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Association Between Serum Ferritin and CD19/CD34 Expression in Pediatric Acute Lymphoblastic Leukemia

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Abstract

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, characterized by malignant proliferation and accumulation of lymphoblasts in the bone marrow. Abnormal immunophenotypic expression and iron balance are always present in acute leukemia. Serum ferritin levels are used to track the body's iron status since ferritin is a crucial component of blood cells. All B lineage cells exhibit the transmembrane glycoprotein known as the CD19 antigen, a B cell lineage hallmark. CD34 is a membrane protein first discovered in hematopoietic stem and progenitor cells and, therefore, is a marker of immaturity. The expressions of CD19 and CD34 antigens are associated with a good prognosis in acute lymphoblastic leukemia. In this investigation, we evaluated the variation in serum ferritin, CD19, and CD34 levels between children with acute lymphoblastic leukemia and healthy children, as well as the degree of association between serum ferritin and CD19/CD34 expression.

It showed that the blood ferritin level was considerably higher ($P<0.05$) in kids with acute lymphoblastic leukemia than in children in good health. CD19 expression was decreased non-significantly in the ALL children, but CD34 expression didn't differ in the pediatric ALL than their expression in normal children. The association between Serum Ferritin and CD19/CD34 Expressions appeared to be a moderate inverse correlation between CD19 level and serum ferritin, while CD34 level has a very weak inverse correlation with serum ferritin in the pediatric ALL patients.

Keywords: Acute lymphoblastic leukemia, Ferritin, CD19, CD34

Introduction

The malignant growth and buildup of immature cells (lymphoblasts) in the marrow cavity are hallmarks of acute lymphoblastic leukemia (ALL), a clonogenic disease. It is the most frequent blood cancer in kids [1,2]. ALL is a malignant disorder that arises from a single blood-forming lineage affecting either the B- or T-cell line [3]. The distribution of ALL categories is as follows: B-cell lineage accounts for 85%, T-cell lineage represents 10-15%, and NK cell lineage comprises less than 1%, with the incidence of ALL varying globally [4,5]. This disease predominantly affects children under 6 years old but also occurs in older children and adults [6]. Although some instances may progress gradually over many months, ALL usually has an abrupt clinical start [7]. The most frequent symptoms are fever (from leukemia or secondary infections from neutropenia), tiredness and weariness (from anemia), and bleeding propensity (from thrombocytopenia) [8]. These symptoms are usually connected to the leukemic cell burden. The three

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most prevalent laboratory abnormalities in children with ALL are anemia, thrombocytopenia, and neutropenia; around 15% of kids also have hyperleukocytosis [9].

Cancer cells have been shown in several studies to increase iron uptake, block iron storage, and reduce iron excretion. Significant changes in iron metabolism occur in leukemia, including the deregulation of the ferroportin-hepcidin regulatory axis and modifications in absorption, storage, transport, and excretion [10]. At the same time, enhanced tumor cell motility, adhesion, and angiogenesis are linked to increased iron storage as ferritin chains [11]. Reactive oxygen species (ROS), a consequence of excess iron, disrupt normal hematopoiesis and result in harmful cellular alterations [12]. Patients with a range of hematologic malignant diseases were analyzed to determine the association between changes in serum ferritin and the clinical state of the patients. Patients with acute lymphoblastic leukemia were found to have considerably increased serum ferritin levels [13,14]. Because elevated serum ferritin predicts both overall survival and relapse, it is a proxy for advanced illness and impacts recurring relapse. Serum ferritin levels are suggestive of acute phase responses and are often associated with iron storage [15,16].

Serum ferritin levels are utilized in clinical settings to track the body's iron status. Ferritin levels are typically stable in healthy people, with children's levels being lower than adults' [17]. However, blood ferritin levels can be impacted by several conditions. Serum ferritin levels can be affected by some factors, including body mass index (BMI), infections, increased iron consumption, liver impairment, and blood transfusions [18,19]. The current study is to give more data regarding the relationship between serum ferritin and acute lymphoblastic leukemia, as there aren't many studies on this type of hematologic malignancy [20].

All cells of the B lineage express the transmembrane glycoprotein known as the CD19 molecule, or B-lymphocyte antigen CD19, which is a member of the immunoglobulin superfamily (IgSF) [21,22]. The two primary roles of CD19 in human B cells are to attract cytoplasmic signaling proteins to the membrane as an adapter protein and to lower the threshold of B-cell receptor signaling pathways by functioning inside the CD19/CD21 complex [23,24]. CD19 is a biomarker for the development of B lymphocytes and the detection of lymphomas, as it is present on all B cells. All stages of B cell development, up until ultimate differentiation into plasma cells, see high expression of CD19[25,26]. Hematopoietic stem cells commit to the B lineage during immunoglobulin gene rearrangement, which initiates CD19 expression during B cell lymphopoiesis. Throughout development, CD19 density is strictly regulated. Compared to immature B cells, mature B cells express CD19 three times more frequently [27-29]. Due to its ubiquity on all B cells, CD19 expression is preserved in B lineage cells undergoing neoplastic transformation, making it a valuable marker and target for immunotherapies targeted at neoplastic lymphocytes [21].

In regenerated bone marrow (BM), CD34 is a marker of immaturity that is important for diagnosis, and its expression pattern helps distinguish hematogones from blasts [1]. First identified on hematopoietic stem and progenitor cells, CD34 is a transmembrane protein. It encourages these progenitor cells to attach to elements of the stromal milieu, which facilitates their differentiation, proliferation, and apoptosis resistance [30]. Around the world, CD34 is utilized in ALL panels as a marker for blast identification. Furthermore, some research has emphasized the importance of CD34 in prognosis, linking its expression to a favorable outcome in acute myeloid leukemia [31].

Nevertheless, there is a paucity of research, particularly from Iraq, on the prognostic relevance of CD19 and CD34 expression in ALL. To ascertain the relationship between ferritin and CD19/CD34 expressions, the current study will examine serum ferritin and CD19/CD34 expression in pediatric acute lymphoblastic leukemia.

Materials and Methods:

Study Subjects:

The biology department of the University of Kufa's Faculty of Science conducted this case-control research from December 2023 to November 2024. The study population comprised samples taken from patients with acute lymphoblastic leukemia (ALL) who were treated at the National Center for Educational Laboratories' Department of Hematology in the Medical City of Baghdad and the National Hospital for Oncology and Hematology Disease in Al-Najaf. Ninety cases of children, ages two to eight, were included in the study. They were split into two groups: 55 patients with newly diagnosed acute lymphoblastic leukemia who were not receiving treatment and whose diagnosis was confirmed by pediatric hematologists; and 35 people who were in the control group and did not have any illnesses that could have interfered with the study. All sick and healthy people gave their informed permission.

Methods:

Each research participant had a vein punctured to yield three milliliters of blood, which were then placed in gel tubes devoid of anticoagulants to prepare serum. The tubes were left to clot at ambient temperature (25°C) for fifteen minutes before being centrifuged for ten minutes at 3500 rpm. After the serum was separated, human enzyme-linked immunosorbent assay (ELISA) kits and an automated ELISA reader (Biotech, USA) were used to estimate serum ferritin, CD19, and CD34 expression.

Statistical analysis:

The data analysis was performed by SPSS version 20, whereas used t-test independent between patients and controls, and correlation in this study.

Results:

1. Ferritin

Table (1) shows the mean of serum ferritin levels in the pediatric ALL and healthy (control) groups. The results of this table have shown the presence of a significantly increased P-value with less than < 0.05 in the term of ferritin level in the acute lymphoblastic leukemia group as it was (595.74 ± 104.54 ng/mL) compared to the control group, where their ferritin was (213.83 ± 19.76 ng/mL).

2. CD19

The results of Table (1) show also a difference in the levels of CD19 expression in the study groups, but this difference was non significantly, where CD19 level appear a non-significant decrease in the acute lymphoblastic leukemia individuals that was (8.81 ± 2.27 ng/ml) compared to the healthy group that whose CD19 level was (10.29 ± 2.13 ng/ml).

3. CD34

The findings of the same table (1) did not show a significant difference in the CD34 levels in the acute lymphoblastic leukemia group as they were (409.27 ± 115.26 pg/ml), compared to the normal group, where their CD34 level was (413.88 ± 100.74 pg/ml).

Correlation of Ferritin and CD19/CD34 Expression

Statistically analyzed in table (2) shows the relationship of serum ferritin concentration with CD19/CD34 levels in the pediatric ALL. Where the CD19 level showed moderate inverse correlation *(Pearson correlation -0.4)* with serum ferritin in the ALL patients.

While the CD34 level showed a very weak inverse correlation *(Pearson correlation -0.11)* with serum ferritin concentration in the pediatric acute lymphoblastic leukemia.

TABLE (1) shows the ferritin and CD19/CD34 in control and pediatric ALL groups

Parameters	Mean ± SD		P-value
	Control (45)	Patient (45)	
Ferritin	213.83 ± 19.76	595.74 ± 104.54	0.00001
CD19	10.29 ± 2.13	8.81 ± 2.27	0.07
CD34	413.88 ± 100.74	409.27 ± 115.26	0.9

TABLE (2) shows the Correlation of ferritin and CD19/CD34 in the pediatric ALL group

Correlation	CD19	CD34	
Ferritin	**-0.4**	**-0.11**	**Pearson correlation**
	0.12	**0.68**	**P-value**

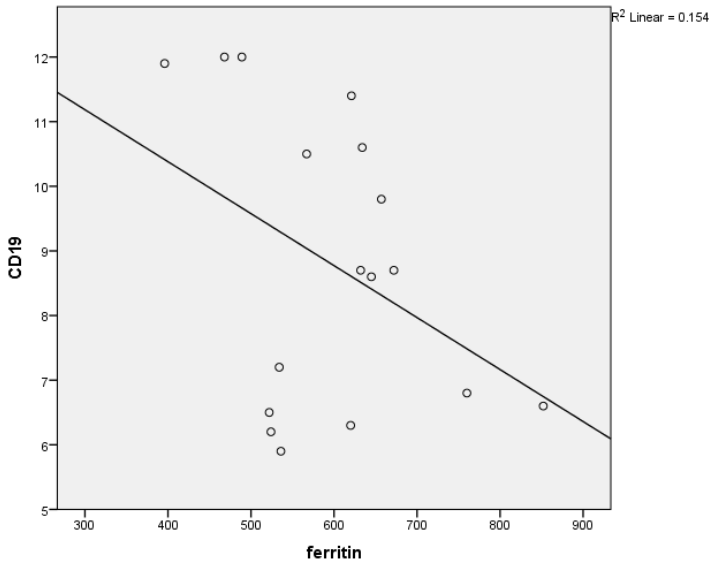

FIGURE (1) Showing the correlation of ferritin and CD19 expression in the pediatric ALL group

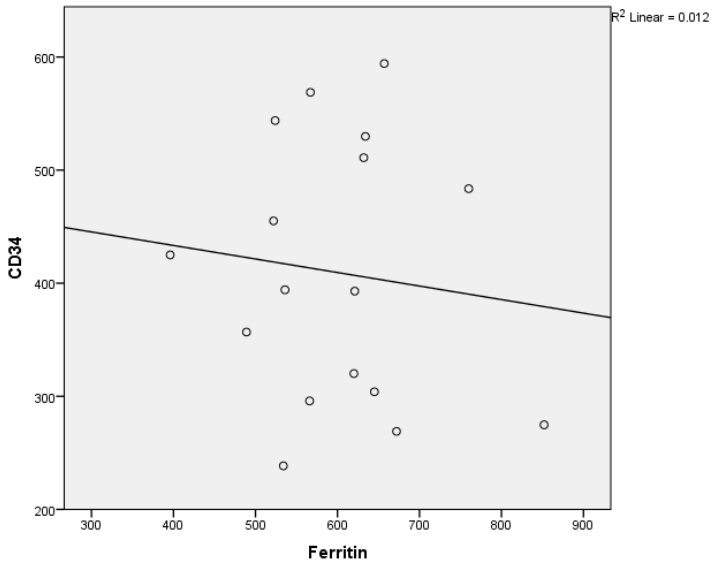

FIGURE (1) Showing the correlation of ferritin and CD34 expression in the pediatric ALL group

Discussion

The serum ferritin levels in this study increased significantly among newly diagnosed acute lymphoblastic leukaemia patients compared with the normal individuals of the same age, and this is in agreement with [10,32]. Ferritin is a protein that stores iron within cells. It is classified as an acute-phase reactant, which means its levels increase in response to inflammation and tissue injury. Numerous studies have indicated that patients with elevated ferritin levels tend to have a worse prognosis compared to those with lower or normal levels [33,34]. In addition, many other studies reported that serum ferritin is significantly increased in acute leukemia and other haematological malignancies, with important prognostic implications [35,36]. In acute leukemia cases, the rate of serum ferritin synthesis is increased. However, individuals with acute leukemia have high serum ferritin levels because the body is unable to remove the extra ferritin from the blood [37]. Iron overload, chemotherapy, and infection are potential causes of increased serum ferritin levels in ALL patients [38]. The primary predictors for the development of tumor lysis syndrome in patients with acute lymphoblastic leukemia include tumor load, as shown by serum ferritin, lactate dehydrogenase (LDH) level, white blood cell count (WBC), and severe bone marrow involvement [39,40]. Unused iron may build up as a result of ALL-related cessation of normal erythropoiesis, which raises serum ferritin levels. Ferritin may be raised as a result of any ongoing systemic inflammatory processes since it is an acute phase reactant. Accordingly, research assessing ferritin's involvement in cancer revealed that leukemias had a markedly elevated serum ferritin level [41]. According to another study, a number of cases with various cancers had elevated serum ferritin levels because of increased transferrin receptors on leukemic cell clones that were malignant. Additionally, as the rate of cell destruction increased, ferritin was exposed, which raised serum ferritin levels [42]. According to several studies, serum ferritin levels vary depending on the stage of ALL illness, with early-stage patients having the highest rate of increase [10].

Since CD19 and CD34 are extensively expressed on both malignant and normal B cells, they are not

thought to be discriminating markers for differentiating between B cell malignancies. The quantities of CD19 and CD34 antigens in a variety of leukemias might be measured thanks to the advent of methods that quantify antigens using flow cytometry [43]. It is feasible to more accurately describe normal and malignant B cell populations by comparing the densities of CD19 and CD34. According to Arif and Jaffat (2017) [44], the two compounds under investigation have a functional role on B cells.

By causing cell cycle arrest or programmed cell death, CD19 acts as a coreceptor that regulates B cell development and differentiation [45]. Along with CD79a, CD19 expression on B cells is highly conserved and characteristic of early B cell progenitors. Throughout pre-B and mature B cell development, CD19 expression rises until it is downregulated in later phases of B cell maturation, such as plasma cells [46]. Our study's ALL blood CD19 values are similar to those of bone marrow-mature B cells and peripheral blood B lymphocytes' CD19 ABC values [47]. Since it proves that leukemia cells are immature, CD34, an immaturity marker that is often expressed in these cells, is employed everywhere. The intensity of CD20 expression on the surface rises as the blasts grow, whereas the CD34 antigen weakens and turns negative. Nonetheless, a significant portion of the pre-BALL blasts, or phenotypically more immature B blasts, test negative for CD34, which explains the instances in which CD34 expression is lacking [48]. Nonetheless, some investigations have revealed that not all B-ALL instances may exhibit consistent expression of CD34 [1]. There is little research on the expression of CD34 in Iraqi ALL, and nothing is known about its prognostic importance. To examine the frequency of CD34 expression and its correlation with other prognostic markers in Iraqi ALL patients, the current study was conducted.

In study instances, the asynchronous co-expression of CD34 and CD19 was observed. Such an asynchronous expression was also noted in ALL instances by Sharma et al., (2016) [49]. First off, this asynchronous production of early and late antigens can help distinguish blasts from hematogones when assessing minimum residual illness since it contradicts the typical antigenic development of B-cell progenitors. Second, a poor prognosis for B-ALL is linked to CD19 expression [50].

Although the correlations were statistically moderate and modest, respectively, we discovered in this study that there was an inverse relationship between serum ferritin levels and CD19/CD34 expression in pediatric ALL. This result is comparable with [51,1], who reported no correlation between ferritin content and CD19/CD34 expression in either ALL or subgroup B-ALL. Nonetheless, an association was discovered by additional investigations [49, 52]. These discrepancies could result from variations in the patient cohort (ALL rather than B-ALL), sample size, and demographics (ethnicity and age group examined).

Conclusion

This study concluded that:

1. A significant increase ($P< 0.05$) in the ferritin level in the acute lymphoblastic leukemia patients compared with the healthy group.
2. Serum ferritin level can become a prognostic marker for ALL and assess the severity of the disease in pediatric patients.
3. CD19 expression level was lower in ALL children than in normal individuals, but this decrease was not significant.
4. The CD34 expression in pediatric ALL does not differ significantly from their expression in normal children.
5. There was a moderate inverse correlation between CD19 level and serum ferritin in the pediatric ALL patients, while CD34 level has a very weak inverse correlation with serum ferritin concentration in the pediatric patients.

Conflict of interest: NIL

Funding: NIL

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