# Study of the Relationship between Heme Oxygenase-1, Interleukins (6, 12) and Coenzyme Q10 in Iraqi Pediatric Patients with Chronic Myeloid Leukemia

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Keywords: HO-1, Chronic Myeloid Leukaemia (CML), Interleukin (6, 12), Coenzyme Q10.

Abstract: A global disorder impacted by both genetic and environmental factors, chronic myeloid leukaemia (CML) is associated with increasing mortality and morbidity rates and has social and economic consequences. This particular kind of cancer affects the bone marrow, a spongy substance found in the center of most bones that produces the majority of the body's blood cells, Mossler was the first to describe the bone marrow biopsy technique for the diagnosis of leukaemia. Wilhelm Epstein coined the word "acute leukaemia" to distinguish the rapidly growing and fatal leukaemia from the more indolent chronic leukaemia, myeloid cells, the malignant cell in acute myeloid leukaemia, were identified by Otto Naegeli, who divided leukaemia into myeloid leukaemia and lymphoid leukaemia. The present study was conducted to determine the level of heme oxygenase-1 enzyme and to study and estimate the level of some biochemical parameters such as: interleukins (interleukin-6, interleukin-12) as well as the enzyme coenzyme COQ10 in the serum of patients with chronic myelogenous leukaemia in paediatric patients. The study included (60) patients who visited the Central Children's Hospital in Baghdad Governorate and who were previously diagnosed with chronic myelogenous leukaemia through a complete blood count and bone marrow examination in addition to other tests used to diagnose patients with leukaemia, and (30) apparently healthy people of both sexes in the same age group and considered them a control group. The results showed no significant increase ($P<0.05$) in the levels of heme oxygenase-1, interleukin-12 and coenzyme Q10 when compared to the control group, but there was a significant difference at the probability level ($P<0.05$) in interleukin-6 when compared to the control group in patients with chronic myeloid leukaemia in children.

## 1 INTRODUCTION

Cancer is a disease in which a group of cells lose the laws of normal cell division and develop uncontrollably, so that cancer cells interact with signals that activate the normal cell cycle, leading to abnormal cell growth and promoting altered cells. [1]. Many diseases are characterized by unchecked or uncontrolled cell growth; the terms "cancer" and "tumors" are often used interchangeably. Cancer is one of the leading causes of death and disability worldwide [2]. Multifactorial cancer is characterized by a number of genetic alterations influenced by both the body and society, Typical hallmarks of this type of cancer include cell death resistance, unregulated gene expression, unchecked replication, and metastasis (spread to other tissues) [3], [4].

The bulk of the body's blood cells are transported by the sponge-like bone marrow, which is located in the middle of most bones and is affected by leukaemia, a kind of cancer. Bone marrow blood-forming stem cells, often called immature blood cells, are the first cells that undergo mutations to become leukaemia-type cells [5]. Abnormal cells in the bone marrow, regardless of the type of leukaemia, prevent the formation of other cells, leading to a variety of negative consequences [6]. Severe anaemia occurs as a result of decreased red blood cell production, and the risk of infection increases when the neutrophil count in the blood is low. As the incidence of thrombocytopenia increases, clotting factors decrease, and the risk of bleeding (low platelet count) increases. Cancer cells infiltrating various organs can lead to enlargement and fibrosis of the liver, spleen, and lymph nodes. When cancer cells invade the brain, they can lead to meningitis, ventricular dilatation, increased

intracranial pressure, nausea, vomiting, papilledema, neck stiffness, loss of appetite, hypoglycaemia, general weakness, muscle atrophy, and sometimes death if the patient does not receive appropriate treatment. All of these are symptoms of hypermetabolic disease, which deprives cells of nutrients [6].

# 2 TYPES OF LEUKEMIA

The kind of injured stem cells determines whether the leukemia is lymphocytic or myeloid. When people refer to blast leukemia or stem cell leukemia, they usually indicate a lymphocytic or myeloid sickness. Leukemia's go by a variety of names depending on the specific kind of cells that are affected, which may be perplexing for patients,

There are four main types of leukemia, and they differ in their treatment methods and response to treatment [6], [7].

1) Acute Lymphoblastic Leukemia (ALL) is a malignancy that impacts lymphocytes, which are progenitor cells. It may occur in locations other than the bone marrow, such as peripheral blood. Research suggests that an aberrant immune response to infections is believed to originate with cellular genes. Lymphocytic leukemia, a kind of malignancy, primarily targets cells that differentiate into B and T lymphocytes [8];
2) Acute myeloid leukemia (AML) has an irregular proliferation of myeloid cells. The number of divisions is more than 20% to diagnose chronic myeloid leukemia in the bone marrow. It is also known as the cancer that affects the stem cells in the bone marrow that will later become granulocytes, erythrocytes and megakaryocytic blood cells [9];
3) Chronic myeloid leukemia (CML): the malignant genetic condition of blood-forming stem cells known as chronic myeloid leukemia leads to an increase in myeloid cells, red blood cells, and platelets in the peripheral blood. The cancerous cells are the myeloid cells in the blood, which include all types of cells found in the blood except for lymphocytes [10];
4) Chronic lymphoblastic leukemia (CLL): there is a wide range of symptoms associated with CLL, a kind of leukemia that mostly affects the elderly. The cells affected by cancer are B and T lymphocytes in the blood. Specific genetic changes that impede clonal programmed cell death lead to the transmission of leukemia [11].

# 3 BIOCHEMICAL VARIABLES

## 3.1 Heme Oxygenase-1 Enzyme (HO-1)

Heme oxygenase-1 is a stress protein, metabolic enzyme, host immune stress inducer and anti-inflammatory. HO activity is represented by two major isoforms, HO-1, HO-2), HO-3.

Encoded by two distinct genes (HMOX1 and HMOX2) respectively, heme oxygenase-1 is a microsomal enzyme with a key antioxidant and anti-inflammatory role in heme degradation.

By lowering biliverdin and carbon monoxide generation, biliverdin reductase also lowers bilirubin and free ferritin Fe+2 synthesis [12]. Byproduct of biliverdin is anti-inflammatory and antioxidant bilirubin. Recent studies suggest that bilirubin enhances health by means of hepatic mechanisms [13].

HO-1 is a heat- and shock-resistant enzyme, and scientists call this family of proteins Heat Shock Proteins (HSPS).

HO-1 enzyme with a molecular weight of 32 kDa contains 288 amino acid residues encoded by the HMOX1 gene. HO-1 activity depends on NADPH-Cytochrome P450 reductase [14].

Some studies have confirmed that HO-1 inhibitors prevent platelet aggregation, increase fibrin dissolution and phagocytosis, and thus prevent tissue damage and clotting. In addition, hemin is an activator of neuroglobulin, a protein involved in the transport and storage of oxygen in nerve cells, which increases the intracellular partial pressure of oxygen in nerve cells and is necessary to protect nerve cells from hypoxia [15].

## 3.2 The Presence of Heme Oxygenase-1 Enzyme

HO-1 is a protein with a molecular weight of 32 kDa that belongs to the stress protein family, which is found in high concentrations in the liver, spleen and bone marrow. The enzyme can be stimulated by a variety of environmental stimuli, including ultraviolet radiation, heavy metals, glycolipids, growth factors, hydrogen peroxide, nitric oxide, inflammatory cytokines, hyperoxidation and hypoxia [16].

HO-1 is located in the membranes of the endoplasmic reticulum, and studies have also shown its presence in liver mitochondria [17].

## 3.3 The Importance of Heme Oxygenase-1 Enzyme

Under physiological conditions, it has been observed that most tissues have low levels of HO-1 enzyme except for the cells of the endoreticular system, in which heme is present at high levels, due to the removal of aged red blood cells. In addition, almost all stressful conditions, such as hypoxia, low oxygen, exposure to heavy metals, mycotoxins, inflammatory factors, and ultraviolet radiation, stimulate the rate of HO-1 enzyme [18].

Cells are unable to engage their defense mechanisms in the absence of functional HO-1, according to the results. By reducing ROS formation during heme breakdown, the HO-1 enzyme protects cells. The HO-1 enzyme pathway generates protective byproducts; increasing their synthesis is one possibility. Hepoxigenase-1 Is Not Without Its Drawbacks [19].

The HO-1 enzyme may be detrimental to human health because to the excess bilirubin, ferritin, and carbon monoxide it creates. A greater consumption of NADPH, an essential molecule for several physiological processes, would occur from an increase in HO-1 enzyme activity. The oxidative pentose phosphate pathway is mainly responsible for replenishing NADPH and making it more resistant to oxidative stress destruction [20].

## 3.4 Interleukin-6 (IL-6)

The gene encoding interleukin-6 Cytokines, tiny proteins with molecular weights between fifteen and twenty kDa, influence autocrine, endocrine, and non-endocrine signaling [21], [22]. Several cytokines have a role in the formation and operation of the immune system, including IL-6 family cytokines, which are linked to hepatic acute phase protein production and B cell activation [23]. Interleukin-6 (IL-6) is a cytokine that exemplifies homeostasis. [24]. When homeostasis is disturbed, IL-6 is rapidly released, after being disrupted by infection or tissue damage, and contributes to host defense in such conditions by activating acute phase and immune responses. However, excessive, prolonged and unregulated The production of IL-6 negatively affects acute systemic inflammatory response syndrome and chronic immune diseases.

Recent research suggest that IL-6 inhibition may be beneficial in managing many disorders, including both acute and chronic systemic inflammatory diseases [25].

## 3.5 Interleukin-12 (IL-12)

Since its discovery in 1953, researchers have characterized the endogenous pyrogen, today known as IL-1. Since then, they have been working to change patients' immune systems in order to fight malignant tumors using exogenous cytokines. In the beginning, the difficulties of consistently producing an adequate amount were the fundamental challenges of cytokine-based immunotherapy.

Antigen-presenting cells, such as macrophages and dendritic cells, are in charge of producing IL-12, a complex cytokine that regulates T lymphocyte recruitment and effector function. It is well recognized as a potent cytokine that induces inflammation. IL-12 is made up of both P40 and P35 subunits. As a result, IL-12 is responsible for a significant improvement in immune responses to malignancies [26], [27].

The IL-12 cytokine family includes a large number of different cytokines. These cytokines include IL-12, IL-23, IL-27, IL-35, and IL-39, which was newly found. Recent research has shed light on the diverse functions of several members of the IL-12 family, including effector and immune regulatory roles. These investigations have also shed insight on the role of IL-12 cytokines in modulating innate and adaptive immune responses in cancer. These cytokines may provide useful choices for improving immune-modulatory treatment methods. The fact that it is thought to be an important effector cytokine has significant implications for anticancer treatments as well as immunotherapies involving natural killer cells and Th1 helper cells. Interleukin-12 (IL-12) activates STAT4 and increases IFN-γ production, facilitating Th1 helper cell differentiation via T-bet transcription. Consequently, interleukin-12 is a key player in the fight against cancer [28].

## 3.6 Coenzyme Q10

First described as a small lipophilic molecule common in cell membranes in 1955, coenzyme Q10's function as an electron carrier in the mitochondrial electron transport chain was shown in 1957. For two decades, its purpose remained unknown until 1986 when the benefits of Coenzyme Q10 treatment in Kearns-Sayre disease were reported [29].

It is named quinone ubiquinone because it is ubiquitous in all cells and its chemical structure consists of two benzoquinone rings with a variable number of isoprenyl units. Its reduced form is known as ubiquinol and the reduced form is

ubiquinone. Through a series of oxidation-reduction reactions, they generate each other (Q Cycle).

Substances found in cell membranes include coenzyme Q10, which is also known as CO Q10 or ubiquinone. The isoprenoid side chain and benzoquinone ring define this small, lipophilic chemical. Complex Q, an enzyme complex located in the mitochondrial interstitial matrix, facilitates its production in humans. Benzoquinone ring and isoprenes 10 are both produced via the cholesterol biosynthetic route; benzoic acid comes from 4-hydroxybenzoic acid, while isoprenes 10 come from mevalonic acid. Electron transport to Complex III is facilitated by the quinone ring, a functional group. Coenzyme Q10 (ubiquinone) may be reduced to ubiquinol by means of a reversible reaction. The polyisoprenoid chain forms hydrophobic membranes at its lipophilic terminus [30].

As part of the electron transport chain (ETC), ubiquinone is present in every cell membrane and helps electrons go from complexes I and II to complex III. The lysosomes at 1.86 μg/mg and the mitochondrial membrane at 2.62 μg/mg were found to have the greatest quantities of ubiquinone (COQ10) in rat liver, respectively. The electron transport pathway inside mitochondria relies heavily on ubiquinone [31]. Consumption of COQ10 has shown epigenetic effects on genes linked to signaling, transport, transcriptional regulation, pathogenic mutations, phosphorylation, and genetic development, suggesting that it may have a role in controlling gene expression. Coenzyme Q10 is an essential antioxidant and performs its primary role in the electron transport chain in addition to stabilizing intracellular membranes, such as the plasma membrane, which in turn prevents phospholipid peroxidation.

Furthermore, Ubiquinone and semiquinone participate in the recycling of other antioxidant molecules, diminishing ascorbate and α-tocopherol levels while assisting in the regulation of cellular redox status. Recent research has associated ubiquinol with the safeguarding of plasma low-density lipoproteins (LDL) from oxidation, an essential anti-atherosclerotic mechanism. The mechanism of CO Q10's pro-oxidant effect remains incompletely understood; however, it plays a function in signaling associated with gene regulation. Its supplementary functions include modulating pore permeability, thereby affecting apoptosis [32].

Coenzyme Q10, synthesized by the human body, is the only lipid-soluble antioxidant. Coenzyme Q10 is synthesized in humans from tyrosine or phenylalanine (benzoquinone ring and mevalonic acid) by a series of enzymes (Complex Q) located in the interstitial membrane of mitochondria and the endoplasmic reticulum, with the majority produced endogenously. The procurement from foreign sources is common in various animal proteins (lamb, beef, chicken, and fish) and cereals (barley and wheat), among others. The recommended daily dosage is 3-5 mg [33].

# 4 MATERIALS AND METHODS OF WORK

Research samples were collected for patients with leukemia from Baghdad Karkh Health Department/Central Children's Hospital in Baghdad Governorate, and the control group for the period from November to May 2024 AD.

The blood samples included 60 patients with leukemia, comprising 30 males and 30 females, aged between 1 and 14 years. Their infection with leukemia was confirmed through diagnostic processes via blood tests, and through their clinical symptoms, diagnosed by the doctor and found in the patients' files and records. The special questionnaire form was relied upon and the required information for each patient was recorded in it.

The control group samples included 30 healthy and disease-free samples, including 15 male samples and 15 female samples. Their ages also ranged from 1 - 14 years.

Diagnostic tests: the levels of heme oxygenase-1, interleukin 6 and 12, and coenzyme Q10 were measured in the serum of pediatric patients with chronic leukemia and compared with the serum of the control group using the diagnostic kit prepared by Sunlong Biotech (China) by the Sandwich-ELISA method. This ELISA uses the "sandwich-ELISA" method. The microelisa plate provided in this kit is pre-coated with an antibody specific for the variant. Standards or samples are added to the appropriate wells of the microelisa plate, where they bind to the specific antibody. Next, a horseradish peroxidase (HRP)-conjugated antibody specific for the variant under study is added to each well of the plate, incubated, and free components are washed off. TMB substrate solution is added to each well containing only the variant under study. The HRP-conjugated antibody will appear blue, turning yellow after the stop solution is added. Finally, the optical density (OD) is measured using a spectrophotometer at a wavelength of 450 nm.

# 5 RESULTS AND DISCUSSION

## 5.1 Heme Oxygenase-1 Levels

The (mean ± standard deviation) of the (heme oxygenase-1) level in the serum of the leukemia patients group and the control group are shown in the Table 1.

Table 1: Mean ± standard deviation of heme oxygenase-1 enzyme level.

| Groups Parameter | Mean ± SD | | p-value |
|---|---|---|---|
| | Patients | Control | |
| Heme oxgenase-1 | 5.086 ± 5.353 | 3.963 ± 3.836 | 0.305 |

The study found no significant difference in predicted heme oxygenase-1 enzyme levels between patients with chronic myeloid leukemia and the control group ($p < 0.05$). This study's results contradict the previous one's [34].

Heme oxygenase-1 (HO-1) has recently been identified as a potential regulator of granulocyte production in stress-induced circumstances such as chemotherapy, in addition to its numerous other functions in cell proliferation and differentiation. According to studies, overexpression of heme oxygenase-1 (HO-1) is associated with enhanced cancer cell proliferation and treatment resistance [34], [35].

The promoter region includes polymorphisms that impact the expression of the HO-1 gene (HMOX1), such as the length polymorphism (GT)n and the single-nucleotide polymorphism (SNP) A(-413T). Variants with shorter GT repeat sequences and 413-A related to HO-1 stimulation are more likely to be identified. According to the previous studies, patients with acute lymphoblastic leukemia showed a greater incidence of short alleles than controls. The fact that short alleles enhance the likelihood of treatment failure lends credence to the theory that HO-1 plays a role in chemotherapy resistance. According to the research, HO-1 might be a feasible target to examine if previous therapies for ALL have failedin total [35].

Recent research indicates that immunodeficiency increases the chance of recurrence in people with acute myeloid leukemia (AML). The research discovered that heme oxygenase-1 (HO-1) is required for both medication resistance and AML cell proliferation. The same study also showed that HO-1 inhibits the development of Human Leukocyte Antigen-C (HLA-C), allowing natural killer cells to avoid immune system detection then [36]. Innate immunity, which includes natural killer cells, is critical for combating cancer, especially when acquired immunity is inadequate. The HO-1/HLA-C axis may lead these cells to function differently in myeloid leukemia. When used to treat acute myeloid leukemia, anti-HO-1 medicines are considered to greatly boost natural killer cell anticancer activity (Fig. 1) [36].

The effects of HO-1 vary. HO-1 has long been recognized for its anti-inflammatory and stress-response effects in the body. HO-1 stops carcinogenesis in its tracks and helps maintain redox balance in healthy cells. Heme oxygenase-1 expression may be linked to pathological traits and clinical outcomes, according to findings from cancer biopsies. Worse survival rates are often associated with increased heme oxygenase-1 levels in tumor tissues. The study's author reached the following conclusion: the efficacy of patient diagnoses and treatments may be dependent on our capacity to understand the relationship between HO-1 and clinical data [37]. Because of its crucial role in cancer development and chemotherapy resistance, the HO-1 enzyme has been the focus of all previous research. Researchers discovered that changing the HO-1 system may boost cancer's susceptibility to treatment. The link between HO-1 regulation levels and a variety of outcomes, including cell cycle arrest, cell death, tumor survival, and progression, supports this [38].

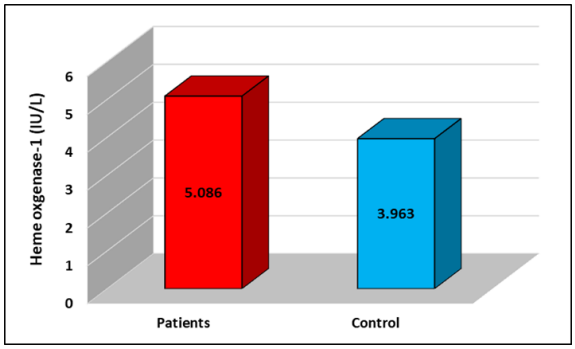


Figure 1: The level of (Heme oxygenase-1) in the sera of patients with leukemia and the control group.

In another study conducted by the researcher, the aim of the study was to draw attention to the effect of HO-1 in circulating monocytes, the presence of bone marrow-derived suppressor cells and complement receptors on a subset of monocytes in advanced cancer patients registered for treatment,

abnormal immune cells were detected in the tumor environment; it was shown in this study that HO-1 levels were clearly high in classical monocytes in all types of cancer studied, and these results are not consistent with the results of our study, where the results of HO-1 levels were analyzed for their diagnostic and predictive potential for clinical outcomes [39].

## 5.2 Levels of (CoEn Q10, IL-12, IL-6)

The (mean ± standard deviation) levels of CoEn Q10, Interleukin 12, and Interleukin 6 in the serum of the leukemia patients group and the control group are shown in Table 2.

Table 2: Mean ± standard deviation of levels (IL-6 IL-12, CoEnQ10) * p < 0.05.

| Groups Parameter | Mean ± SD | | p-value |
|---|---|---|---|
| | Patients | Control | |
| CoEn Q10 | 0.767±0.370 | 0.856±0.339 | 0.265 |
| IL-12 | 4.962±1.174 | 5.186±1.680 | 0.455 |
| IL-6 | 6.422±0.412 | 7.250±1.316 | 0.002* |

The results shown in the table above showed that there was no significant difference at the probability level of p<0.05 for the level of the enzyme coEn Q10. These results differed from the results reached by the researcher Rasha (2024), as the coenzyme (CoQ10) is considered an essential cofactor in the electron transport chain in the mitochondria, which is useful in treating liver disorders. The polycyclic aromatic hydrocarbon (DMBA) -dimethylbenz[a]-anthracene 7,12 is what causes and promotes carcinogenesis when this study was conducted on mice with leukemia caused by DMBA)) and the analysis was evaluated Biochemical, immunological and histological examination of the liver to determine whether CoQ10 would treat or alleviate liver injury caused by DMBA-induced leukemia in a mouse model. The results of the researcher showed that CoQ10 treatment significantly reduced liver enzyme levels compared to leukemia model animals. Malondialdehyde (MDA) levels were significantly lower in the CoQ10 group compared to the DMBA group, while glutathione (GSH) and superoxide dismutase (SOD) levels increased significantly. Histological examination of the livers of DMBA-infected mice revealed loss of normal hepatic structure, which was restored after CoQ10 administration (Fig. 2) [40].

In another study, it was shown that CoQ10 provides some protection against cardiac or hepatic toxicity during cancer treatment [41]. Also, through the results shown in the table above, it was found that there was no significant difference at the probability level of p <0.05 for the level of IL-12. These results differed from the results reached by researchers when a study was conducted on patients with acute myeloid leukemia (AML). The level of IL-12 was estimated. Clearly lower values of IL-12 were observed among AML patients compared to the control group. The aim of this study was to analyze IL-12 and to determine the possibility of using IL-12 as a potential anti-cancer drug [42]. IL-12, which is mainly produced by dendritic cells, monocytes, macrophages, and B cells, activates many groups of immune cells that can recognize and destroy cancer cells, and stimulate immunity during the cancer immunity cycle. IL-12 can also be used as an immune regulator in cancer immunotherapy. It has shown great potential in inhibiting tumor growth and improving the tumor environment through many previous clinical models [43].

Cytokines and IL-12 show strong anticancer activity but suffer from a narrow therapeutic window due to the activation of immune cells outside the tumor (Fig. 3) [44].

The above results showed a significant difference at the probability level of p<0.05 for IL-6 (Fig. 4). This study agrees with many researchers and shows the existence of associations between the level of IL-6 and types of leukemia [45]. In many studies, cytokines secreted by cells infected with acute myeloid leukemia in an endogenous or exogenous manner affect the proliferation of acute myeloid leukemia cells, where IL-6 can be used as a biomarker to target myeloid leukemia cells [46].

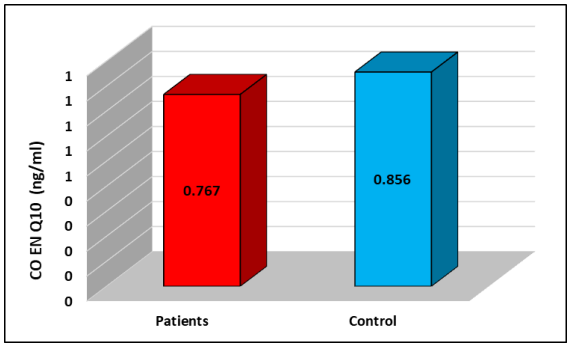


Figure 2: The level of (CoEn Q10) in the sera of patients with leukemia and the control group.

In another study conducted on infants, a statistically significant association was found between pediatric patients with polycythemia and the control group, where IL-6 values for the polycythemia group in children were higher than the control group [47]. IL-6 and IL-10 provide good predictive value for the diagnosis of severe infection (SI) in children with SI. Resulting from leukemia [48].

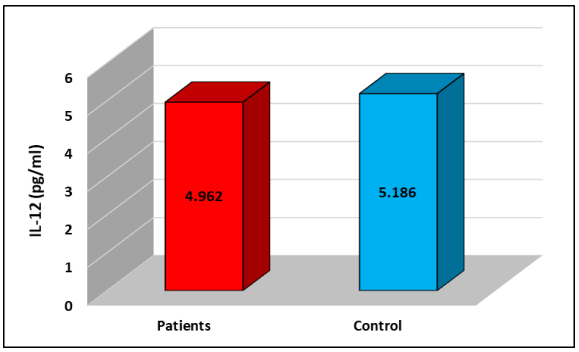


Figure 3: The level of (IL-12) in the sera of patients with leukemia and the control group.

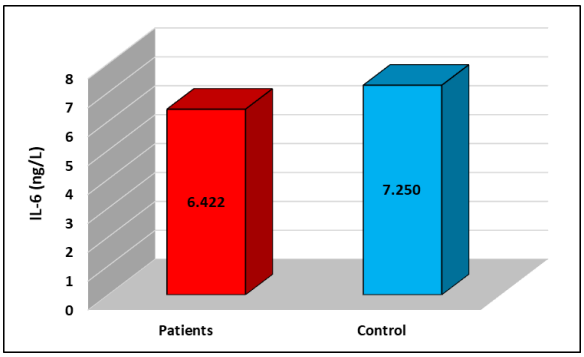


Figure 4: Level of (IL-6) in the sera of patients with leukemia and the control group.

## 5.2 Coefficient of Correlation

The correlation between heme oxygenase-1 (HO-1) and the above-mentioned biochemical variables was studied for chronic myeloid leukemia patients in children, to clarify the nature of the relationship between (HO-1) and other biochemical measurements (Fig. 5-7).

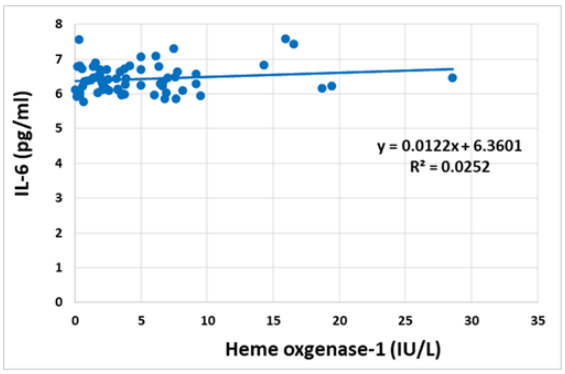


Figure 5: The correlation between heme oxygenase-1 and IL-6 level.

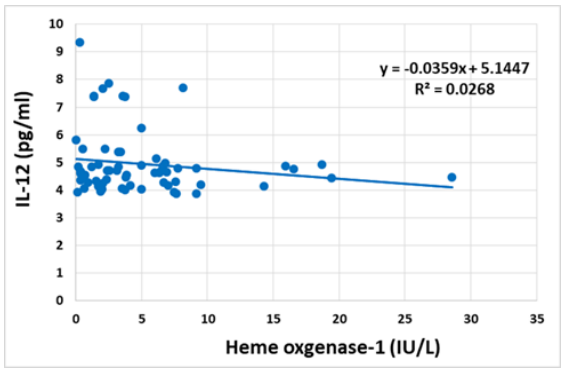


Figure 6: Correlation between heme oxygenase-1 and IL-12 level.

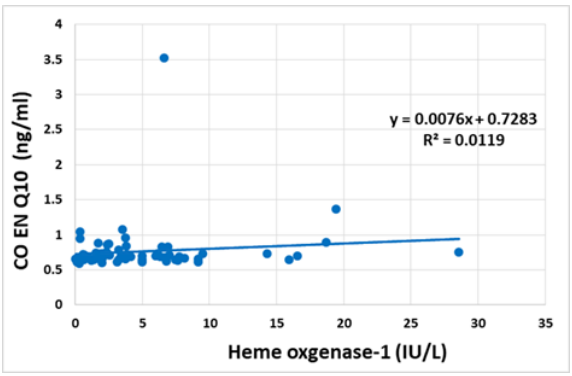


Figure 7: The correlation between heme oxygenase-1 and COENQ10 level.

# 6 CONCLUSIONS

Based on the study findings, interleukin-6 (IL-6) emerges as a potential biomarker for childhood chronic myeloid leukemia (CML), showing a statistically significant association that may be useful for diagnosis or disease monitoring. The analysis also indicated no significant gender-based differences among CML patients, suggesting that the disease progression and biomarker expression levels are not influenced by sex in the pediatric population. Furthermore, the results revealed no significant differences in serum levels between heme oxygenase-1 (HO-1), interleukin-12 (IL-12), and Coenzyme Q10 (CoEQ10), indicating that these factors may not independently distinguish CML pathology in children. However, a notable and statistically significant difference was observed between HO-1 and IL-6, implying a possible immuno-inflammatory interaction between oxidative stress markers and pro-inflammatory cytokines in the CML microenvironment. This could point toward underlying mechanisms linking oxidative imbalance and immune dysregulation in the pathogenesis of childhood CML.

These findings warrant further investigation into IL-6 as a clinical indicator, and into the biological roles of HO-1 and IL-6 in disease progression. Larger cohort studies and longitudinal monitoring are recommended to validate these relationships and potentially inform targeted therapies or diagnostic frameworks.

# REFERENCES


[1] D. Hanahan and R. A. Weinberg, “The hallmarks of cancer,” Cell, vol. 100, no. 1, pp. 57–70, 2000.

[2] I. N. Olver, “Prevention of breast cancer,” Med. J. Aust., vol. 205, no. 10, pp. 475–479, Nov. 2016, doi: 10.5694/MJA16.01007.

[3] Z. Abbas and S. Rehman, “An overview of cancer treatment modalities,” in Neoplasm. London, U.K.: IntechOpen, 2018.

[4] A. Amaro et al., “The biology of uveal melanoma,” Cancer Metastasis Rev., vol. 36, no. 1, pp. 109–140, 2017.

[5] C.-H. Pui, W. L. Carroll, S. Meshinchi, and R. J. Arceci, “Biology, risk stratification, and therapy of pediatric acute leukemias: an update,” J. Clin. Oncol., vol. 29, no. 5, p. 551, 2011.

[6] W. Lockwood, “Leukemia: AML, CML, ALL and CLL,” 2019.

[7] J. E. Niederhuber et al., Abeloff's Clinical Oncology, 6th ed. Philadelphia, PA, USA: Elsevier, 2020. [Online]. Available: https://www.clinicalkey.com. Accessed Oct. 16, 2020.

[8] T. Terwilliger and M. Abdul-Hay, “Acute lymphoblastic leukemia: a comprehensive review and 2017 update,” Blood Cancer J., vol. 7, no. 6, pp. e577–e577, 2017.

[9] L. D. Bastian, “Clinical and cytogenetic features of leukemias in children treated in the University Hospital of Split from 2000 to 2017,” M.S. thesis, Univ. Split, Split, Croatia, 2018.

[10] C. L. Sawyers, “Chronic myeloid leukemia,” N. Engl. J. Med., vol. 340, no. 17, pp. 1330–1340, 1999.

[11] M. Hallek, “Chronic lymphocytic leukemia: 2020 update on diagnosis, risk stratification and treatment,” Am. J. Hematol., vol. 94, no. 11, pp. 1266–1287, 2019.

[12] L. L. Dunn et al., “New insights into intracellular locations and functions of heme oxygenase-1,” Antioxid. Redox Signal., vol. 20, no. 11, pp. 1723–1742, 2014.

[13] T. D. Hinds Jr. et al., “Rats genetically selected for high aerobic exercise capacity have elevated plasma bilirubin by upregulation of hepatic biliverdin reductase-A (BVRA) and suppression of UGT1A1,” Antioxidants, vol. 9, no. 9, p. 889, 2020.

[14] J. Wang and P. R. Ortiz de Montellano, “The binding sites on human heme oxygenase-1 for cytochrome P450 reductase and biliverdin reductase,” J. Biol. Chem., vol. 278, no. 22, pp. 20069–20076, 2003.

[15] N. Batra et al., “The HMOX1 pathway as a promising target for the treatment and prevention of SARS-CoV-2 of 2019,” Int. J. Mol. Sci., vol. 21, no. 17, p. 6412, 2020.

[16] S. W. Ryter, J. Alam, and A. M. K. Choi, “Heme oxygenase-1/carbon monoxide: from basic science to therapeutic applications,” Physiol. Rev., vol. 86, no. 2, pp. 583–650, 2006.

[17] D. P. Converso et al., “HO-1 is located in liver mitochondria and modulates mitochondrial heme content and metabolism,” FASEB J., vol. 20, no. 8, pp. 1236–1238, 2006.

[18] S. Li et al., “Protective role of heme oxygenase-1 in fatty liver ischemia–reperfusion injury,” Med. Mol. Morphol., vol. 52, no. 2, pp. 61–72, 2019.

[19] J. D. Belcher et al., “Haptoglobin and hemopexin inhibit vaso-occlusion and inflammation in murine sickle cell disease: Role of heme oxygenase-1 induction,” PLoS One, vol. 13, no. 4, p. e0196455, 2018.

[20] A. Kathagen-Buhmann et al., “Glycolysis and the pentose pathway are differentially associated with the dichotomous regulation of glioblastoma cell migration versus proliferation,” Neuro Oncol., vol. 18, no. 9, pp. 1219–1229, 2016.

[21] H. P. Kim et al., “Caveolae compartmentalization of heme oxygenase-1 in endothelial cells,” FASEB J., vol. 18, no. 10, pp. 1080–1089, 2004.

[22] F. Vallelian et al., “Proteasome inhibition and oxidative reactions disrupt cellular homeostasis during heme stress,” Cell Death Differ., vol. 22, no. 4, pp. 597–611, 2015.

[23] S. Rose-John, “Interleukin-6 family cytokines,” Cold Spring Harb. Perspect. Biol., vol. 10, no. 2, pp. 1–17, 2018.

[24] T. Tanaka, M. Narazaki, A. Ogata, and T. Kishimoto, “A new era for the treatment of inflammatory autoimmune diseases by interleukin-6 blockade

strategy," Semin. Immunol., vol. 26, no. 1, pp. 88–96, 2014.

[25] T. Tanaka, M. Narazaki, and T. Kishimoto, "Interleukin (IL-6) immunotherapy," Immunotherapy, pp. 1–15, 2018.

[26] E. M. Cheng, N. W. Tsarovsky, P. M. Sondel, and A. L. Rakhmilevich, "Interleukin 12 as an in situ cancer vaccine component: a review," Cancer Immunol. Immunother., vol. 71, no. 9, pp. 2057–2065, 2022.

[27] D. M. Weiner, J. S. Durgin, M. Wysocka, and A. H. Rook, "The immunopathogenesis and immunotherapy of cutaneous T cell lymphoma: Current and future approaches," J. Am. Acad. Dermatol., vol. 84, no. 3, pp. 597–604, 2021.

[28] L. S. Guedes and R. M. Martinez, "An overview on topical administration of carotenoids and coenzyme Q10 loaded in lipid nanoparticles," 2021.

[29] E. C. Naylor and R. E. B. Watson, "Molecular aspects of skin ageing," 2011.

[30] I. P. de Barcelos and R. H. Haas, "CoQ10 and aging," 2019.

[31] K. Žmitek and J. Žmitek, "Effects of a combination of water-soluble coenzyme Q10 and collagen on skin parameters and condition: Results of a randomised, placebo-controlled, double-blind study," 2020.

[32] "Topical treatment with coenzyme Q10-containing formulas improves skin's Q10 level and provides antioxidative effects," 2015.

[33] K. Bukowska-Strakova et al., "Heme oxygenase 1 affects granulopoiesis in mice through control of myelocyte proliferation," Immunobiology, vol. 222, pp. 506–517, 2017.

[34] K. Bukowska-Strakova et al., "Role of HMOX1 promoter genetic variants in chemoresistance and chemotherapy induced neutropenia in children with acute lymphoblastic leukemia," Int. J. Mol. Sci., vol. 22, no. 3, p. 988, 2021.

[35] C. Feng et al., "Heme oxygenase-1 inhibits the cytotoxicity of natural killer cells to acute myeloid leukemia by downregulating human leukocyte antigen-C," Cytotherapy, vol. 25, no. 7, pp. 728–738, 2023.

[36] M. Nitti, C. Ivaldo, N. Traverso, and A. L. Furfaro, "Clinical significance of heme oxygenase 1 in tumor progression," Antioxidants, vol. 10, no. 5, p. 789, 2021.

[37] G. Sferrazzo et al., "Heme oxygenase-1 in central nervous system malignancies," J. Clin. Med., vol. 9, no. 5, p. 1562, 2020.

[38] A. R. Vachanaram, "Myeloid derived suppressor cells (MDSCs), heme-oxygenase-1 (HO-1) and C88 expression in circulating monocytes: a study of impact on outcome in advanced cancer patients treated with immune checkpoint inhibitors (ICIs)," 2023.

[39] R. A. Alshali, "The potential chemotherapeutic effect of coenzyme Q10 against liver injury in a leukemia rat model by 7,12-dimethylbenzanthracene: Histological and morphometric study," 2024.

[40] L. Roffe, K. Schmidt, and E. Ernst, "Efficacy of coenzyme Q10 for improved tolerability of cancer treatments: A systematic review," J. Clin. Oncol., vol. 22, no. 21, pp. 4418–4424, 2004.

[41] R. A. Hassan and M. M. El-Masry, "Levels of interleukins 12 (IL-12) and 13 (IL-13), hepatitis B and C serology, and blood cultures among acute myeloid leukemia (AML) patients in Egypt," J. Venom. Anim. Toxins Incl. Trop. Dis., vol. 17, pp. 293–299, 2011.

[42] Y. Xu, X. Sun, and Y. Tong, "Interleukin-12 in multimodal tumor therapies for induction of anti-tumor immunity," Discover Oncol., vol. 15, no. 1, p. 170, 2024.

[43] J. A. Stinson et al., "Tumor-localized interleukin-2 and interleukin-12 combine with radiation therapy to safely potentiate regression of advanced malignant melanoma in pet dogs," Clin. Cancer Res., vol. 30, no. 18, pp. 4029–4043, 2024.

[44] R. A. Al-Qaisi, A. M. Al-Gebori, and M. H. M. Alosami, "Evaluation of bone turnover markers in patients with acute and chronic leukemia," Indian J. Clin. Biochem., vol. 39, no. 3, pp. 401–407, 2024.

[45] M. Q. Mohammed, A. H. Alwan, and A. A. Almukhtar, "Estimation of serum TLR-9, TNF-α, and IL-6 levels in the Iraqi patients diagnosed as acute myelogenous leukemia," Baghdad Sci. J., vol. 21, no. 7, p. 2182, 2024.

[46] R. Tamer, Ş. S. O. Ünal, and C. Y. Yozgat, "Elevated interleukin-6 levels as a potential marker of neonatal morbidity in full-term infants with polycythemia: A prospective study," J. Pediatr. Hematol. Oncol., 2024.

[47] S. P. Lin et al., "The predictive utility of cytokines, procalcitonin and C-reactive protein among febrile pediatric hematology and oncology patients with severe sepsis or septic shock," Pediatr. Hematol. Oncol., vol. 41, no. 1, pp. 1–14, 2024.