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Submission date: 31-Dec-2022 07:30PM (UTC+0700)
Submission ID: 1987627669
File name: oamjms-10b-2586.pdf (400.11K)
Word count: 3899
Character count: 19800

Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Jul 10; 10(B):2586-2590.
https://doi.org/10.3889/oamjms.2022.9417
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Hematology*

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Edited by: Ksenija Bogoeva-Kostovska
Citation: Ridha NR, Mustakim GA, Ganda IJ. Evaluation of Interleukin-6 Level Before Chemotherapy in Acute Lymphoblastic Leukemia L1 Standard-Risk and High-risk Patients. OpenAccessMacedJMedSci.2022Jul10;10(B):2586-2590. https://doi.org/10.3889/oamjms.2022.9417
Keywords: Interleukin-6; Acute lymphoblastic leukemia; Cytokine
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Received: 17-Mar-2022
Revised: 12-Apr-2022
Accepted: 02-May-2022

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Acute lymphoblastic leukemia (ALL) is a malignancy originating from the clonal expansion of lymphoid progenitors that have undergone neoplastic transformation at various stages of differentiation. Interleukin-6 (IL-6) is a pleiotropic inflammatory cytokine produced by various cell types, including T-cells, macrophages, and stromal cells in response to tumor necrosis factor-alpha and interleukin-1.

AIM: This study aims to evaluate serum levels of IL-6 before chemotherapy in standard-risk (SR) and high-risk (HR) ALL patients.

METHODS: The research method was a cross-sectional study conducted on ALL patients who were treated at Wahidin Sudirohusodo hospital from April 2021 to June 2021. A total of 60 ALL patients were included in the study. Serum IL-6 specimens were examined before the patient received chemotherapy.

RESULTS: The results showed that from 60 samples of ALL patients, 30 were SR and 30 were HR. Elevated levels of IL-6 before chemotherapy were found in both SR and HR ALL but were significantly higher in the HR group compared to the SR group with p value = 0.022. The cutoff point of 64.23 ng/mL for HRALL patients was obtained through ROC with a sensitivity of 63.3%, specificity of 63.3%, a positive predictive value of 63.3%, and a negative predictive value of 63.3%. Adjusted odds ratio are 2,983 with 95% confidence interval of 1.044–8.527.

CONCLUSION: IL-6 levels among HR ALL were higher than SR. Elevated levels of IL-6 were found in both SR and HR ALL.

Introduction

Leukemia is a malignancy of blood cells originating from the bone marrow that is characterized by the proliferation of white blood cells, manifested by the presence of young cells in the peripheral blood. This malignancy is the most common type of cancer in children. Acute childhood leukemia accounts for 30–40% of malignancies. The average incidence is 4–4.5 cases per year per 100,000 children under 15 years of age. The composition of acute leukemia in developing countries consists of 83% acute lymphoblastic leukemia (ALL) and 17% acute myeloblastic leukemia. The peak incidence at the age of 2–5 years, specifically for white children with ALL, is due to a large number of cases of pre-B-ALL in this age range [1].

Interleukin-6 (IL-6) is a pleiotropic inflammatory cytokine. It was previously discovered as a B-cell growth factor and is produced by various cell types, including T-cells, macrophages, and stromal cells, in response to tumor necrosis factor-alpha and interleukin-1 [2]. IL-6 also has a role in malignancy, it is progression and severity. Several previous studies have shown that leukemia blast cells produce various cytokines, one of which is IL-6. IL-6 is a cytokine that has an important role in maintaining cancer stem cells in the microenvironment of leukemia cells. These various mechanisms are the basis of IL-6 influence on the severity of ALL [3], [4], [5].

In a previous study, it was found that IL-6 activity was significantly increased in patients with ALL. The study showed that IL-6 supports the proliferation of leukemic cells, thus supporting the notion that high levels of IL-6 in patients with acute leukemia are related to the pathogenesis of the disease. Several studies have also shown that IL-6 levels are associated with survival rates, and low levels of IL-6 indicate a better prognosis in patients. Several studies have shown that elevated levels of IL-6 in hematological malignancies are associated with a poorer prognosis. Therefore, this cytokine can be considered as a prognostic factor in ALL and as a therapeutic target. Based on this, this research needs to be carried out so that in clinical applications, it can later be used as a prognostic indicator to distinguish the severity of disease in standard-risk (SR) and high-risk (HR) ALL [2]. This study aimed to evaluate serum levels of IL-6 before chemotherapy in pediatric patients with SR and HR ALL.

Methods

Design and variables

This research is an observational study with a cross-sectional approach that was conducted from April 2021 to July 2021 at Dr. RSUP, Wahidin Sudirohusodo Makassar. The sample in this study consisted of 60 patients, consisting of 30 SR ALL patients and 30 HR ALL patients, who had not undergone chemotherapy aged 1 month to 18 years. HR ALL was specified by age over 10 years, hyperleukosis, mediastinal mass, Philadelphia chromosome, T- or B-cells without CD-10, and central nervous system infection. In addition to these criteria, it is classified as SR ALL. The exclusion criteria were all patients who suffered from other malignancies, had severe liver disorders, had undergone major surgical procedures, suffered from burn trauma, or were obese. The research sample testing was carried out at the research laboratory unit of Hasanuddin University Hospital using the enzyme-linked immunosorbent assay (ELISA) method.

Ethical clearance

This study was declared to meet the ethical requirements by the Ethics Committee for Biomedical Research in Humans, Faculty of Medicine, Hasanuddin University.

Method of collecting data

The sample, in the form of venous blood from the patient, was centrifuged to collect the serum. Then, they are placed in a tube without anticoagulant and stored at a stable temperature of 2–8°C for 2 days or at a temperature of −20°C until the desired number of samples is reached. The kit uses the ELISA sandwich technique, where the plate has been coated with an IL-6 antibody. IL-6 in the sample will bind to the antibody in the well.

Data analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 26.0. The Chi-square test was used to test relationships between categorical variables. An independent t-test or Mann–Whitney U-test was performed to compare mean values between the two groups. A normality test was performed using Kolmogoro–Smirnov. Fisher Exact test was performed to calculate the prevalence odds ratio with 95% CI and to determine the probability of HR ALL based on IL-6 levels. p-value of <0.05 was considered statistically significant.

Results

During the study period, there were 62 patients aged 1 month to before the age of 18 years who were diagnosed with L1 ALL (SR and HR). Of the 62 patients diagnosed with ALL, 60 patients met the inclusion criteria, consisting of 30 SR ALL patients and 30 HR ALL patients. There were two patients who were excluded due to obesity.

The characteristics of the research sample from 60 samples that participated in this study are shown in Table 1. Based on gender, patients with L1 ALL were 45 men (75%) and 15 women (25%). Based on age, there were no patients under 1 year of age, 46 people (76.7%) aged 1–10 years old, and 14 people over 10 years old (23.3%). Based on nutritional status, patients with L1 ALL who had good nutritional status were 31 (51.7%), undernourished 12 people (20%), and poor nutrition was 17 people (28.3%). Moreover, based on the initial leukocyte count, patients with ALL L1 with an initial leukocyte count <50,000 were 47 people (78.3%) and 50,000 were 13 people (21.7%) Table 1.

Table 1: Characteristic of the study subjects

Characteristics	Acute lymphoblastic leukemia
	n = 60 (%)
Sex	
Male	45 (75.0)
Female	15 (25.0)
Age (Year)	
1–10	46 (76.7)
> 10	14 (23.3)
Nutritional status	
Severely wasted	17 (28.3)
Wasted	12 (20.0)
Normal	31 (51.7)
Initial leucocytes count (/ul)	
< 50000	47 (78.3)
≥ 50000	13 (21.7)

A comparison of IL-6 levels in SR and HR ALL patients showed that the median IL-6 level of SR ALL patients was 60.09 ng/L and the HR was 88.4 ng/L. The results of the Mann–Whitney U-test showed a significant difference between the IL-6 levels of SR and HR lymphoblastic leukemia, with p value = 0.022 ($p < 0.05$), as shown in Table 2.

Table 2: Comparison of interleukin-6 levels in standard-risk and high-risk acute lymphoblastic leukemia

IL-6 levels (ng/L)	Acute lymphoblastic leukemia	
	High-risk (n = 30)	Standard-risk (n = 30)
Median	88.42	60.09
Minimum – maximum	19.27–551.48	19.17–206.10

Uji Mann–Whitney U-test, p value = 0,022 (p < 0.05).

Based on the values of sensitivity and specificity, the most optimal cutoff point for age is in Data No. 31, which has a sensitivity of 63.3% and a specificity of 63.3% with an area under curve of 0.672 so that the interleukin level-6 of 64.23 ng/ml was chosen as the cutoff value for interleukin level-6 between the SR and HR ALL groups, as shown in Figure 1.

The sensitivity value is 63.3%, the specificity is 63.3%, the positive predictive value is 63.3%, the negative predictive value is 63.3%, and the odds ratio

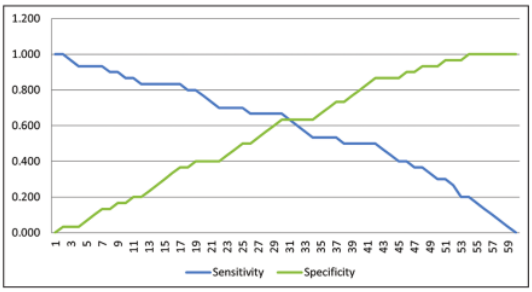

Figure 1: Interleukin-6 cutoff point between standard-risk lymphoblastic leukemia group and high-risk

(OR) is 2,983 with a 95% confidence interval (CI) (1.044–8.527). The IL-6 level of 64.23 ng/mL statistically has a significant relationship with the severity of ALL ($p < 0.05$), as shown in Table 3.

Table 3: Relationship of IL-6 levels with severity of acute lymphoblastic leukemia using cut off point 64.23 ng/mL

IL-6 (ng/mL)	Acute lymphoblastic leukemia		Total
	High-risk	Standard-risk	
≥ 64.23	19 (63.3%)	11 (36.7%)	30 (50%)
< 64.23	11 (36.7%)	19 (63.3%)	30 (50%)
Total	30 (100%)	30 (100%)	60 (100%)
*Chi Square test X^2 df = 1		p = 0.039, p < 0.05	
OR 2.983 IK95% (1.044–8.527)			

Discussion

This study found 76.7% of the sample population aged 1–10 years and 23.3% aged >10 years. This is a study conducted in the United States that examined the characteristics of childhood acute leukemia for two decades from 1992 to 2013, which found that the peak incidence of ALL ranged from 2 to 3 years of age for all racial/ethnic groups and then decreased when aged over 8 years [6]. The epidemiological study of leukemia conducted by Miranda-Filho in 2018 in 184 countries found the peak incidence of acute leukemia in children aged 0–4 years [7]. The peak incidence was in the age range of 1–4 years in the studies conducted by Woo *et al*. in 2014 and O'Brien *et al*. in 2015. They were associated with high hyperploidy (chromosomes 51–65), which is one of the cytogenetic abnormalities in B-cell leukemia that was most detected at that age. However, although this hyperploidy is associated with a peak incidence of leukemia, it is also associated with a better prognosis [8], [9].

In this study, the number of samples that were male was 45 (75%) and female was 15 (25%). This is by following the study by Kakaje *et al*., who found that the incidence of ALL was higher in boys compared to girls with p value = 0.0019 [10]. Likewise, research conducted by O'Brien *et al*. showed that the incidence of ALL was higher in boys and is often associated with T-cell ALL [9]. Several previous studies have been conducted to find out why the male sex is more susceptible to malignancy in children and this is associated with sex hormones, genetic differences, differences in susceptibility to environmental exposures (infections, radiation, etc.), epigenetics, and in recent studies, many have investigated microchimerism (a condition in which there is one cell with genetic characteristics other than the majority of body cells in an individual), which is more common in boys, and autophagy (the ability to regenerate at the cellular level in the body), which is lower in the male sex. Susceptibility to malignancy in boys is also associated with the lower immune surveillance in boys. In general, girls have better non-specific and adaptive immune responses than boys. The influence of sex hormones also plays a role. Estrogen has been studied to increase immune response, decrease IL-6 production, and increase activation of antigen presenting cells, while androgens can cause a decreased immune response, decreased antibody production, and increased production of IL-6 and interleukin 10, which are also related to the mechanism of carcinogenesis in leukemia [11].

Research conducted by Medina-Sanson *et al*. (2015), there is a linear relationship between baseline leukocyte levels and the outcome in children with ALL. The threshold for prognostication is 50,000/ul and patients with an initial leukocyte count above 50,000/ul have a poorer prognosis. The t(9;22)(q34;q11.2)/BCR-ABL1 translocation, known as the Philadelphia chromosome, occurs in 1–3% of ALL children with older age and high baseline leukocyte levels. This translocation leads to the production of chimeric proteins with tyrosine kinase activity that causes activation of various cell-signaling pathways that contribute to the conversion of hematopoietic cells to mixed-lineage leukemia [12].

In this study, the median serum IL-6 level in SR L1 ALL patients was 60.09 ng/L, and the median serum IL-6 level in HR L1 ALL patients was 35.42 ng/L. Statistical analysis showed that there was a significant difference between serum levels of IL-6 in SR and HR ALL with p value = 0.022 ($p < 0.05$). This is in line with the study conducted by Pérez-Figueroa *et al*, namely, an increase in IL-6 levels in pediatric patients with ALL compared to the control group (non-oncological patients). In this study, the levels of IL-6 in the control population were 3.20 pg/ml (range 0.00–87.85 pg/ml) and 8.79 in the ALL population (range 0.00–615 pg/ml). However, to the researchers' knowledge, there have been no studies comparing IL-6 levels between SR and HR groups [4].

In determining the cutoff point, IL-6 levels for the incidence of HR ALL, namely, 64.23 ng/ml, had a sensitivity of 63.3%, specificity of 63.3%, positive predictive value of 63.3%, and negative predictive value of 63.3% with an area under curve of 0.672 and an adjusted OR (AOR) of 2.983 with a 95% CI of 1.044–8.527. This shows that if children have IL-6 levels of 64.23 ng/ml ng/mL, they have a HR of developing ALL of 2983 with an accuracy value of 63.3%. This study

also obtained a positive predictive value of 63.3%, which means that in children with HR lymphoblastic leukemia, the possibility of IL-6 levels of 64.23 ng/mL is 63.3%. While the negative predictive value is 63.3%, which means that in children with lymphoblastic leukemia, the SR is that the IL-6 level may be <64.23 ng/mL by 63.3%.

The results of this study also found an increase in IL-6 levels, which were quite high in both the HR and SR groups, proving the role of IL-6 in the pathogenesis of ALL as in the study by Luo *et al*., Zhao *et al*., and Farsani *et al*. [13], [14], [2] Therefore, it is necessary to consider the administration of anti-IL-6 as in the study [15]. In addition, the increase in IL-6 levels in both groups was also caused by an infection in both groups, as in the research conducted by Xu XJ [16]. This is also in accordance with a study conducted by Pérez-Figueroa *et al*. in 2016, which saw an increase in IL-6 levels in patients with ALL. The patients studied often presented with fever associated with sepsis and elicited an inflammatory response that led to elevated levels of IL-6 [4].

This study also found that in the SR group, the mean IL-6 level was 60.09, with a range value of 19.17–206.10 ng/L. The high level of increase in the SR group can be caused by several factors, such as the occurrence of infection or sepsis in the sampled patients. Research conducted by Ramanathan *et al*. in 2020 on IL-6 showed that IL-6 levels were affected by infection and could also be influenced by physical activity, changes in circadian rhythm, pharmacotherapy, and immunometabolic comorbidities such as obesity. In this study, the obesity factor was excluded from the sample [17].

The following is the study's strengths: (1) It was conducted at Wahidin Sudirohusodo hospital, which is the largest referral hospital in Eastern Indonesia. This means that patients with ALL treated at the Wahidin Sudirohusodo hospital come from most of eastern Indonesia, so it can be used as a reference to get a picture of IL-6 levels in patients with ALL in eastern Indonesia. (2) Patients who were sampled in this study were newly diagnosed patients and had not received chemotherapy, so they were able to provide an overview of IL-6 levels in accordance with the progression of cancer cells. The disadvantages of this study are that it is still not possible to rule out factors that can affect the results (confounding factors), namely, the presence of sepsis or infection, because most leukemia patients are susceptible to infection. Another limitation is that it has not been able to provide specific data on factors from the diagnostic criteria for HR groups that have the greatest role in increasing IL-6 levels.

Conclusion

The investigators concluded that IL-6 levels were elevated in both HR ALL and SR ALL. IL-6 levels among HR ALL were higher than in SR ALL. At the cutoff point, IL-6 levels of 64.23 ng/ml were associated with the incidence of HR ALL with a sensitivity value of 63.3%, specificity of 63.3%, and an AOR of 2983 times, which means that IL-6 levels of 64.23 have a risk of 2,983 times the occurrence of HR ALL with a 95% CI of 1,044–8,527. Researchers suggest that in children with SR and HR ALL, IL-6 levels should be considered. The examination of IL-6 levels in children with ALL was important to determinate risk stratification and disease progression. It is necessary to do further research using a prospective cohort design using the sample of this study to see levels of IL-6 after chemotherapy.

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