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Role of calpain-2, omentin-1, interleukin-6 and antioxidants in patients with leukemia

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Leukemia is a cancerous disorder marked by the abnormal growth of hematopoietic cells, resulting in immune dysfunction and oxidative stress. The aim of this research is to examine the predictive role of some physiological parameters in the progression of leukemia. The study was conducted at the Medical City's Baghdad Teaching Hospital. Blood samples were obtained from 50 patients with acute leukemia (new diagnosis) and from 30 healthy people, whose ages ranged between 15–60 years, during the period from 25/3/2024 – 25/4/2024. After collecting blood samples, separating them using a centrifuge, and obtaining blood serum, the levels of the studied variables (calpain-2, omentin-1, interleukin-6, glutathione – GSH, and malondialdehyde – MDA) were estimated. Serum concentrations of calpain-2, omentin-1, IL-6, MDA were higher in the patients compared to the healthy people. Also the results showed a significant decrease in antioxidants such as GSH in patients with leukemia compared with the healthy people. High levels of calpain-2, omentin-1 and IL-6 and low levels of antioxidants may be important diagnostic variables to predict the severity of acute leukemia.

Keywords: calpain-2; omentin-1; interleukin-6; IL-6; antioxidants; oxidative stress; leukemia.

Introduction

A malignant tumor that starts in the bone marrow and spreads to other parts of the body is called leukemia, or blood cancer. It ranks as the third leading cause of death for people with cancer worldwide, affecting people of all ages and genders. It is thought to be among the most common types of cancer on the globe (Sulaeman et al., 2018). Between 2005 and 2015, the total number of leukemia cases increased by 26% globally (Bispo et al., 2020). This alarming rise highlights the global burden of the disease and the urgent need for more effective diagnostic and therapeutic strategies.

A study conducted in the city of Karbala revealed that acute myelogenous leukemia is the third most common type of blood cancer, with an average patient's age of 36 and comprising 19.2% of leukemia cases (Mjali et al., 2019). According to Lowenberg et al. (2010), the disease's symptoms arise from a reduction in myeloid cells' capacity to develop into mature forms of blood-forming cellular components. This condition causes aberrant, immature, and inefficient cells to be produced when the regular course of blood cell production is disrupted (Lowenberg et al., 2010). They do not perish at the appointed period, and their population grows significantly. The uncontrolled proliferation of these abnormal cells not only suppresses the production of normal hematopoietic cells but also leads to severe clinical manifestations, such as anemia, recurrent infections, and tendencies to bleeding (Shapovalov et al., 2022; Neamah et al., 2024).

Calpain-1 and calpain-2, which were first discovered in the 1960s, are the original members of cysteine proteases that are dependent on calcium (Ca^{2+}) and are being investigated as potential treatment targets for conditions including Alzheimer's and various cancers (Haque et al., 2024). They participate in many biological processes, including invasion, migration, autophagy, gene expression, and programmed cell death. Although there are numerous calpain subtypes, the widely expressed heterodimers of calpain-1 and calpain-2 are composed of catalytic subunits specific to each isoform (Niapour et al., 2012). Interestingly, in acute myeloid leukemia (AML), blast cells exhibit variable calpain activity that is markedly elevated across a broad spectrum, suggesting their possible role in disease pathogenesis and progression (Niapour et al., 2012).

For the first time, human omentin-1 was isolated in 2001 utilizing a library of complementary DNA (cDNA) from the small intestine. Numerous investigations have since suggested that omentin-1 may play a part in the development of tumors. Omentin-1 is crucial for the growth and control of apoptosis in a variety of cancer cell types (Dec et al., 2023). Additionally, omentin-1 can encourage the spread of cancer cells by increasing blood vessel permeability. It is an adipokine with demonstrated anti-inflammatory properties. Its link to cancer has generated debate; some research indicates that it might shield against carcinogenesis, while other investigations contend that it might contribute to tumor malignancy. This dual role makes omentin-1 an intriguing but complex biomarker whose precise role in leukemia remains to be clarified (Zoroddu et al., 2024).

Interleukin-6 (IL-6), one of the most important cytokines in the bone marrow (BM), plays a central role in shaping the AML microenvironment. It aids in the development of chemoresistance in acute myeloid leukemia (AML) and is strongly associated with malignancy progression and severity. IL-6 is one of the cytokines that leukemia blast cells produce, according to several earlier studies, and it is considered crucial for maintaining the survival niche of leukemia stem cells. These diverse pathways underlie IL-6's effect on acute lymphoblastic leukemia (ALL) severity (Al-Naqeeb et al., 2020; Hou et al., 2023).

An imbalance between the production of reactive oxygen species (ROS), which can activate different transcription factors and alter their transcriptional pathways, and antioxidant defense mechanisms results in oxidative stress. Leukemia formation and occurrence are significantly influenced by oxidative stress, which is also strongly associated with leukemia treatment and prognosis (Gahzi et al., 2020). An excess of malondialdehyde (MDA) is produced as the number of free radicals rises. Typically, the MDA level is referred to as a biomarker to measure the antioxidant status of cancer patients and oxidative stress (Ridha et al., 2022). Glutathione (GSH) is the primary antioxidant found in cells throughout the body, including the brain. It is a potent endogenous antioxidant and plays a vital role in neutralizing free radicals and maintaining the cellular redox state. Alterations in GSH levels have been reported in leukemia patients, further confirming the strong link between oxidative stress and hematological malignancies. The purpose of this study is to evaluate the predictive role of selected physiological parameters in the progression of leukemia. Iden-tifying such markers may enhance early detection, improve prognosis, and support the development of personalized therapeutic approaches for affected patients.

Materials and methods

In compliance with the Declaration of Helsinki, the study was authorized by the Institutional Review Board (IRB) of College of Nursing, University of Baghdad, and each participant completed a written informed consent form.

The present case–control study was conducted at the Medical City's Baghdad Teaching Hospital during the period from March 25, 2024, to April 25, 2024 to investigate the predictive role of selected physiological parameters in leukemia progression. A total of 50 blood samples were obtained from patients newly diagnosed with acute leukemia (prior to receiving chemotherapy) and compared with 30 samples from apparently healthy individuals aged 15–60 years. Inclusion criteria comprised newly diagnosed leukemia patients without previous treatment, while individuals with chronic illnesses, prior chemotherapy, or other hematological disorders were excluded. Blood samples were collected by venipuncture under aseptic conditions, then centrifuged to separate the serum. Subsequently, the levels of calpain-2, omentin-1, interleukin-6, glutathione, and malondialdehyde (MDA) were estimated. Measurement of serum concentrations was performed using ELISA kits manufactured by Fine Test, China, following the manufacturer's instructions. This methodological approach allowed accurate evaluation of biomarkers that may serve as predictors of disease progression and prognosis in acute leukemia.

The data collected from the study samples were analyzed using the SPSS software, which enabled the calculation of descriptive statistics, including the arithmetic mean and standard deviation for all measured variables. Comparative analyses between the main (patients) and secondary (control) groups were conducted to evaluate differences in biochemical and physiological parameters. Statistical significance was determined using appropriate tests, with a P-value of less than 0.05 considered significant. This approach ensured a rigorous assessment of variations between groups, allowing the study to identify meaningful patterns and relationships among the biomarkers, thereby supporting reliable conclusions regarding their diagnostic and predictive value in leukemia.

Results

The study results showed clear and significant differences between leukemia patients and the control group in all measured parameters ($P < 0.0001$). Calpain-2 levels were significantly higher in patients compared to healthy individuals, and omentin-1 levels were significantly higher in patients, reflecting increased biological activity associated with the disease. Interleukin-6 (IL-6) levels also increased significantly, indicating the role of inflammation in leukemia progression. Conversely, a significant decrease in glutathione (GSH) levels was observed in patients, reflecting impaired antioxidant defense, while malondialdehyde (MDA) levels were significantly elevated, indicating increased oxidative stress. Together, these results indicate an imbalance between inflammatory, oxidative, and antioxidant factors in leukemia patients and illustrate the biochemical changes that accompany disease progression and their impact on the patient's overall health as shown in Figure 1.

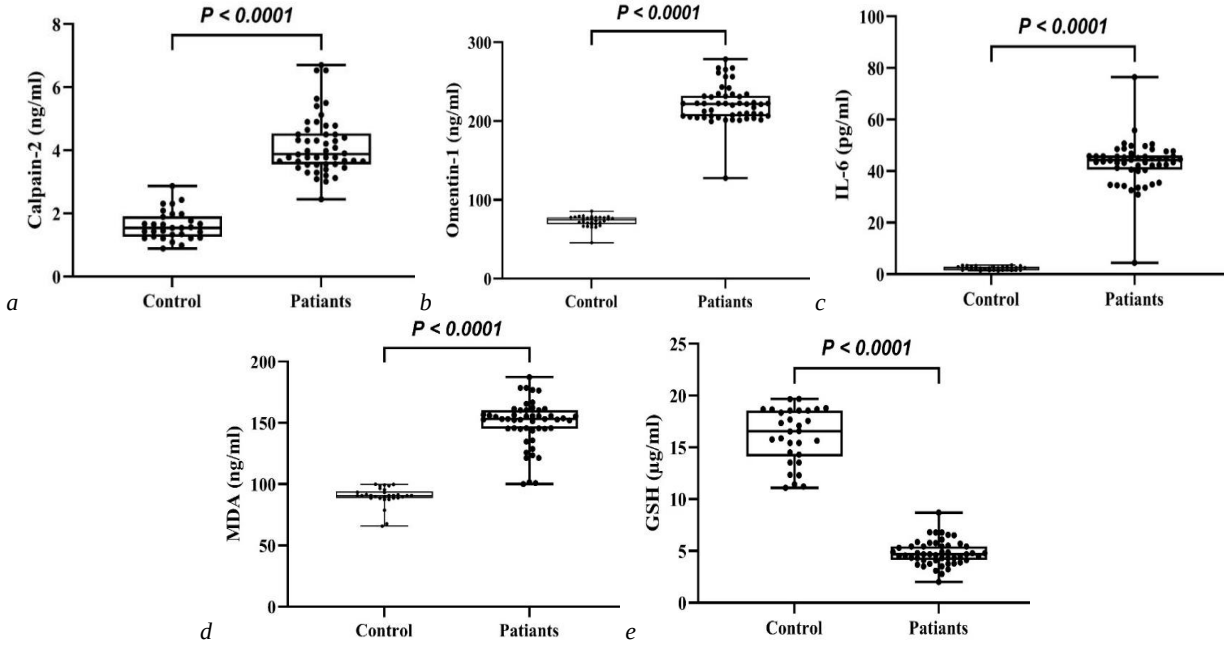

Fig. 1. Calpain-2 concentration in the blood serum of both groups'(*a*), omentin-1 concentration in the blood serum of both groups (*b*), IL-6 concentration in the blood serum of both groups (*c*), MDA concentration in the blood serum of both groups (*d*), GSH concentration in the blood serum of both groups (*e*)

Analytical results of the diagnostic ability of the measured biochemical markers demonstrated very high performance for all studied factors. For calpain-2, the cutoff value was set at >2.87 ng/mL, demonstrating 98% sensitivity and 100% specificity, with an estimated precision of 0.9800 and an AUC value of 0.999, indicating its significant importance in distinguishing between patients and healthy individuals ($P < 0.0001$). For glutathione (GSH), we set a cutoff value of ≤8.7 µg/mL, achieving optimal sensitivity, specificity, and accuracy of 100% for each, with an AUC value of 1.000, demonstrating its optimal potential as an accurate diagnostic marker ($P < 0.0001$). Similarly, malondialdehyde (MDA) showed excellent performance at >99.87 ng/mL, with perfect sensitivity, specificity, and accuracy, and an AUC value of 1.000, confirming its role as a key indicator of oxidative stress in patients ($P < 0.0001$). Regarding inflammatory markers, interleukin-6 (IL-6) recorded a level of >3.5 pg/mL and demonstrated optimal sensitivity, specificity, and accuracy with an AUC value of 1.000, reflecting its vital role in pathological progression of leukemia ($P < 0.0001$). Finally, omentin-1 showed similar performance at >85.5 ng/mL, with all diagnostic measures achieving optimal sensitivity, specificity, and accuracy with an AUC value of 1.000, confirming its importance as an accurate marker for patient assessment ($P < 0.0001$) as shown in Figure 2.

Discussion

The current study's findings demonstrated that patients' blood serum levels of calpain-2 were higher than those of healthy individuals.

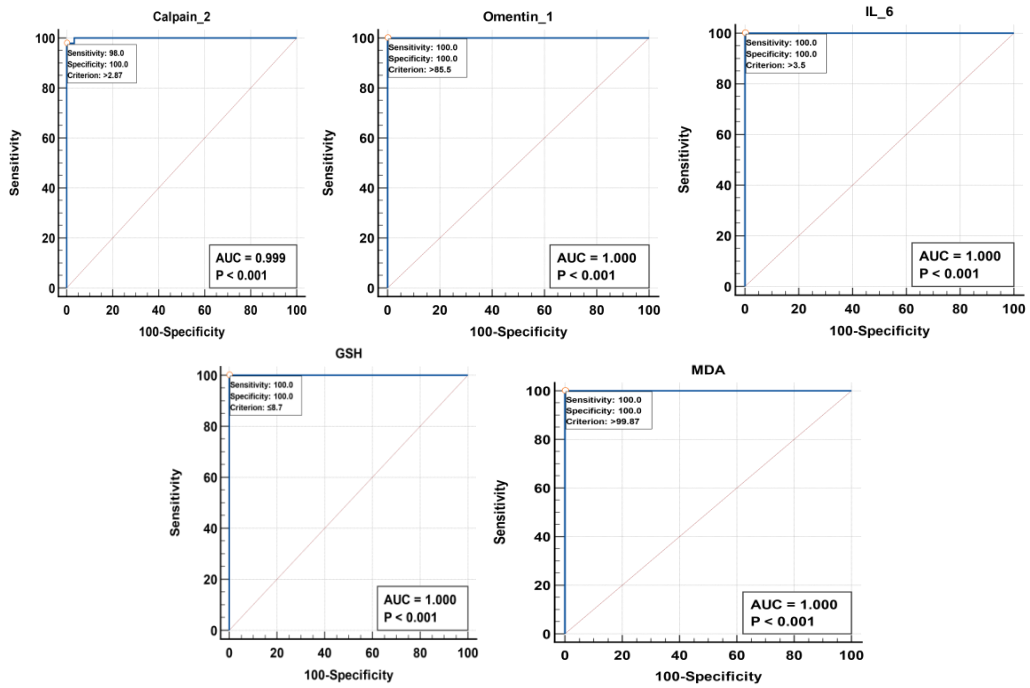

Fig. 2. Analysis of the receiver operating characteristic (ROC) curve (AUC) for each physiological parameter in the group under study

The increase in calpain-2 protein is thought to be caused by the breakdown of both cancer and healthy cells, which releases calpain-2 protein as it breaks down proteins in the bloodstream. Alternatively, calpain-2 protein may be involved in programmed cell death by stimulating the death process with calcium in order to eliminate cancer cells.

Similarly, the study revealed that the patients' blood serum included higher levels of adipose tissue hormones, such as omentin-1, than that of healthy individuals. One of the main cell types in the bone marrow microenvironment, adipose tissue, is essential to the initiation and spread of cancer. The bulk of cells in adipose tissue are called adipocytes, and they have unique metabolic functions, capacities for replication and development, the ability to produce cytokines, and responses to external stimuli. Bone marrow is a critical site of metastasis for solid tumors and a vital milieu for hematological malignancies. It contains a large number of adipocytes. Acute leukemia cells affect adipocytes in several ways, changing their ability to undergo adipogenic differentiation, causing adipocyte lipolysis, and encouraging adipocyte remodeling in the bone marrow. Adipocytes are essential for both the therapy and survival of acute leukemia cells (Maurya et al., 2021).

Pro-apoptotic and anti-inflammatory, omentin-1 is an adipokine that helps adipocytes and surrounding tissues communicate in order to regulate the metabolism of fat and glucose. Many malignancies, such as pancreatic adenocarcinoma, breast cancer, gastric cancer, cancers of the liver, prostate, colon, and colorectal cancer have been linked to higher expression of omentin-1. Depending on the kind, low or high omentin1 levels may be a sign of cancer progression. According to some data, blood levels of serum of omentin-1 are positively correlated with the development of cancer. Clinical evidence, for instance, showed plasma omentin-1 levels were higher among those suffering from colorectal cancer, which alone could be a potential risk factor for patient survival and recurrence (Poladian et al., 2023).

Furthermore, the study's results indicated that the blood IL-6 levels in the serum in patients exceeded that of healthy individuals. When patients showed improvement after receiving induction chemotherapy (i.e., their bone marrow's blast cell count decreased to >5%), their levels of IL-6 dropped. As opposed to the group under control, newly diagnosed IL-6 levels in AML patients were significantly higher. Our research showed that following induction chemotherapy, patients with AML had lower serum levels of two indicators, including IL-6. This suggests that measuring these markers' levels could be useful in prognosticating patients and assessing the effectiveness of treatment (Liguori et al., 2018).

Leukemic blast development has been shown to be impacted differently by the cytokine interleukin-6 (IL-6), which has pleiotropic inflammatory effects (Giovan et al., 2024). Through raising the amount of cortisol, interleukin-1 receptor antagonist (IL-1ra), and interleukin-10 (IL-10) in human plasma, it might also have biological benefits that reduce inflammation (Feng et al., 2020).

Additionally, Abd El-Hhafez et al. (2018) discovered that the blood levels of IL-6 of the study group (newly diagnosed) before induction chemotherapy were significantly higher than those after chemotherapy and the control group. Elevated IL-6 levels decreased when patients reacted to chemotherapeutic induction, indicating that IL-6 concentration measurements are possibly useful in evaluating treatment efficacy. On the other hand, our results also concurred with the findings of Shenghui et al. (2011), who found that the ND and relapsed patient groups had notably greater levels of blood IL-6 compared to the control group, while the levels of serum IL-6 in the remission group was within the normal range. Additionally, it was discovered that there was a positive link with total leukocyte count and an inverse relationship with serum level of IL-6 in ND and AML in patients who had relapsed, as well as hemoglobin percent. The 95% CI range for the adjusted OR (AOR) was 1.044–8.527, and it was 2.983 and an area under the curve of 0.672. According to this, children with IL-6 levels of 64.23 ng/mL had a 63.3% accuracy value and a 2983 HR of developing ALL (Steensberg et al., 2003).

In addition to being closely associated with leukemia therapy and prognosis, one important element is oxidative stress. Reduced antioxidant components and enhanced oxidative stress offer a clear picture of malignancies during leukemia subtypes. Research indicates that a significant portion of all patients under treatment do not consume enough anti-oxidant micronutrients (Dawood et al., 2011).

Glutathione (GSH) is essential for many cellular functions, including as apoptosis, Many human diseases, including cancer, are associated with the beginning and progression of abnormalities in GSH homeostasis, proliferation, and differentiation. As many cancer cells exhibit, elevated GSH levels increase antioxidant capability and tolerance to oxidative stress (Dong et al., 2021), whereas GSH deficiency, or a decrease in the GSH/glutathione disulphide (GSSG) ratio, increases vulnerability to oxidative stress associated with the development of cancer (Abiri et al., 2021).

In general, significant variations in MDA concentrations were seen over the course of treatment for AML patients in comparison to healthy controls. This is consistent with earlier research that showed increased ROS levels in cancer cells, which might significantly affect

how cancer develops and spreads (Ballatori et al., 2009). Prior to transplantation, AML patient samples had the greatest MDA concentration, which may have been caused by their conditioning protocols (Haro Girón et al., 2023).

Conclusion

The present study demonstrated that patients with acute leukemia exhibited a significant reduction in antioxidant defenses, including glutathione, alongside a marked increase in oxidative stress markers, such as malondialdehyde (MDA). Concurrently, the levels of calpain-2, omentin-1, and interleukin-6 were significantly elevated compared to healthy controls, indicating their active involvement in disease pathophysiology. These findings highlight a strong correlation between oxidative stress, inflammatory mediators, and the progression of leukemia. Importantly, the evaluated biomarkers showed high diagnostic sensitivity, specificity, and accuracy, suggesting their potential as reliable predictive indicators for disease development. Monitoring these parameters could provide clinicians with valuable insights for early detection, prognosis assessment, and tailoring personalized therapeutic strategies. Overall, the study supports the clinical relevance of oxidative stress-related markers and inflammatory proteins in leukemia, emphasizing their role not only in understanding disease mechanisms but also as practical tools for improving patient management and outcomes.

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