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The effect of Gender and age on vital biomarkers in leukemia patients

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Abstract. We examined the influence of gender and age on several biomarkers in three subtypes of leukemia patients. This research had 150 individuals who were separated into four groups: individuals suffering from acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), and patients suffering from chronic myeloid leukemia (CML), and healthy controls. The measurement of serum miRNA-223 gene expression for patients with acute myeloid leukemia (AML) showed that the concentration of miRNA-223 was significantly higher in all age groups (30-39, 40-49, 50-59, and 60-69 years) comparing to the control. The measurement of serum malondialdehyde [MDA (mM)] for (ALL, AML, and CML) patients showed that the concentration of MDA was significantly higher in all age groups (30-39, 40-49, 50-59, and 60-69 years) comparing to the control. Interestingly, the measurement of serum catalase activity (CAT) U/ml for patients (ALL, AML, and CML) showed that the activity of CAT was significantly low in all ages comparing to the control group. The measurement of serum heme oxygenase 1 [HO-1 (ng/mL)] for patients ALL, AML, and CML showed that the concentration of HO-1 was significant higher in all ages comparing to the control group, with a high significant elevation was clearly shown in ages over 50 years in all leukemia patients These data might suggest possible correlation between the age and HO-1 levels in leukemia patients. However, the impact of age on HO-1 expression was not demonstrated and remain unclearThis decline has been clearly shown in ages over fifty years in all leukemia patients. On the other hand, the clinical significance of patients sex on leukemia patients was also evaluated and the results showed On the other hand, to compare the difference in HO-1 levels between the genders, HO-1 was estimated in males and compared to the females in patients with ALL, AML, and CML and was compared to the controls. The result shows that HO-1 levels were insignificantly high in males compared to the females in patients with ALL and CML, but not in patients with AML, with no significant difference between males and females in the control. These data might refer to a possible relstion between HO-1 levels and the gender in leukemia, since the change in hemogenase-1 levels was clearly shown in males but not in females. However, the impact of gender on HO-1 levels in leukemia was not yet mentioned.

Keywords: Gender, age, leukemia, MDA, CAT, miRNA223, HO-1

Introduction

Leukemia is a form of blood tissue cancer. The delicate inside of the body, called bone marrow. Hematopoietic stem cells are composed of bone marrow. It evolves into multiple blood components such as white blood cells (WBCs), platelets, and red blood cells (RBCs), which each have distinct functions (1). When the equilibrium of pro-oxidants and antioxidants is disrupted, oxidative stress occurs, and it plays a role in the development of leukemia (2). Reactive oxygen species (ROS) such as hydrogen peroxide, superoxide anions, and hydroxyl radicals are capable of abstracting a hydrogen atom from polyunsaturated fatty acids in membrane lipids to initiate lipid peroxidation. These free radicals can evoke extensive tissue damage, reacting with macromolecules, such as membrane lipids, proteins, and nucleic acids (3). Previously, enhanced lipid peroxidation and impairment in antioxidant defense mechanisms have been demonstrated in patients with leukemia (4). CAT is an antioxidant enzyme present in peroxisomes that contributes to the cell's antioxidant system (5). CAT can protect cells from tumor initiation and progression, due to its role in preventing the accumulation of dangerous levels of oxidants. In line with this, some studies have reported the downregulation of CAT expression in some cancers (6). However, CAT expression is highly expressed in other cancer cells, which require high antioxidant detoxifying systems and upregulation of CAT for tumor progression and metastasis to compensate for high ROS production and to prevent ROS-mediated cell death processes (7).

In biological samples, malondialdehyde (MDA) is an excellent indicator of free radical-mediated damage and oxidative stress, with polyunsaturated fatty acid peroxidation being the main source of MDA (8). The MDA level has been shown to have value as a biomarker for oxidative stress and disease progression in a number of types of cancer including solid tumors, gastric carcinoma, breast cancer and leukemia. MDA is a mutagen and a genotoxic agent that may contribute to the development of human cancer (9). Heme is degraded to free iron, carbon monoxide (CO) and biliverdin, which is subsequently converted to bilirubin by biliverdin reductase. Of the three known heme oxygenases, HO-1 (heat shock protein 32) is the only inducible isoform(10). Loss of HO-1 leads to profound changes in cellular homeostasis in genetically deficient mice and humans (12). HO-1 knockout mice and human HO-1 deficiency are associated with increased inflammation and oxidative stress, as manifested by diffuse inflammation in the liver and kidney, prominent endothelial damage with subsequent coagulation activation, hemolytic anemia, low bilirubin levels, and elevated ferritin levels with iron accumulation in liver and kidney (13). In addition, HO-1 is a potential target for cancer therapy because this enzyme gives survival and growth advantages to malignant cells by means of its anti-apoptotic activity (14).MicroRNA-223 (miRNA-223) is a short RNA molecule. MicroRNAs function to regulate the expression levels of other genes by several mechanisms.

miRNA-223 is a hematopoietic specific miRNA with crucial functions in myeloid lineage development (15). miRNA may regulate the expression of redox sensors and other reactive oxygen species (ROS) modulators, such as the key components of cellular antioxidant machinery, while ROS can induce or suppress miRNA expression and contribute to downstream biological function through the regulation of target genes (16). miRNA-223 is associated with hematopoiesis, immune response, and different types of cancer development (17)

The aim of this modern study is to find out the effect of both age and gender on miRNA223, MDA, CAT and HO-1 levels in leukemia patients,

Material and Methods

Experimental Part:

This research had 150 individuals who were separated into four groups: individuals suffering from acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), and patients suffering from chronic myeloid leukemia (CML), and healthy controls. All patients data, including sex, age, and length of illness, were recorded. The control group was carefully chosen to make sure that none of the participants had any other diseases or disorders. The mean age of the population ranged from 30 to 70 years were chosen from (October 2022 to February 2023). All laboratory test analysis was performed at Al-Kindi laboratory/ Al-Qadisiyah.

From each study group, five milliliters of blood were drawn. The blood was centrifuged for 15 minutes at (4000 rpm) after being allowed to clot for 15 minutes. The separated serum was split and distributed in eppendorf tubes (were kept at -20 ˚C), were all used in the study.

Statistical Analysis

The data was assembled, examined, and shown using GraphPad Prism 9.2.0. . Numbers are expressed as mean and SEM. For regularly distributed variables, a one-way ANOVA test was used to compare the means of different groups. If the P value was less than 0.05, it was considered significant.

Results

The measurement of serum miRNA-223 gene expression for patients with acute lymphoid leukemia (ALL, Figure 1) showed that the levels of miRNA-223 was higher in all ages (30-39, 40-49, 50-59, and 60-69 year) comparing to the control group, this elevation was clearly significant in the ages 40-49, 50-59, and 60-69 years.

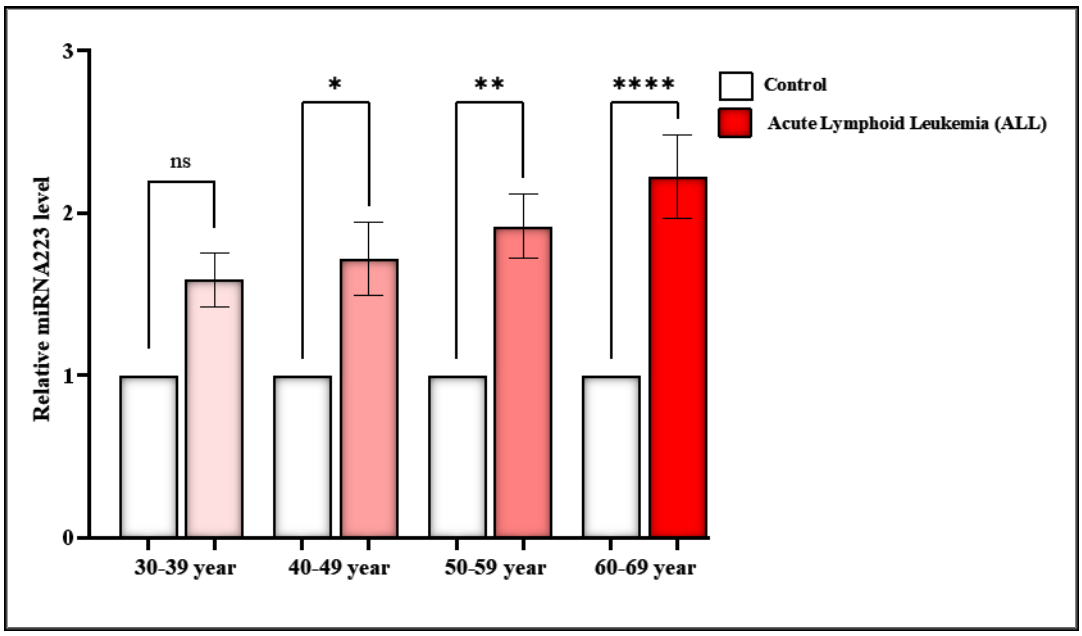

Figure 1 : Serum miRNA-223 gene expression in patients with ALL and among different age groups. Data are expressed as means ± SEM. Indicates **** p-value <0.0001

The measurement of serum miRNA-223 gene expression for patients with acute myeloid leukemia (AML, Figure 2) showed that the concentration of miRNA-223 was significantly higher (P<0.0001) in all age groups (30-39, 40-49, 50-59, and 60-69 years) comparing to the control.

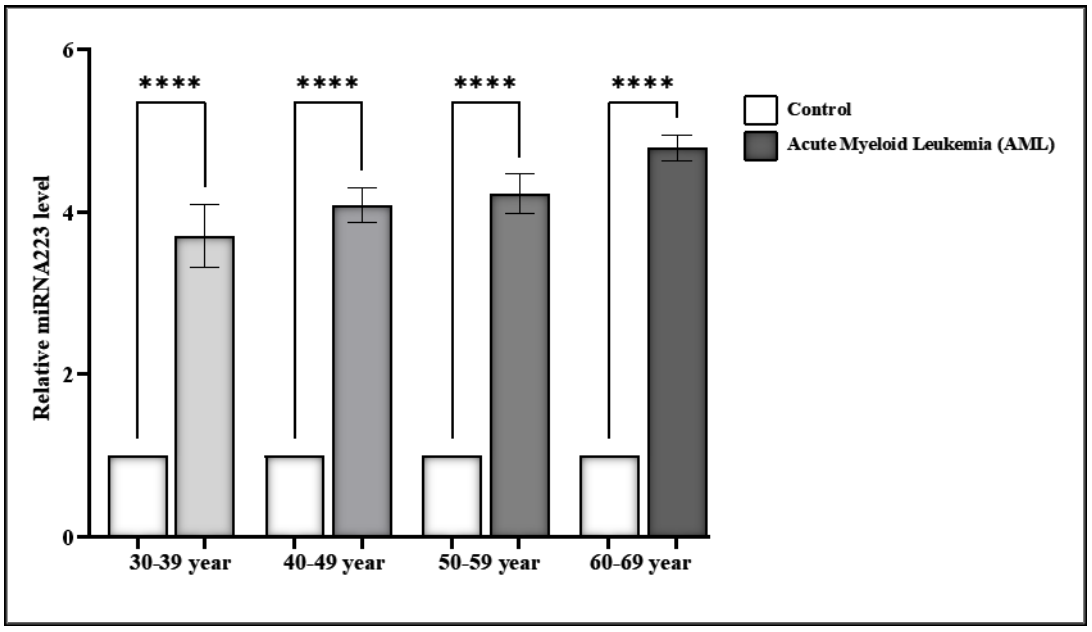

Figure 2: Serum miRNA-223 gene expression in patients with AML and among different age groups. Data are expressed as means ± SEM. Indicates **** p-value <0.0001

The measurement of serum miRNA-223 gene expression for patients with chronic myeloid leukemia (CML, Figure 3) showed that the levels of miRNA-223 was higher in ages (40-49, 50-59, and 60-69 year) comparing to the control group, this elevation was clearly significant in the ages 50-59, and 60-69 years.

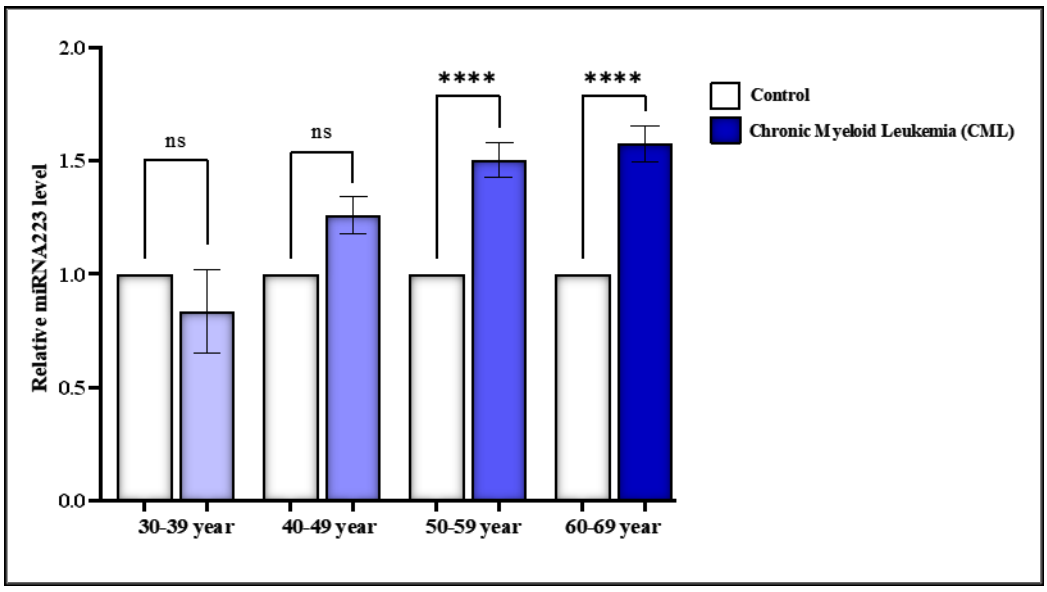

Figure 3: Serum miRNA-223 gene expression in patients with CML and among different age groups. Data are expressed as means ± SEM. Indicates **** p-value <0.0001

On the other hand, to compare the difference in miRNA-223 levels between the genders, miRNA-223 was estimated in males and compared to the females in patients with ALL, AML, and CML and was compared to the controls (Figure 4). The result shows that miRNA-223 levels were insignificantly high in females compared to the males in patients with ALL and AML, but not in patients with CML, with no significant difference between males and females in the control.

Collectively and according to these current findings, elderly patients between 6o to 69 years might be more sensitive to the change in miRNA-223 expression levels when compored to younger age leukemia patients (30-49 years). However the gander been male of female might be slightly related to the change in miRNA expression leveles.with no significant impact has be shown on its levels.

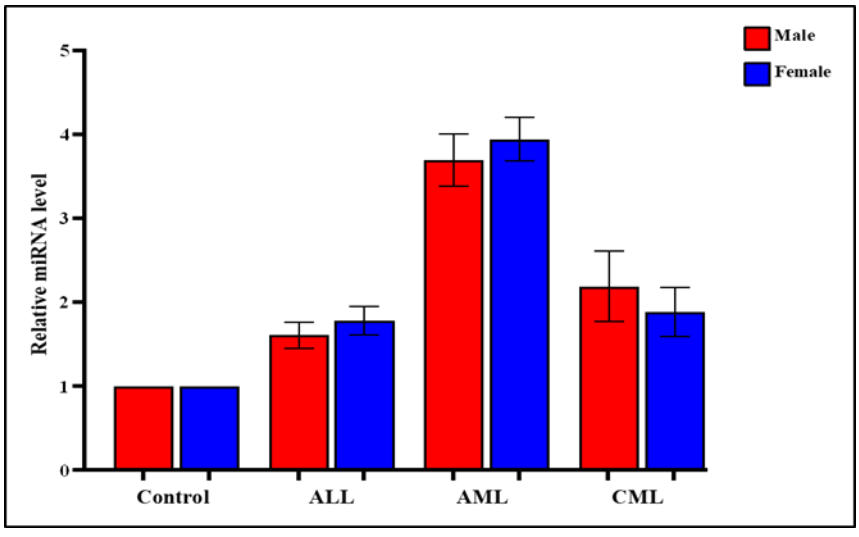

Figure 4: Estimation of relative miRNA-223 gene expression in males and females in all patients with (ALL, AML and CML) as compared with control.

The measurement of serum malondialdehyde [MDA (mM)] for (ALL, AML, and CML) patients showed that the concentration of MDA was significantly higher (P<0.0001) in all age groups (30-39, 40-49, 50-59, and 60-69 years) comparing to the control, Figures 5, 6 and 7 consequently.

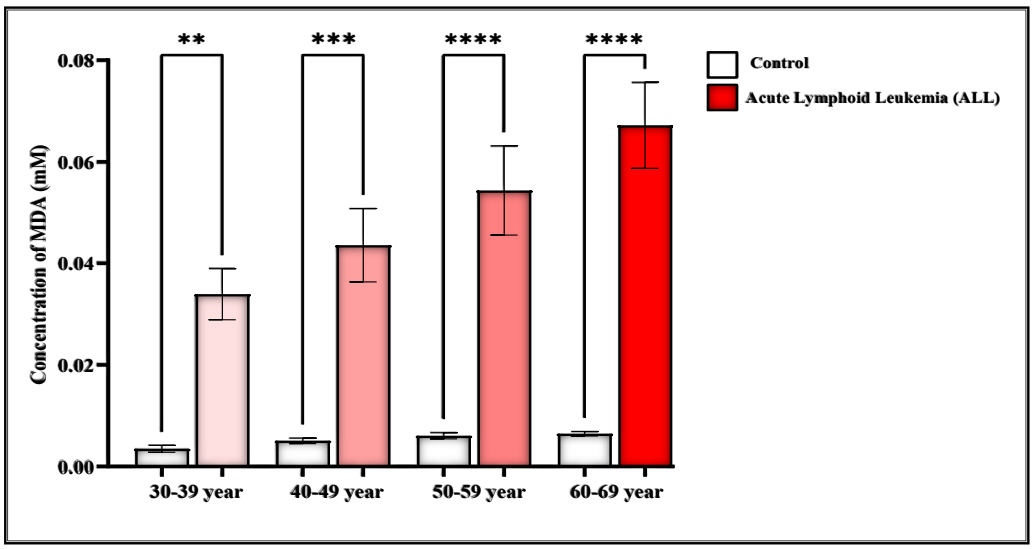

Figure 5: Serum MDA levels in patients with ALL and among different age groups. Data are expressed as means ± SEM. Indicates **** p-value <0.0001

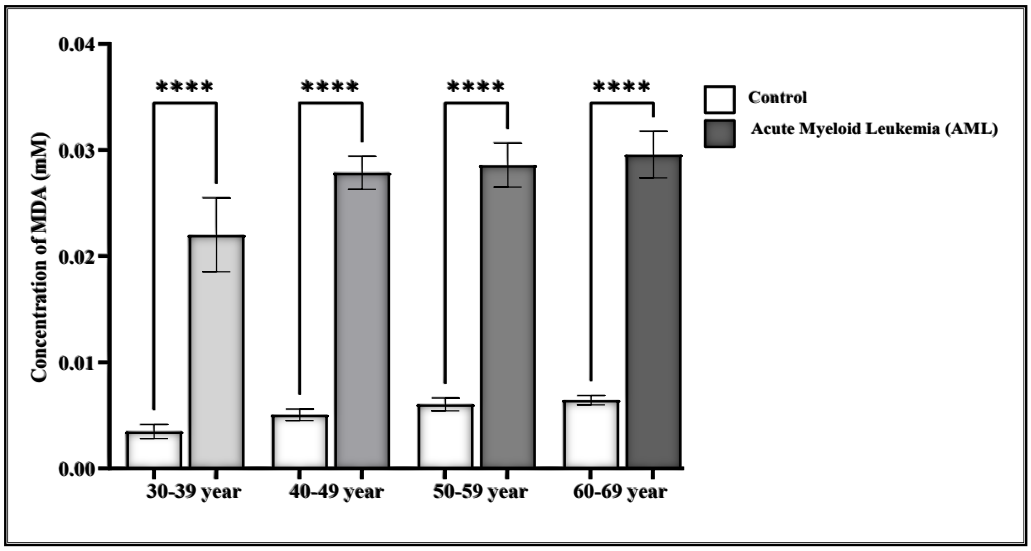

Figure 6: Serum MDA levels in patients with AML and among different age groups. Data are expressed as means ± SEM. Indicates **** p-value <0.0001

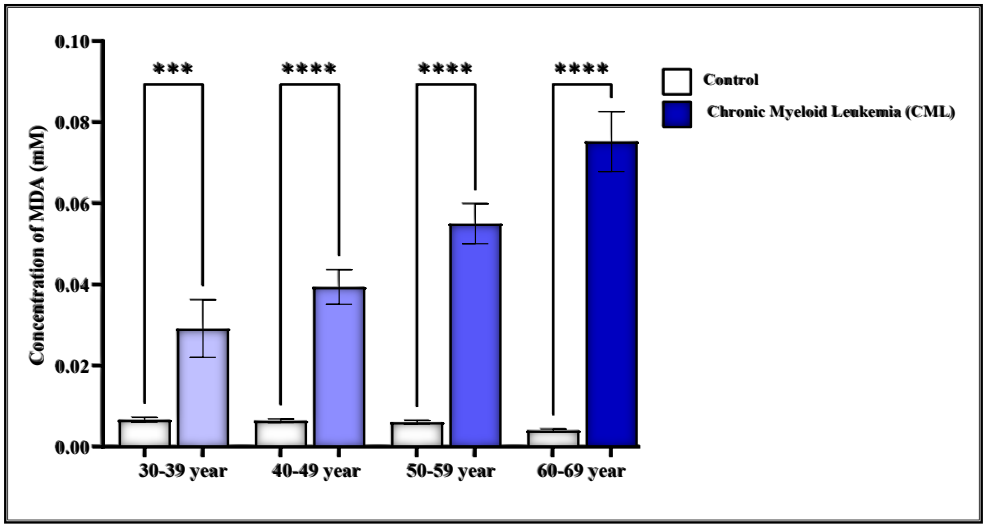

Figure 7: Serum MDA levels in patients with CML and among different age groups. Data are expressed as means ± SEM. Indicates **** p-value <0.0001

On the other hand, to compare the difference in MDA levels between the genders, MDA was estimated in males and compared to the females in patients with ALL, AML, and CML and was compared to the controls (Figure 8). The result shows that MDA levels were insignificantly high in males compared to the females in all patients groups, with no significant difference between males and females in the control.

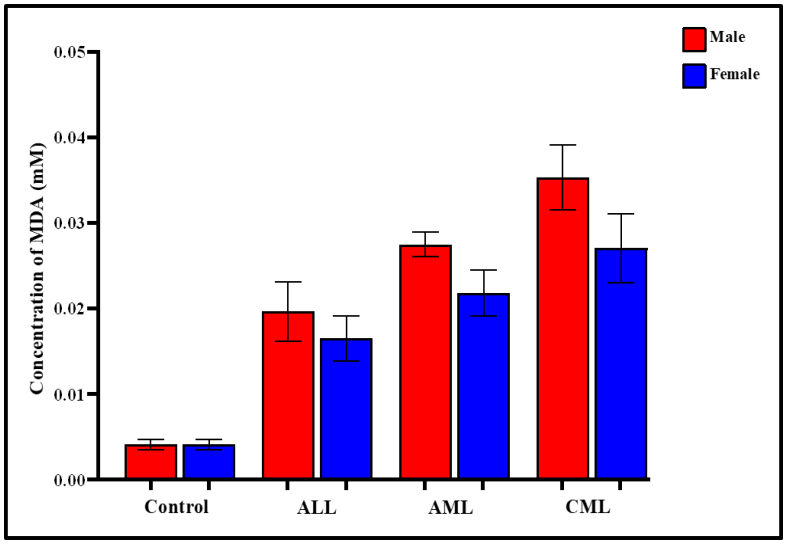

Figure 8: Estimation of serum [MDA (mM)] levels in males and females in all patients with (ALL, AML and CML) as compared with control. No significant difference was found between males and females in all patients with (ALL, AML and CML) as compared with the control.

Interestingly, the measurement of serum catalase activity (CAT) U/ml for patients (ALL, AML, and CML) showed that the activity of CAT was significantly low ($p < 0.0001$) in all ages comparing to the control group. This decline has been clearly

shown in ages over fifty years in all leukemia patients as shown Figures 9, 10 and 11 consequently.

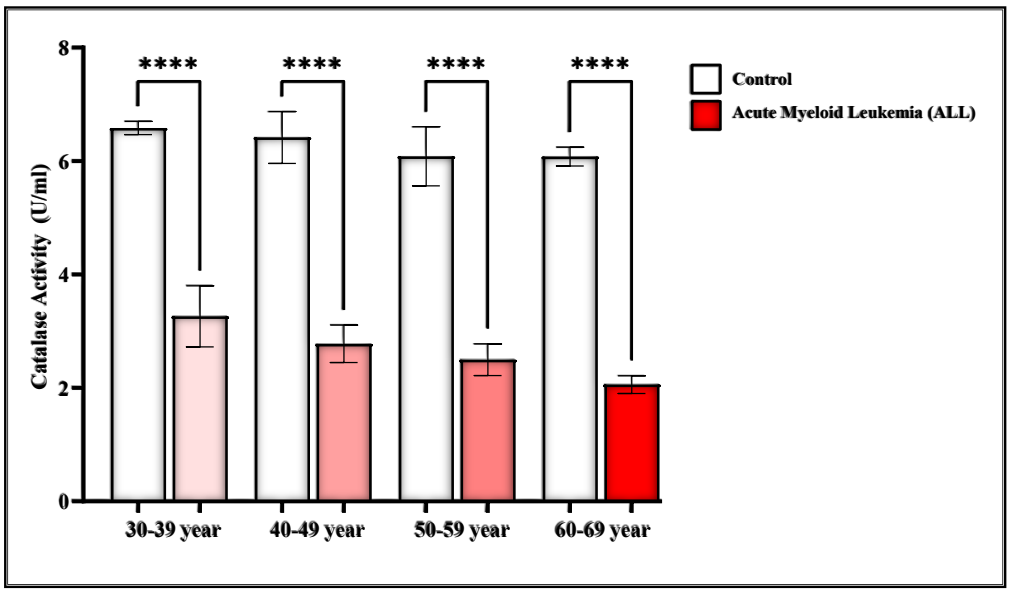

Figure 9: Serum CAT activity in patients with ALL and among different age groups. Data are expressed as means ± SEM. Indicates **** p-value <0.0001

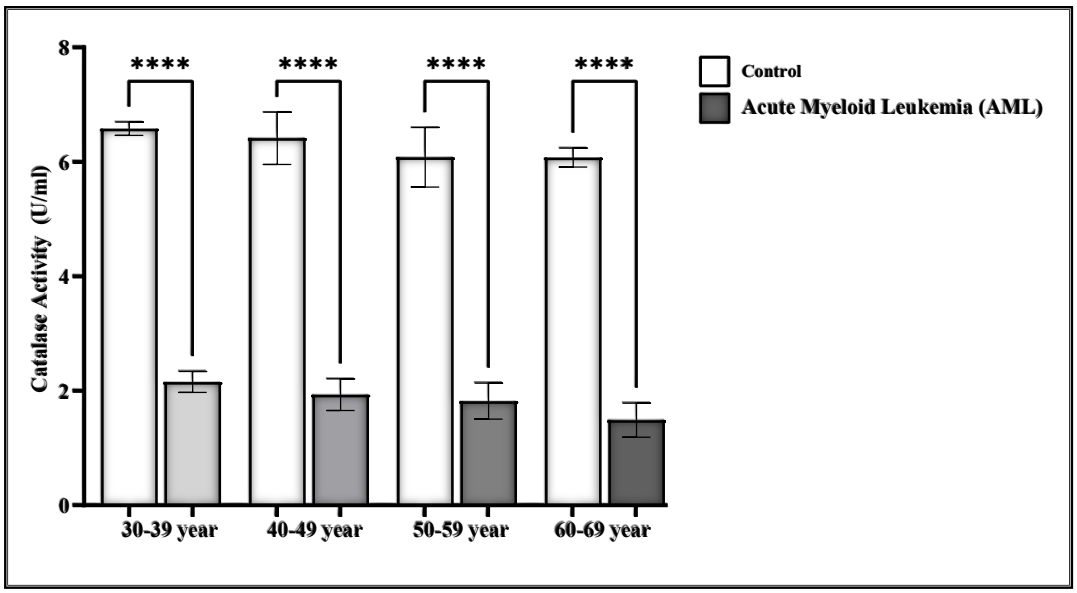

Figure 10: Serum CAT activity in patients with AML and among different age groups. Data are expressed as means ± SEM. Indicates **** p-value <0.0001

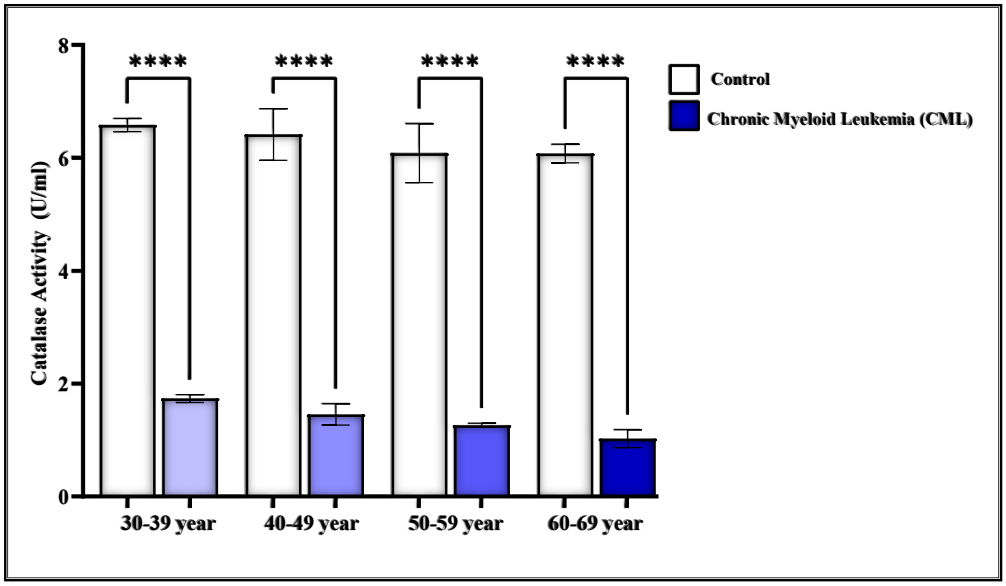

Figure 11: Serum CAT activity in patients with CML and among different age groups. Data are expressed as means ± SEM. Indicates **** p-value <0.0001.

On the other hand, to compare the difference in CAT activity between the genders, CAT was estimated in males and compared to the females in patients with ALL, AML, and CML and was compared to the controls. The result (Figure 3.48) shows that CAT activity were insignificantly high in females compared to the males in patients with AML and CML, but not in patients with ALL, with no significant difference between males and females in the control.

A negligible change in CAT activity between male and female in leukemia patients might not reflect a strong relation between type of gender and the levels of catalase activity. However, more studied are needed to find the effect of age and gender type on most biochemical markers in leukemia patients.

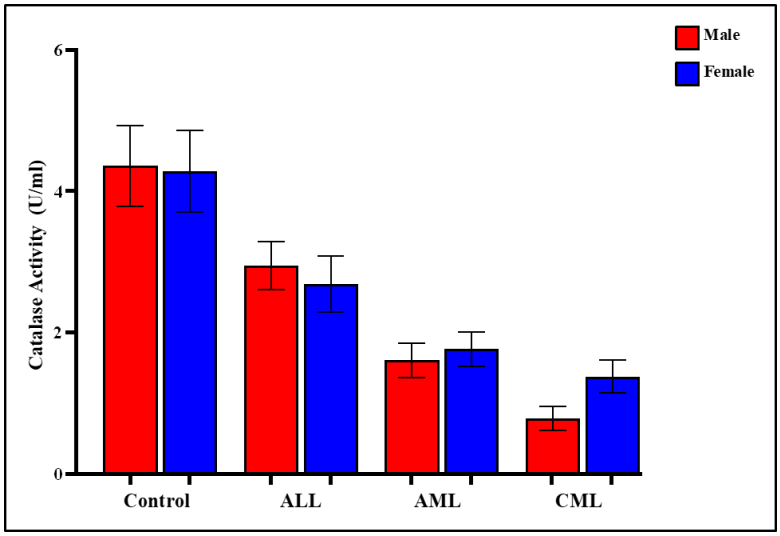

Figure 12: Estimation of serum [CAT (U/ml)] activity in males and females in all patients with (ALL, AML and CML) as compared with control. No significant difference was found between males and females in all patients with (ALL, AML and CML) as compared with the control.

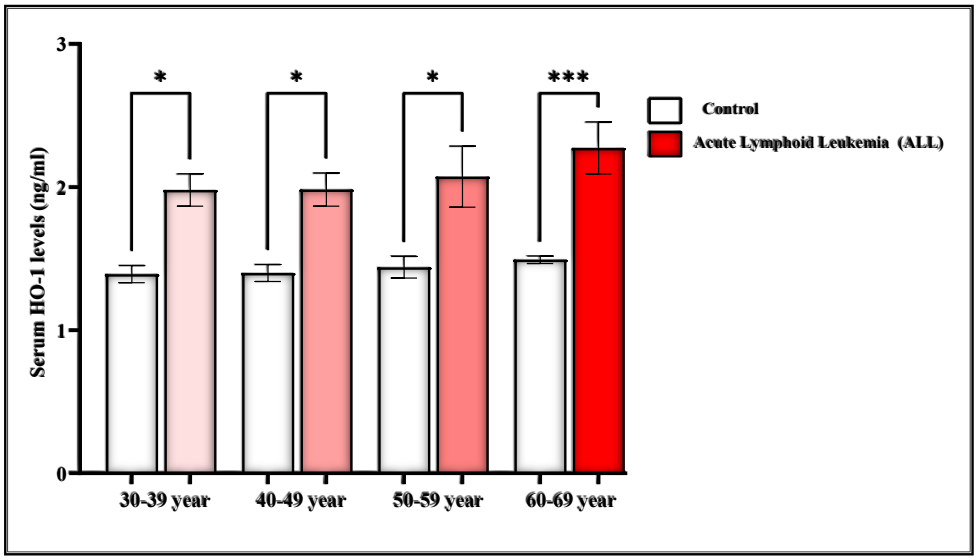

Figure 13: Serum HO-1 concentrations in patients with ALL and among different age groups. Data are expressed as means ± SEM. Indicates **** p-value <0.0001

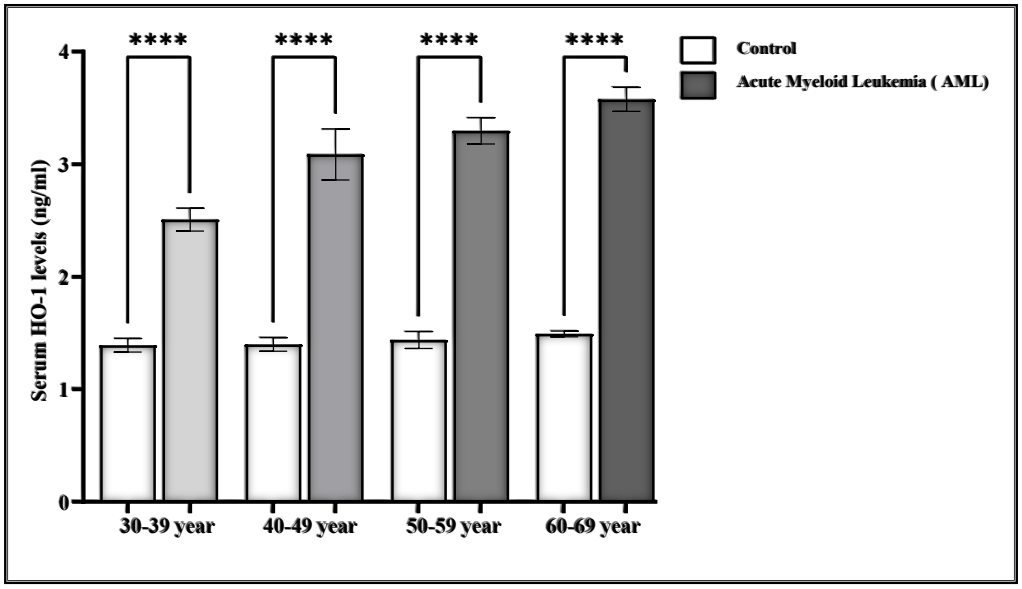

Figure 14: Serum HO-1 concentrations in patients with AML and among different age groups. Data are expressed as means ± SEM. Indicates **** p-value <0.0001

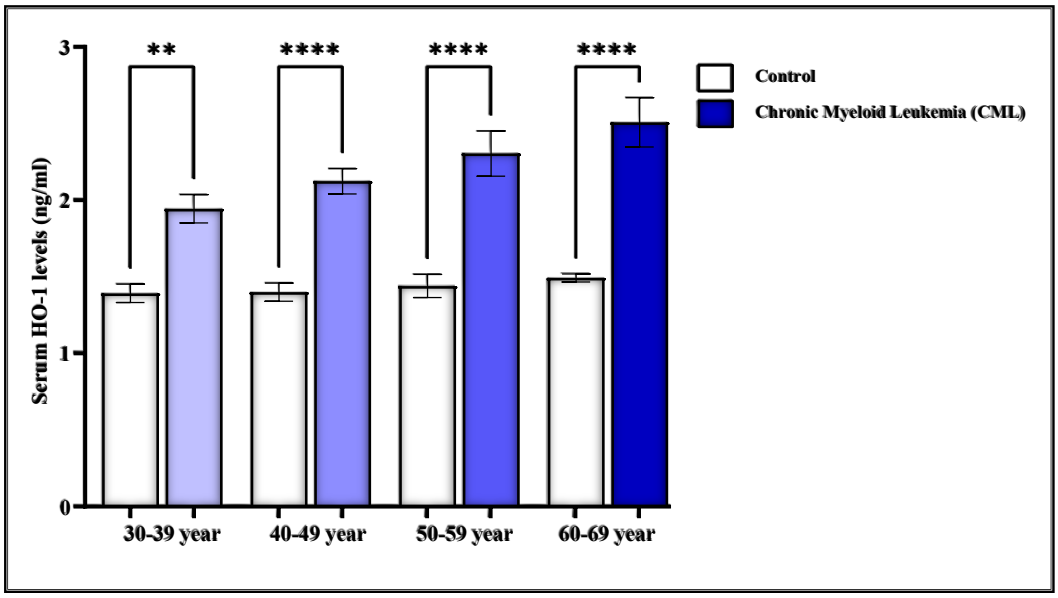

Figure 15: Serum HO-1 concentrations in patients with CML and among different age groups. Data are expressed as means ± SEM. Indicates **** p-value <0.0001

On the other hand, to compare the difference in HO-1 levels between the genders, HO-1 was estimated in males and compared to the females in patients with ALL, AML, and CML and was compared to the controls. The result shows that HO-1 levels were insignificantly high in males compared to the females in patients with ALL and CML, but not in patients with AML, with no significant difference between males and

females in the control. These data might refer to a possible relstion between HO-1 levels and the gender in leukemia, since the change in hemogenase-1 levels was clearly shown in males but not in females. However, the impact of gender on HO-1 levels in leukemia was not yet mentioned.

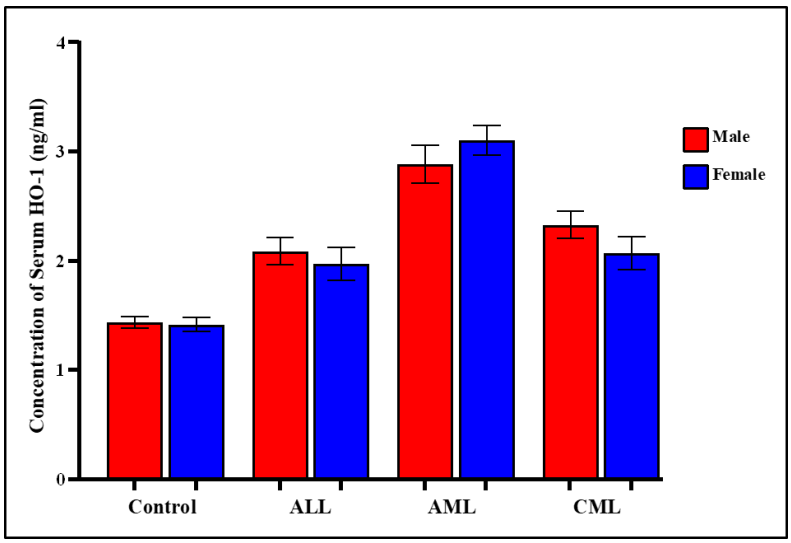

Figure 16: Estimation of serum [HO-1 ng/mL] levels in males and females in all patients with (ALL, AML and CML) as compared with control. No significant difference was found between males and females in all patients with (ALL, AML and CML) as compared with the control.

Discussion

MicroRNA-223 (miRNA-223) is a short RNA molecule. MicroRNAs function to regulate the expression levels of other genes by several mechanisms. miRNA-223 is a hematopoietic specific miRNA with crucial functions in myeloid lineage development (18). miRNA may regulate the expression of redox sensors and other reactive oxygen species (ROS) modulators, such as the key components of cellular antioxidant machinery, while ROS can induce or suppress miRNA expression and contribute to downstream biological function through the regulation of target genes (19). miRNA-223 is associated with hematopoiesis, immune response, and different types of cancer development (20).

The above results agreed with both Daschkey, Röttgers *et al.,* (2013), and Gentner, Pochert *et al.,* (2015) (171, 172). Distinct functions of miRNA-223 in tumor initiation, progression, and metastasis strongly suggest it works as a novel drug target

or therapeutic tool for human cancer treatments. Moreover, a single miRNA-223 can be involved in different oncogenic pathways by targeting various genes, including Mef2c, FBXW7, and EPB41L3. Thus, modulating the level of miRNA-223 could eventually affect several pathways at the same time. With the progress in profiling, miRNA-223-based treatment may be customized (21).

Mounting evidences have revealed pleiotropic effects of miRNA-223 in different types of cancer. miRNA-223 functions as an oncomiR in some cancer types, such as T-cell acute lymphoblastic leukemia (T-ALL) (22) and acute myeloid leukemia (AML) 23), it functions as a tumor suppressor. Particularly, miRNA-223 has a prominent role in the immune system and its functions in T-ALL and AML have relatively better understanding. As yet, the function of miRNA-223 in carcinogenesis has still not been fully characterized and understood. Glucocorticoids, which induce apoptosis in T-ALL, also increase miRNA-223 expression in glucocorticoid-sensitive cell lines, which indicates that increased miR-223 levels do not always support oncogenesis (24).

Malondialdehyde is an organic highly reactive chemical that occurs naturally as the enol; it is a sign of oxidative stress. It is generated when polyunsaturated fatty acids are degraded by reactive oxygen species. MDA very stable, and low molecular weight end product of membrane lipid peroxidation generated together with other byproducts, is the most often utilized biomarker as an indication of lipid peroxidation (25).

In the present study, significant increased in serum MDA levels was observed in leukemia patients with AML, ALL, and CML as compared with healthy control This could be attributed to the increased formation or inadequate clearance of free radicals by cellular antioxidants. The present observations are in agreement with other reports on hematological malignancies, including various human cancers (26)

Oxidative stress may occur in patients with leukemia due to the higher number of mature and immature myeloid series cells as well as other unknown factors. Malondialdehyde (MDA) which is a stable end product of free radical induced-lipid peroxidation was used as a surrogate marker for oxidative damage to tissues (27).

Additionally, the results of this study show increased levels of malondialdehyde (MDA) (0.0323 ± 0.00315) mM in patients with chronic myeloid leukemia (CML) compared to acute myeloid leukemia (AML) (0.0252 ± 0.0025), acute lymphocytic leukemia (ALL) (0.0194 ± 0.00426) and control (0.0039 ± 0.000795) mM. High levels of lipid peroxidation in CML patients was also proved by study of Ahmed *et al.*(2008), this study presented malondialdehyde as a biomarker for oxidative stress and disease progression in CML patients (28).

Our data indicate that oxidative stress increases with age, especially in CML. Notable, in new study noticed that both total antioxidant capacity (TAC) and ROS values progressively increased in CML age groups, reaching the maximum in the age group over 80 years. This may be due to complicated mechanisms generated by the interaction between the chronic myelogenous disease, the aging processes and treatment. It is possible that, in CML, the production of ROS is more accelerated vs.

the natural aging process and that oxidative stress levels vary also due to the therapy employed, as in other hematological malignancies (29).

Interestingly, the measurement of serum catalase activity (CAT) U/ml for patients (ALL, AML, and CML) showed that the activity of CAT was significantly low ($p < 0.0001$) in all ages comparing to the control group. This decline has been clearly shown in ages over fifty years in all leukemia patients (Figures 3.45, 3.46, 3.47). On the other hand, to compare the difference in CAT activity between the genders, CAT was estimated in males and compared to the females in patients with ALL, AML, and CML and was compared to the controls. The result shows that CAT activity were insignificantly high in females compared to the males in patients with AML and CML, but not in patients with ALL, with no significant difference between males and females in the control. A negligible change in CAT activity between male and female in leukemia patients might not reflect a strong relation between type of gender and the levels of catalase activity.

On the other hand, to compare the difference in HO-1 levels between the genders, HO-1 was estimated in males and compared to the females in patients with ALL, AML, and CML and was compared to the controls. The result shows that HO-1 levels were insignificantly high in males compared to the females in patients with ALL and CML, but not in patients with AML, with no significant difference between males and females in the control. These data might refer to a possible relstion between HO-1 levels and the gender in leukemia, since the change in hemogenase-1 levels was clearly shown in males but not in females. However, the impact of gender on HO-1 levels in leukemia was not yet mentioned.

However, more studied are needed to find the effect of age and gender type on the most significant biochemical markers in leukemia patients.

Conclusions

The results obtained for this study, show that there is a reliable correlation between age and gender and significant biomarkers in leukemia patients. Our findings could shed new light on the biology of the three different leukemia types. Moreover, understanding the reasons for the different outcome by gender may improve patients managements.

Authors Contribution

Zainab Mohammed Hillel and Dr. Zainab Nejim Al-Abady were involved in the design of the study, analysis of the results, and report writing. The authors confirmed the final version before it was submitted

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