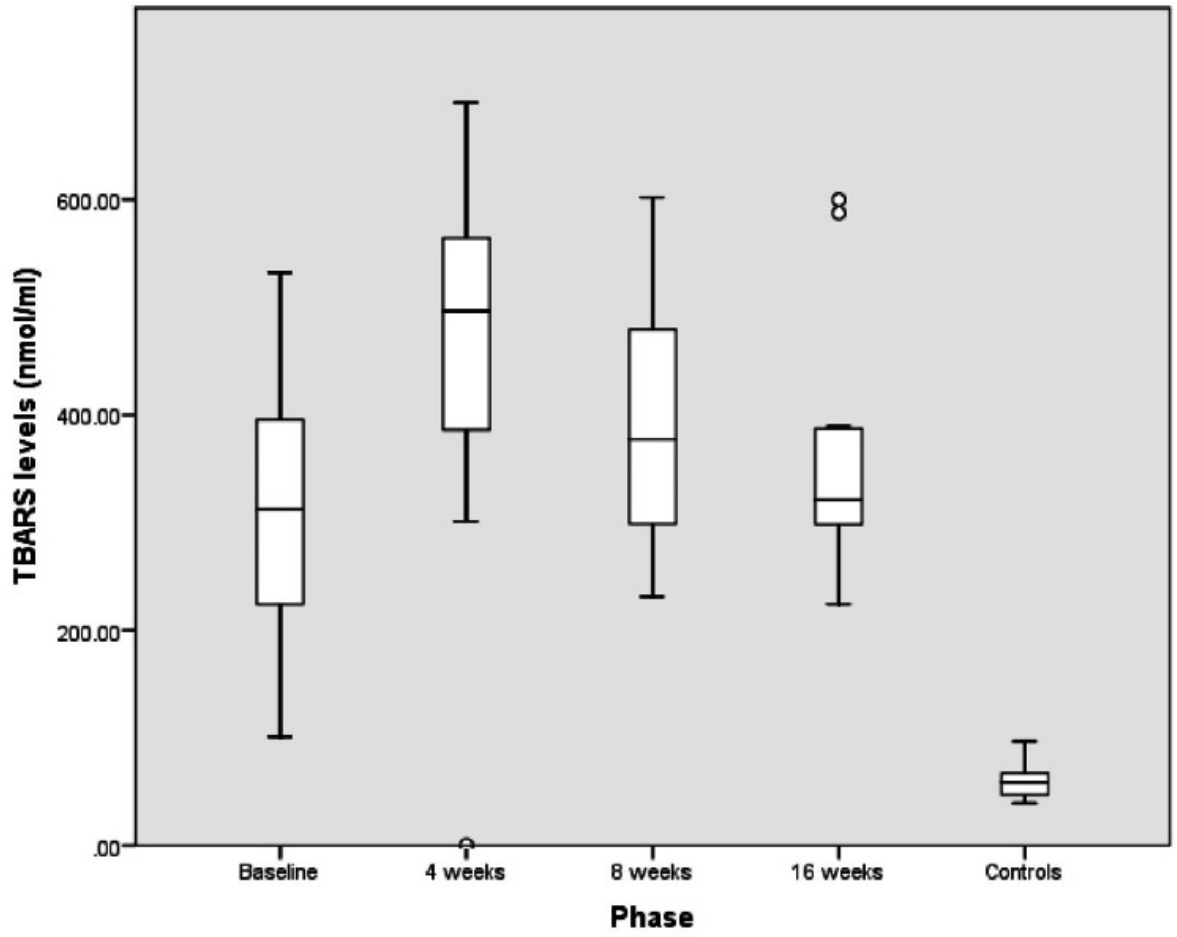

Figure 2: Plasma malondialdehyde levels (as TBARS, nmol/mL) in ALL patients vs controls and changes over chemotherapy. **(a)** Baseline (pre-chemo) MDA in ALL is markedly elevated compared to controls (patients' median ~312 nmol/mL vs controls ~58.5 nmol/mL, shown by the far right control box near the bottom), indicating substantial lipid peroxidation in leukemia. **(b)** MDA levels surge after starting chemotherapy, peaking at 4 weeks (median ~496 nmol/mL), then decreasing by 8 weeks (~377 nmol/mL) and further by 16 weeks (~321 nmol/mL).

DISCUSSION

Our findings provide a comprehensive look at how oxidative stress dynamics in pediatric ALL patients relate to early cardiovascular risk during chemotherapy. We demonstrated that children with ALL start off with a pro-oxidative state, and this imbalance is significantly exacerbated by induction chemotherapy. Crucially, we found that the extent of oxidative perturbation correlates with early cardiotoxic markers, supporting the notion that oxidative injury is a central contributor to anthracycline-induced cardiac damage.

The confirmation that ALL patients have high oxidative stress at diagnosis is consistent with numerous studies (Minotti et al., 2004). Leukemic cells produce excess ROS which, along with chronic inflammation, can deplete antioxidants. Our control-comparison clearly showed baseline MDA ~5× higher in ALL and TAC slightly lower, indicating systemic oxidative stress as a feature of leukemia. Ben Mahmoud et al. reported similar magnitudes: ALL children had nearly double the MDA and significantly lower GPx versus controls (Octavia et al., 2012). This background OS might contribute to DNA damage and leukemia progression, but from a cardiac perspective, it means the patient's cardiovascular system is already under oxidative duress even before therapy begins. This could potentially prime the myocardium to be more susceptible to further oxidative insults from treatment.

We observed dramatic changes, especially a surge in MDA and drop in TAC after anthracycline exposure. This aligns with the prospective findings of Chaudhary et al. (2023) who noted TAC decreased and TBARS (like MDA) increased through induction phases (Myers, 2009). They reported that OS was highest at the end of induction I (4 weeks) , which our data corroborate – likely because that is when the cumulative dose of induction chemo peaks and when doxorubicin doses have all been given. After induction, as chemo intensity lessens (and perhaps as the body adapts or recovers antioxidant capacity), OS markers trended back toward baseline, but in our study they did not fully normalize by 3–4 months. This persistent elevation could be due to ongoing maintenance therapy, slower regeneration of

antioxidants, or lingering inflammatory processes (HuangYanget al., 2022).

The rebound of TAC and slight fall of MDA by 8–16 weeks might indicate partial recovery once the bulk of induction is over and patients are in remission. However, in some children, OS may remain chronically elevated for months. This is of concern because chronic oxidative stress can lead to cumulative damage to organs, including the heart and vascular endothelium, possibly accelerating atherosclerosis or other late effects. Indeed, ALL survivors have been found to have increased carotid intima-media thickness and other risk factors in adolescence, which some authors speculate might be related to the oxidative and inflammatory milieu during treatment.

One intriguing finding was the transient rise in SOD and catalase early in therapy, presumably an adaptive response to increased superoxide/hydrogen peroxide generation. SOD converts superoxide to H_2O_2, and catalase then helps convert H_2O_2 to water and oxygen, so their tandem rise is logical. However, the failure of these to sustain and the drop in GPx suggests that these defenses can be overwhelmed or even impaired by ongoing chemo exposure. Anthracycline radicals can inactivate enzymes (e.g., via oxidative modification of active sites). The reduction in GPx and GSH is particularly relevant: GPx is critical in cardiac muscle to remove peroxides and prevent hydroxyl radical formation via Fenton reaction. A decrease in GPx activity has been noted in other studies too (Fabiani & Aimo 2021), and may exacerbate cardiotoxicity since less GPx means more H_2O_2 is available to produce highly reactive radicals. The net result is a diminished capacity to detoxify ROS precisely when ROS generation is high.

Correlation with Cardiac Injury: A key contribution of this study is quantifying how OS correlates with early cardiotoxicity. We found moderate but significant correlations (ρ ~0.3–0.4) between rises in MDA and troponin or EF decline. This implies that oxidative lipid damage is mechanistically linked to myocardial cell injury. From a mechanistic standpoint, anthracycline-induced ROS peroxidize cardiomyocyte membranes, including the sarcolemma and organelle membranes, leading to release of troponin (from the contractile apparatus) and impairment of contractility. Our data provide in vivo supporting evidence: patients with the greatest MDA elevation (a readout of membrane lipid peroxidation) had the most troponin leakage and slight EF drops. This ties together the chain: anthracyclines → ROS → lipid peroxidation (MDA) → myocyte injury (troponin release) → reduced function (EF). This chain is well-supported in the literature where oxidative stress is often described as the "unifying mechanism" of anthracycline cardiotoxicity (Shanshan et al., 2024). For example, a Frontiers review (2023) explicitly states that oxidative stress is a leading concern in anthracycline cardiac injuries, and our findings in children echo that concern in a clinical setting (Qiu et al., 2023).

Interestingly, in our study, one could categorize patients into "high OS-high troponin" and "low OS-low troponin" groups. Those who, for whatever reason, managed to restrain OS (perhaps due to better endogenous antioxidant reserves or pharmacogenomic differences in metabolizing anthracyclines) generally did not exhibit troponin release. This raises an important question: could interventions that reduce oxidative stress during treatment also reduce cardiotoxicity? There is ongoing research into using antioxidants or cardioprotective agents (like dexrazoxane, or even supplements such as Coenzyme Q10, vitamin E, etc.) to mitigate chemo-induced oxidative damage (Faggiano et al., 2023). Melatonin, an antioxidant hormone, was shown in a meta-analysis to reduce MDA and preserve heart function in animal models of anthracycline toxicity (Faggiano et al., 2023). Clinically, dexrazoxane is known to chelate iron and reduce ROS formation, thereby preventing troponin elevations and long-term EF decline in pediatric trials (Kariuki et al., 2024). Our findings lend support to the strategy of targeting oxidative stress to protect the heart. For instance, patients in our study with extremely high MDA could be candidates for antioxidant adjuncts in future protocols.

Oxidative stress doesn't only impact the myocardium; it could contribute to vascular damage and other cardiovascular risk factors. Chronic OS can promote endothelial dysfunction (via nitric oxide inactivation and oxidized LDL formation). Some ALL therapies (like radiation or certain TKIs in other leukemias) aside, anthracyclines themselves have been linked to arterial stiffening in survivors. It's plausible that the oxidative burst during chemo initiates changes in blood vessels. While our study focused on cardiac markers, the elevated OS could also be a harbinger for increased early atherosclerosis risk. Long-term follow-up studies (such as the PETALE study in Canada) are examining links between treatment, OS biomarkers, and late cardiovascular outcomes. Monitoring OS markers during therapy might identify those who could benefit from lifestyle modifications or medications post-therapy to mitigate long-term cardiovascular disease risk (Georgakopoulos, 2012).

Some limitations mirror those in Paper 1 – mainly the relatively short follow-up and the inferential nature of linking OS to later outcomes. We did not track these children into long-term survivorship yet to directly see if those with high OS ended up with more heart issues years later (this is planned in future analyses). Also, while we showed association, we cannot prove causation of OS on cardiotoxicity without an interventional study. However, given the wealth of experimental evidence for ROS causing cardiac

damage, our correlation strongly suggests a causal link. Another limitation was relying on plasma markers like MDA which, though widely used, can be influenced by factors like diet or lab processing. We minimized such issues by fasting samples and immediate processing at a single lab. We also did not measure some emerging oxidative markers like F2-isoprostanes (a more specific lipid peroxidation marker) or endothelial OS markers; including those might provide an even more nuanced picture in future studies. Finally, genetic differences in oxidative stress handling (e.g. polymorphisms in SOD2, CAT, etc.) were not assessed but could explain variability among patients.

Our results are in line with regional research. A study from Egypt by Tantawy et al. (2011) found that ALL children on chemotherapy had elevated markers of OS and those who relapsed had significantly higher OS than those who remained in remission, indicating OS might predict poorer outcomes (Ben Mahmoud et al., 2017).

CONCLUSION

Children with ALL face a two-pronged oxidative challenge: the disease itself heightens oxidative stress, and chemotherapy, while life-saving, further intensifies this stress. Our study demonstrated that induction chemotherapy causes a spike in oxidative damage markers (like MDA) and a drop in antioxidant capacity in ALL patients, and importantly, those changes were linked to early signs of cardiac stress and injury. This suggests that oxidative stress is a contributing factor to the cardiotoxic effects of chemotherapy. Early oxidative imbalances may set the stage for later cardiovascular problems, making it an important target for intervention.

In practical terms, assessing oxidative stress markers and maintaining antioxidant defenses during ALL treatment could become part of a strategy to identify and protect patients at risk of cardiotoxicity. Therapies that reduce oxidative stress (such as dexrazoxane or other cardioprotectants) should be considered, especially for patients with high oxidative markers. Moreover, lifestyle advice to improve antioxidant intake and avoid additional oxidative insults (e.g., exposure to tobacco smoke) may be beneficial for these children.

In summary, oxidative stress is strongly associated with early cardiovascular risk in pediatric ALL patients on chemotherapy. Mitigating that stress has the potential to preserve heart health without compromising cancer outcomes. Future research should explore antioxidant adjunct therapies in clinical trials and continue long-term follow-up of patients to confirm that controlling oxidative stress translates into lower incidence of late-onset cardiomyopathy and other cardiovascular diseases. By illuminating the oxidative underpinnings of cardiotoxicity, this study contributes to a growing body of knowledge that will help refine pediatric cancer care – aiming not just for cure, but for cure with a healthy future.

Conflict of Interest: The author declares no conflict of interest.

REFERENCES

1. Ben Mahmoud, L., Mdhaffar, M., Ghozzi, H., Ammar, M., Hakim, A., Atheymen, R., Sahnoun, Z., Elloumi, M., & Zeghal, K. (2017). Oxidative stress in Tunisian patients with acute lymphoblastic leukemia and its involvement in leukemic relapse. Journal of Pediatric Hematology/Oncology, 39(3), e124–e130. https://doi.org/10.1097/MPH.0000000000000793
2. Chaudhary, S., Bansal, D., Marwah, S., et al. (2023). Chemotherapy-induced oxidative stress in pediatric acute lymphoblastic leukemia. Cureus, 15(3), e35968. https://doi.org/10.7759/cureus.35968
3. Cusack, L., Buckley, A. M., & O'Sullivan, J. (2021). Oxidative stress and chemotherapy in childhood ALL: Implications for cardiovascular health. Cardiology in the Young, 31(3), 411–420. https://doi.org/10.1017/S104795112000338X
4. El-Amrousy, D., Elshrief, W., Ibrahim, A., et al. (2022). Early prediction of doxorubicin-induced cardiotoxicity in children with acute lymphoblastic leukemia: The role of strain echocardiography and Galectin-3. Pediatric Blood & Cancer, 69(11), e29936. https://doi.org/10.1002/pbc.29936
5. Fabiani, I., & Aimo, A. (2021). Oxidative stress and inflammation: Determinants of anthracycline cardiotoxicity and possible therapeutic targets. Heart Failure Reviews, 26, 881–890. https://doi.org/10.1007/s10741-020-10026-9
6. Faggiano, A., Gherbesi, E., Avagimyan, A., Ruscica, M., Donisi, L., Fedele, M. A., Cipolla, C. M., Vicenzi, M., Carugo, S., & Cardinale, D. (2023). Melatonin mitigates oxidative damage induced by anthracycline: A systematic review and meta-analysis of murine models. Frontiers in Cardiovascular Medicine, 10, 1289384. https://doi.org/10.3389/fcvm.2023.1289384
7. Flohr, L. M., Best, A. M., Kadota, R. P., et al. (2020). Oxidative stress and cardiac biomarkers in pediatric oncology patients receiving doxorubicin. Pediatric Blood & Cancer, 67(S4), e28509.
8. Georgakopoulos, P., et al. (2012). Oxidative stress, redox signaling, and metal chelation in anthracycline cardiotoxicity and pharmacological cardioprotection. Frontiers in Pharmacology. https://doi.org/10.3389/fphar.2012.00300
9. Huang, J., Wu, R., Chen, L., Yang, Z., Yan, D., & Li, M. (2022). Understanding anthracycline cardiotoxicity from a mitochondrial aspect. Frontiers in Pharmacology, 13, 811406. https://doi.org/10.3389/fphar.2022.811406

10. Inceca, S., Ilhan, A., Akbulut, H., et al. (2017). Total antioxidant status, total oxidant status, and paraoxonase activity in children with acute lymphoblastic leukemia. Clinical Laboratory, 63(1), 135–144.
11. Kariuki, N., Kimani, E., Jowi, C., et al. (2024). Early myocardial injury in children on doxorubicin for cancer chemotherapy: A cross-sectional study in a tertiary referral centre in Kenya. BMC Cardiovascular Disorders, 24, 260. https://doi.org/10.1186/s12872-024-03922-y
12. Minotti, G., Menna, P., Salvatorelli, E., Cairo, G., & Gianni, L. (2004). Anthracyclines: Molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. Pharmacological Reviews, 56(2), 185–229. https://doi.org/10.1124/pr.56.2.6
13. Myers, C. S. (2009). Anthracycline-induced cardiotoxicity: Overview of studies examining roles of oxidative stress and free cellular iron. Pharmacological Reports, 61(2), 151–158. PMID: 19307704
14. Myrehaug, S., Hoskin, P. J., Pong, W., et al. (2022). Late adverse effects and biomarkers in childhood ALL survivors (PETALE study). Pediatric Blood & Cancer, 69(S2), e28074. https://doi.org/10.1002/pbc.28074
15. Octavia, Y., Tocchetti, C. G., Gabrielson, K. L., Janssens, S., Crijns, H. J., & Moens, A. L. (2012). Doxorubicin-induced cardiomyopathy: From molecular mechanisms to therapeutic strategies. Journal of Molecular and Cellular Cardiology, 52(6), 1213–1225. https://doi.org/10.1016/j.yjmcc.2012.03.006
16. Peng, X., Chen, B., Lim, C. C., & Sawyer, D. B. (2005). The cardiotoxicology of anthracycline chemotherapeutics: Translating molecular mechanism into preventative medicine. Molecular Interventions, 5(3), 163–171. https://doi.org/10.1124/mi.5.3.8
17. Qiu, Y., Jiang, P., & Huang, Y. (2023). Anthracycline-induced cardiotoxicity: Mechanisms, monitoring, and prevention. Frontiers in Cardiovascular Medicine, 10, 1242596. https://doi.org/10.3389/fcvm.2023.1242596
18. Shanshan, L., Weihua, N., Chunyan, W., Jie, Z., Na, Z., Yue, Y., Mei, J., & Liyan, C. (2024). Exploring anthracycline-induced cardiotoxicity from the perspective of protein quality control. Reviews in Cardiovascular Medicine, 25(6), 213. https://doi.org/10.31083/j.rcm2506213
19. Singh, A., Bhakta, N., Groarke, J. D., et al. (2020). Anthracycline-induced cardiotoxicity in survivors of childhood cancer. Nature Reviews Clinical Oncology, 17(12), 733–744. https://doi.org/10.1038/s41571-020-0403-3
20. Venkatesulu, B. P., Mahadevan, L. S., Ramanjappa, T., et al. (2018). Development of early atherosclerosis in pediatric cancer survivors: Role of oxidative stress. Cardio-Oncology, 4, 4. https://doi.org/10.1186/s40959-018-0036-x