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Serum ferritin level in pediatric patients with acute lymphoblastic leukemia (ALL) in the early stage of diagnosis and remission phase

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ABSTRACT

Background: Cancer cells increase iron absorption, interfere with iron storage, and reduce iron excretion. Acute lymphoblastic leukemia (ALL) condition may interfere with the iron synthesis, and the patients usually receive a blood transfusion which leads to iron buildup. Excess iron is linked to a poor prognosis and significantly becomes morbidity and mortality factors. Serum ferritin levels that can be assessed from complete blood count may become a low-cost and sensitive biomarker and prognostic marker for ALL. The aim of this research is to assess serum ferritin levels in pediatric patients with ALL in the diagnosis and remission phases.

Methods: An analytical observational cross-sectional study was conducted on pediatric patients with ALL in the pediatric ward Haji Adam Malik hospital Medan from July – October 2021. Physical examination and blood sampling for complete blood count and serum ferritin level assessment were carried out. Bivariate analysis using the Chi-square test was used to compare serum ferritin levels during early diagnosis and remission phases in ALL pediatric patients.

Results: Ferritin levels were higher in the newly diagnosed patient group with a median value of 951 µg/L (28.07-6632 µg/L) than the group in remission phase with a median value of 374.5 µg/L (29-2426 µg/L). There were no significant relationships between ferritin levels and BMI, SGOT, and SGPT in the newly diagnosed group. In contrast, the ferritin levels of the patients in the remission group were significantly correlated with SGOT and SGPT.

Conclusion: Serum ferritin level can become a prognostic marker for ALL and assess the severity of the disease in pediatric patients.

Keywords: *acute lymphoblastic leukemia, cancer, remission phase, serum ferritin level.*
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INTRODUCTION

Leukemia is a blood cell malignancy from the bone marrow characterized by the proliferation of white blood cells and the manifest presence of young cells in the peripheral blood that is most commonly observed in children and adolescents.[1,2] Acute lymphoblastic leukemia (ALL) and acute myeloblastic leukemia (AML) are the two types of leukemia.[3] Many investigations have reported that cancer cells increase iron absorption, interfere with iron storage, and reduce iron excretion. The study by Hamad *et al.* showed a significant increase in serum ferritin levels in ALL patients, which was correlated with the increase in blast cells ($p<0.0001$), LDH ($p<0.0001$), uric acid ($p<0.0001$), and white blood cells.[4]

Iron metabolism changes significantly in leukemia cases, including changes in iron absorption, storage, transportation, and excretion, as well as dysregulation of the ferroportin-hepcidin regulatory axis. The increase in iron absorption results in the overexpression of transferrin receptor 1 (TfR1), transferrin receptor 2 (TfR2), and lipocalin 2 (LCN2). At the same time, the increase in iron storage in the form of ferritin heavy chain (FTH) and ferritin light chain (FTL) has been linked to the increase in tumor cell motility, adhesion, and angiogenesis. Then ferroportin levels drop, resulting in the accumulation of iron in cells.[5] Excess iron and byproduct reactive oxygen species (ROS) disturb normal hematopoiesis activities and induce cellular-damaging mutations.[6,7] Because of their role in increasing the breakdown of DNA double-strand-breaks, ROS can promote dysregulation and transformation into malignant hematopoietic cells.[8] In addition, iron also plays an important role in the progression of leukemia because the cells require iron for the creation of the enzyme ribonuclease reductase, which is essential for DNA synthesis.[9]

Clinically, serum ferritin levels are used to monitor iron status in the body.[10] Normal serum ferritin levels range from 15-300 µg/l, with children having lower levels than adults. Ferritin levels in healthy people are normally steady. However, there is a number of disorders that may affect ferritin levels in the blood. Ferritin levels can be affected by non-hereditary factors, such as body mass index (BMI), impaired liver function, alcohol consumption, increased iron intake, iron supplementation, blood transfusion, or infections that affect serum ferritin levels.[11-14]

The research carried out by Liu *et al.*

involving patients with AML and ALL reported higher serum ferritin levels in newly diagnosed patients who did not have remission or relapse ($p<0.005$).[15] The research showed that newly diagnosed patients with AML experienced a 76.6% increase in ferritin levels, the non-relapse group experienced a 90.9% increase in ferritin levels, and the relapse group experienced a 20% increase in ferritin levels. While for patients with ALL, newly diagnosed patients experienced an 83.3% increase, the non-relapse group experienced an 84.6% increase in ferritin levels, and the relapse group experienced a 30% increase in ferritin levels.[15]

Under normal circumstances, ferritin levels are proportional to iron reserves. In certain pathological conditions, such as inflammation, malignant tumors, and liver damage conditions, ferritin levels rise in proportion to the severity of the diseases rather than in proportion to iron reserves in the body. There is a significant increase in the rate of synthesis of serum ferritin in acute leukemia cases, and the excess ferritin cannot be removed from the blood in a timely manner, resulting in an increase in serum ferritin levels in patients with acute leukemia.[15]

In children with leukemia, iron can become a prognostic factor.[16] Iron overload that develops in children with leukemia is due to receiving many blood transfusions, which is linked to a poor prognosis and significantly becomes morbidity and mortality factors. This research aims to investigate the therapeutic approach that targets iron metabolism, specifically looking at iron status levels, particularly serum ferritin, in patients with ALL in the early phase of diagnosis and at remission. This research examines serum ferritin levels during the early stage of diagnosis and at remission, as well as their correlation with IMT, SGOT, and SGPT.

METHODS

This research was an analytical observational study with a cross-sectional design to assess the difference between serum ferritin levels during early diagnosis and remission phases. The study was done in the pediatric ward at Haji Adam Malik hospital Medan for four months, from July to October 2021. The research samples were children aged 1 month – 18 years old diagnosed with Acute Lymphoblastic Leukemia (ALL) and hospitalized between July and October 2021. Exclusion criteria were ALL pediatric patients with obesity (BMI >25) and severe liver dysfunction and patients who consumed alcohol and received iron supplementation.

Acute lymphoblastic leukemia (ALL) was diagnosed and confirmed by the oncologist at Haji Adam Malik hospital. The research subjects who were in the early stage of the diagnosis group had been diagnosed and confirmed with ALL but had not undergone chemotherapy. At the same time, the patients in the remission group had been declared to have no complaints and were free of leukemia symptoms. On the bone marrow aspiration, these patients had a number of blast cells below 5% nucleated cells, above 10 g/dL hemoglobin without transfusion, and above 3,000/ml leukocyte count.

Research subjects in this study were gathered using a consecutive sampling technique. The size of the sample was determined using the sample size formula with a comparative analysis of numerical data between two unpaired groups. With a 95% confidence interval, the minimum sample size for each early diagnosis and remission phase group was 15 subjects. Thus, making the minimum sample size in this research was 30 subjects.

Patients meeting the inclusion criteria were selected as the research subjects, and those with the exclusion criteria were exempted from the study. Consent was obtained from parents or guardians who signed the consent form after receiving an explanation about the research. Basic demographic data were collected from interviews. Physical examination and blood sampling for complete blood count and serum ferritin level assessment were done on the research subjects. Ferritin level was examined from the blood sample using Roche Cobas E411. A blood sample was collected with a syringe, and it was inserted into blood collection tubes without anticoagulants. After that, the blood was stored for 20 minutes and centrifugated at 3000 rpm for 10 minutes. Blood serum ferritin was separated and analyzed using Roche Cobas E411. After approximately 20 minutes, test results were obtained and recorded.

Data analysis

Univariate and bivariate analyses were done by using the statistical software SPSS version 22. The univariate analysis determined the frequency distribution of serum ferritin levels in the research subjects. Meanwhile, the bivariate analysis compared serum ferritin levels during early diagnosis and remission phases in ALL pediatric patients using the Chi-square test.

RESULTS

Research subject's demographic characteristics

This research involved 54 ALL pediatric patients meeting the exclusion criteria and were hospitalized in the pediatric ward of Haji Adam Malik hospital Medan. There were 28 (51.9%) male and 26 (48.1%) female patients participating in the study. The average age was 9.22 years old, with the youngest and oldest ages being 2 and 17 years old, respectively. Twenty patients (37%) were in the early phase group, while 34 (63%) patients were in the remission phase. Hemoglobin results showed an average of 11.17 g/dL (SD = 2.36 g/dL), and the leucocyte average was 18.75 thousand/µL. Table 1 shows the basic demographic data of the research subjects.

Table 2 shows the difference between the demographic and laboratory characteristics based on the ALL phases. There were 11 (55%) male subjects in the early phase group, and 17 (50%) male patients were in the remission phase. For female patients, there were 9 (45%) female subjects in the early phase group, and 17 (50%) were in the remission phase. No significant difference was observed between the two groups based on gender ($p = 0.723$).

The average patient's age in the early phase of ALL was 10.5 years old. A younger average age was recorded for the remission group, such as 8.47 years old. No significant difference was observed between the two groups based on age ($p = 0.075$). Similarly, there were no significant differences observed in BMI, leukocyte levels, SGOT value, and SGPT value between the early phase and remission group, with $p = 0.151$, $p = 0.922$, $p = 0.635$,

and p = 0.667, respectively.

The mean hemoglobin level in ALL early phases was 9.16 g/dl. Meanwhile, a higher mean hemoglobin level was observed in the remission phase group, such as at 12.35 g/dL. Using T independent test, hemoglobin level was significantly different between the two groups (p >0.001).

The difference in ferritin level based on the assessment phase

Table 3 shows the difference in ferritin levels among ALL research subjects in the early diagnosis and remission phases. In the early diagnosis phase, only one subject (5%) had a normal ferritin level. While in the remission phase group, three subjects (8.8%) had normal ferritin levels. The median ferritin level in the early phase group was 951 µg/L with the lowest level of 28 µg/L dan the highest level of 6.632 µg /L. Meanwhile, the ferritin level in the remission phase was 374.5 µg/L, with the lowest and highest levels of 29 µg/L and 2.426 µg/L, respectively. There was a significant difference in the ferritin level between the two groups (p = 0.023).

Table 4 shows the relationship between serum ferritin and BMI, SGOT and SGPT. In the early phase group, no significant difference was observed between ferritin and BMI, SGOT, and SGPT (p>0.05). In the remission phase, however, significant differences were observed between ferritin and both SGOT and SGPT (p >0.05).

By using the Spearman test, a correlation coefficient (r) = 0.348 between ferritin and SGOT levels was found. This suggested a weak positive correlation between ferritin and SGOT levels where the increase in ferritin level is followed by the increase in SGOT. Similarly, a significant correlation with correlation coefficient (r) = 0.395 between ferritin and SGPT levels was found. This suggested a weak positive correlation between ferritin and SGPT level, where the increase in ferritin level is followed by the increase in SGPT.

Table 1. Research subjects' characteristics.

Characteristics	n = 54 (%)
Gender, n (%)	
Male	28 (51.9)
Female	26 (48.1)
Age, years	
Mean (SD)	9.22 (4.06)
Median (min-max)	10 (2 – 17)
ALL phase, n (%)	
Early	20 (37)
Remission	34 (63)
Laboratory test	
Hemoglobin, g/dL	
Mean (SD)	11.17 (2.36)
Median (min-max)	11.35 (4.1 – 15.4)
Leukocytes, thousand/µL	
Mean (SD)	18.75 (28.45)
Median (min-max)	7.27 (1.84 – 106.11)

Table 2. Research subjects' characteristics based on the assessment phase.

	Early phase (n = 20)	Remission phase (n = 34)	p
Characteristics			
Gender, n (%)			
Male	11 (55)	17 (50)	0.723[a]
Female	9 (45)	17 (50)	
Age, years			
Mean (SD)	10.5 (4.31)	8.47 (3.76)	0.075[b]
BMI			
Median (min-max)	15.65 (10.18 – 18.91)	16 (6 – 36)	0.151[c]
Laboratory test			
Hemoglobin, g/dL			
Mean (SD)	9.16 (2.28)	12.35 (1.44)	<0.001[b]
Median (min-max)			
Leukocytes, thousand/µL	7 (1.84 -106.11)	7.43 (3.26 – 23.41)	0.922[c]
SGOT, µ/L			
Median (min-max)	20.5 (8 – 111)	21.5 (8 – 91)	0.635[c]
SGPT, µ/L			
Median (min-max)	16.5 (10 – 59)	15.5 (6 – 146)	0.667[c]

[a]Chi Square, [b]T Independent, [c]Mann-Whitney

Table 3. The difference in ferritin level based on the assessment phase.

Characteristic	Early Phase (n = 20)	Remission Phase (n = 34)	p
Ferritin, µg/L			
Median (min-max)	951 (28.07-6632)	374.5 (29-2426)	0.023[a]

[a]Mann Whitney

DISCUSSION

Cancer cells have been demonstrated in many studies to increase iron absorption, interfere with iron storage and reduce iron excretion. The study by Hamad *et al.* showed a significant increase in serum ferritin levels in ALL patients.[4] Similar results were also discovered in this research, where the median serum ferritin level in the early diagnosis stage was 951 mcg/L, while at the remission phase, the median serum ferritin level was 374.5 mcg/L. Both values indicated hyperferritinemia condition.

The study by Liu *et al.* involving AML and ALL patients reported higher ferritin levels in newly diagnosed patients who did not have remission or relapse (p<0.05). The research showed that newly diagnosed patients with AML experienced a 76.6% increase in ferritin levels, the non-relapse

Table 4. Correlation between ferritin with BMI, SGOT, and SGPT.

Phase	Analyze	Ferritin	
		r	p*
Early phase	BMI	-0.014	0.952
	SGOT	0.128	0.591
	SGPT	-0.077	0.748
Remission phase	BMI	0.148	0.403
	SGOT	0.348	0.025
	SGPT	0.395	0.021

**Spearman*

group experienced a 90.9% increase in ferritin levels, and the relapse group experienced a 20% increase in ferritin levels. While for patients with ALL, newly diagnosed patients experienced an 83.3% increase, the non-relapse group experienced an 84.6% increase in ferritin levels, and the relapse group experienced a 30% increase in ferritin levels.[15]

This research also found that patients at the early phase of diagnosis had a higher serum ferritin level than patients at the remission stage. The median serum ferritin level at the early ALL diagnosis phase was 951 mcg/L, with the lowest value of 28 µg/L and the highest value of 6,632 µg/L. Meanwhile, patients at the remission stage had a median ferritin level of 374.5 µg/L with the lowest value of 29 µg/L and the highest value of 2,426 µg/L. A significant difference in serum ferritin levels between the early-stage diagnosis and remission stage group was observed ($p<0.05$) by using the Mann-Whitney test. Normally, serum ferritin level is proportional to iron storage in the body. Therefore, serum ferritin level is a very reliable and sensitive marker for iron deficiency diagnosis in anemia patients. However, in certain pathological conditions, such as inflammation, malignant tumors, and liver damage conditions, ferritin levels rise in proportion to the severity of the diseases rather than in proportion to iron reserves in the body. There is a significant increase in the rate of synthesis of serum ferritin in acute leukemia cases, and the excess ferritin cannot be removed from the blood in a timely manner, resulting in an increase in serum ferritin levels in patients with acute leukemia.[15]

The research carried out by Ragab *et al.* in Egypt reported that serum ferritin and hepcidin levels were significantly higher in children with ALL than in the control group. They also found that ferritin and hepcidin levels were higher prior to therapy compared to the levels at remission or during treatment.[16-18] The production of hepcidin is regulated by three factors, such as excess iron, the stimulation of interleukin-6 as an inflammatory marker, and hematopoiesis disorders. Those three factors occur in ALL cases. The link between hepcidin, anemia and a lower reticulocyte count in leukemia patients further suggests that the etiology of anemia in leukemia patients is due to inflammation and impaired erythrocyte production activity in the bone marrow.[17]

The incidence of anemia was discovered in this research, where the mean hemoglobin level in the early ALL diagnosis was 9.16 g/dL, whereas the patients in the remission group had higher hemoglobin levels, such as at 12.35 g/dL. There was a significant difference in hemoglobin levels in the two study groups ($p<0.001$) by using the T-independent test. Pattnaik *et al.* reported a similar finding with a high incidence rate of anemia (80%) in pediatric patients with ALL. Anemia is caused by hemorrhage, bone marrow infiltration, red blood cell death in the peripheral blood circulation, low red blood cell synthesis, and decreased hematopoiesis due to problems in the iron metabolism.[18] Anemia can also be induced by the loss of bone marrow function because of the progressive infiltration by the white blood cells into the bone marrow. Consequently, preventing bone marrow from producing appropriately.[19]

Another study by Hamodat *et al.* reported higher ferritin levels in newly diagnosed children patients with ALL than in patients who were already in remission (450 ± 171.7 ng/ml; 52.1± 5.6 ng/ml, P<= 0.001).[20] The increase in ferritin levels at the early stage of diagnosis was nine-fold high than at remission. There was no significant difference in serum ferritin levels between ALL patients in remission and normal children as the control group. This result shows that serum ferritin level can become a fast and accurate biomarker to diagnose ALL and predict the disease prognosis at various stages.[20] Ferritin protects cells from oxidation reactions by storing soluble and non-toxic iron. Iron is usually found in small amounts in the bone tissues, small intestine, kidneys, bone marrow, placenta, and heart, and it is particularly abundant in the liver, bone marrow, and spleen. Higher ferritin levels are found in AML and ALL patients who had not received any prior treatment.[4] This finding could be related to cellular injury, which causes greater ferritin to be released into the bloodstream. Furthermore, the increase in serum ferritin level is also affected by the increase in iron receptors generated by leukemic cell malignancy.[20] The transfer and increase in ferritin level are also affected by increasing cell damage. In pediatric patients with AML, higher levels (>400 ng/ml) are correlated with a worse 5-year-interval event-free-survival.[22]

On the order hand, in the research by Moafi *et al.* involving pediatric patients with ALL, iron levels were the same at the beginning of diagnosis between the case and control group.[23,24] In the research, however, the number of samples was small. Therefore, the role of iron in ALL development could not be concluded. Iron levels in the bone marrow, however, showed different results. The logistic regression analysis showed that low iron levels in the bone marrow had 3.6 times higher therapeutic success rate. Moreover, patients with higher iron levels in the bone marrow had a higher relapse rate.[23]

Iron can become a prognostic factor in children with leukemia.[16] Iron overload that develops in children with cancer is due to receiving many blood transfusions, which is linked to a poor prognosis and significantly becomes morbidity and mortality factors. The excess amount of iron in the body can cause damage to the tissues because of the formation of persistent free radicals, which later damage the liver, heart, and endocrine dysfunction and even cause death. A very high ferritin

level (>3,000 µg/L) was reported as one of the independent risk factors associated with death.[24] Several other studies have linked total blood count to iron excess, with >1,000 ml of packed red cells (PRC) being the cut-off value to screen iron overload due to blood transfusion.[25]

The drawback of this research was a shorter sampling duration, where the time between early diagnosis and remission phases was roughly only eight weeks. A short span of time would not change the serum ferritin level much. A larger number of samples can also provide a better description of the differences in the ferritin levels in both the diagnosis and remission stages. Nonetheless, this research showed that serum ferritin levels could become a prognostic factor and assess the severity of the disease in children with ALL.

CONCLUSION

Serum ferritin level can become a prognostic marker for ALL and assess the severity of the disease in pediatric patients.

ETHICAL CONSIDERATIONS

All research subjects were asked for parental consent after a prior explanation of the disease conditions, the effects of the disease, and the observations. This research has been approved by the Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara (No. 501/KEPUSU/2021).

CONFLICT OF INTEREST

None declared.

AUTHOR'S CONTRIBUTION

All the authors were responsible for the data gathering and analysis until the published article.

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