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Original Research

Differences in Vitamin D Levels at Diagnosis and after Induction Phase Chemotherapy in Children with Acute Lymphoblastic Leukemia in Tertiary Hospital in West Java Indonesia

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Objective: We examined differences of vitamin D levels at initial diagnosis and after induction phase chemotherapy in children with Acute Lymphoblastic Leukemia (ALL).
Methods: A cross-sectional study was conducted on newly diagnosed children with ALL from October 2021 until October 2022 at Dr. Hasan Sadikin Hospital−Bandung, West Java, Indonesia. Vitamin D levels were measured twice using blood samples: at initial diagnosis and after the remission induction phase of chemotherapy. A paired t-test was applied and the value of $p<0.05$ is considered as statistically significant.
Result: There were 53 subjects that fulfilled research criteria. Thirty−six subjects met the inclusion criteria while 17 were excluded. Majority of ALL patients were male (52.8%) and aged 1−10 years (83.3%). Mean vitamin D level of ALL children at initial diagnosis was 16.68±9,56 ng/mL. After the induction phase of chemotherapy, mean vitamin D level was 11.84±7,8 ng/mL. Paired t-test was performed to obtain p value = 0.000.
Conclusion: The prevalence of hypovitaminosis D in ALL children is 88.8%. Vitamin D levels after chemotherapy are lower than at initial diagnosis.

Introduction

Leukemia is hematology malignancy that commonly found in children, approximately 30% of all cancer cases in children. There are three main subtypes of leukemia, Acute Lymphoblastic Leukemia (ALL), Acute Myeloblastic Leukemia (AML) and Chronic Myeloblastic Leukemia (CML). Acute lymphoblastic leukemia is the most common subtype, contributing up to 80% of leukemia cases [1].

The five-year survival rate for ALL patients in developing countries is 80-90% and two-thirds of patients can reach adolescence. Factors that affect survival rates include limited resources, infections, delays in diagnosis and deficiencies of macronutrients and micronutrients. Among micro-nutrients, anti-oxidants (vitamins A, C, and E) have been extensively studied in ALL patients, and the rate of micro-nutrient deficiency has increased due to the side effects of chemotherapy.

Vitamin D deficiency is a world health problem, and children with cancer have a higher risk than healthy children [2, 3]. Vitamin D deficiency is associated with an increased incidence of several

types of cancer such as leukemia. The majority of pediatric patients with acute leukemia had low vitamin D levels, which were further reduced after induction-remission in patients who did not receive vitamin D replacement [4]. Kalsidiol levels ≥20 ng/mL at diagnosis and during cancer therapy brings out a better prognosis [5, 6].

Management patients with ALL is chemotherapy. The first stage of chemotherapy is remission induction, which aims to reduce tumor burden by clearing as many leukemic cells as possible from the bone marrow. Typically, induction regimens are based on a Vincristine, corticosteroids (e.g., prednisone, dexamethasone), and L-asparaginase with or without anthracyclines form the backbone (eg, daunorubicin, doxorubicin) [7].

However, serum vitamin D levels in acute leukemias such as ALL have received less attention. Hasanein H. Ghali et al (2020) [4] studied about 66 childrens who newly diagnosed acute leukemia and 50 childrens as control group. Serum vitamin D levels were below normal in children with acute leukemia; at the time of diagnosis, the mean serum level was 13 ng/dl, while the control group had 21 ng/dl. There was a statistically significant difference between the patient and control groups (p-value 0.001) [4]. Arhsi Naz at al (2012) studied the majority of patients with acute leukemia had vitamin D insufficiency, and vitamin D levels were further reduced after remission induction when compared to the untreated group, a difference that was statistically significant when compared to each group [8].

Previous study in Padang Indonesia showed the average vitamin D level in patients with acute leukemia was 24.017.21 ng/ml and vitamin D status was 50.9% deficient [9]. The studied about effect chemotherapy in ALL patients were limited in Indonesia and this research aims to analyze the differences in vitamin D levels in children with ALL before and after chemotherapy.

Materials and Methods

We performed a cross−sectional study of children newly diagnosed with ALL undergoing induction phase chemotherapy from October 2021 to October 2022 at Dr. Hasan Sadikin Hospital, Bandung. The inclusion criteria were patients aged ≤18 years who had just been diagnosed with ALL based on the results of Bone Marrow Puncture or immunophenotyping. Parents gave written consent for participating in the research (filling in informed consent). Exclusion criteria were ALL patients who consumed vitamin D supplementation and did not complete the induction phase of chemotherapy.

Patients newly diagnosed with ALL and fulfilling the inclusion criteria were included as research samples. Each parent/guardian of the subject diagnosed with ALL was given a detailed explanation of the research before signing the informed consent form. Subjects' identities were recorded in the case record form, anamnesis was carried out, and medical record data were recorded. The data includes name, age, gender, type of leukemia, address, and telephone number. Blood is taken for the first vitamin D level check before starting chemotherapy and stored in the laboratory. After completing the induction phase of chemotherapy (after BMP evaluation), a second sample of vitamin D levels will be taken. An examination of vitamin D levels was carried out after all samples were collected. Examination of 25(OH)D levels was carried out using Competitive Enzyme-linked immunosorbent assay (ELISA). Descriptive analysis was performed on demographic data, type of ALL, and vitamin D levels. Statistical analysis was performed to compare the differences in vitamin D levels at diagnosis and after induction phase chemotherapy. Numerical data that are normally distributed will be analyzed using t-test analysis, while the Wilcoxon test will be applied for data that is not normally distributed to compare before and after chemotherapy. The significancy of the results was determined based on the p-value <0.05. This study has obtained ethical approval from the Ethics Committee of Hasan Sadikin Hospital Bandung, No. LB. 02.01/X.6.5/252/2021.

Results

The Comparative research on vitamin D levels at diagnosis and after induction phase chemotherapy was carried out in newly diagnosed ALL children. In this research, 53 samples met the research criteria. Of the 53 samples, 36 met the inclusion criteria, and 17 were excluded because seven samples dropped out and ten died. Seven samples dropped out due to the difficulty of access to the hospital and financial problems. Ten samples died due to; intracranial bleeding in 2 patients, 4 with septic shock, and 4 due to hospital-acquired pneumonia. The data collected included demographic data; age, gender, clinical signs and symptoms, hemoglobin, leukocyte, platelet,and vitamin D levels, which were examined two times, at the time of diagnosis and after the induction phase of chemotherapy. The characteristics of the subjects in this study included gender, age, clinical signs and symptoms, leukocyte count, hemoglobin level, platelet count, and ALL types, which can be seen in Table 1.

Characteristics	N (%)
1. Sex	
Male	19 (52,8)
Female	17 (47,2)
2. Age	
≤ 10 years	30 (83,3)
> 10 years −18 years	6 (16,7)
3. Sign and Symptoms	
Pale	34 (94,4)
Fever	31 (86,1)
Bleeding	16 (44,4)
Bone pain	11 (30,6)
Lymphadenopathy	25 (69,4)
Splenomegaly	23 (63,9)
Hepatomegaly	26 (72,2)
4. Leukocyte (uL)	
<10.000	15 (41,7)
10.000−49.000	13 (36,1)
>50.000	8 (22,2)
5. Hemoglobin (g/dL)	
<7,0	10 (27,8)
7,0−11,0	22 (61,1)
>11,0	4 (11,1)
6. Thrombocyte (uL)	
<20.000	11 (30,6)
20.000−99.000	19 (52,8)
>100.000	6 (16,7)
7. ALL	
High Risk	18 (50)
Standard Risk	18 (50)

Table 1. Demographic Data and Clinical Manifestations (n=36).

Table 1 shows that most ALL patients were male (52.8%) and aged 1−10 years (83.3%). The most frequent clinical signs and symptoms were pallor (94.4%), fever (86.1%), hepatomegaly (72.2%), lymphadenopathy (69.4%), and splenomegaly (63.9%) consecutively. Laboratory examination results at the time of diagnosis showed that the majority of patients had leukocyte levels <10,000/uL (41.7%), hemoglobin levels 7−11 g/dL (61.1%), and platelet levels 20,000−99,000/uL (52.8%). Bone marrow puncture results showed the same high-risk ALL and standard risk (50%).

Table 2 shows that the average vitamin D level in ALL at diagnosis was 16.68±9.56 ng/mL and after

induction chemotherapy was 11.84±7.18 ng/mL.

Levels of Vitamin D 25(OH)D at diagnosis	n (%)	Mean	SD	p
At diagnosis				
Standard Risk ALL	18 (50)	19,97	10,25	
High Risk ALL	18 (50)	13,39	8,78	
ALL	36 (100)	16,68	9,56	
After induction chemotherapy				0,000*
Vitamin D levels after chemotherapy	n (%)	Mean	SD	
Standard Risk ALL	18 (50)	14,55	8,22	
High Risk ALL	18 (50)	9,14	4,43	
ALL	36 (100)	11,84	7,18	

Table 2. Level of Vitamin D 25(OH)D at Diagnosis (n=36) after Induction Phase Chemotherapy (n=36).

*paired t test

The hypovitaminosis D status of standard-risk and high-risk ALL patients at diagnosis can be seen in Table 3 (a-e).

			Statistic	Std. Error
Vitamin D level after induction chemotherapy	Mean		11.844	1.1773
	95% Confidence Interval for Mean	Lower Bound	9.454	
		Upper Bound	14.234	
	5% Trimmed Mean		11.341	
	Median		11	
	Variance		49.897	
	Std. Deviation		7.0638	
	Minimum		2	
	Maximum		38.4	
	Range		36.4	
	Interquartile Range		9.7	
	Skewness		1.481	0.393
	Kurtosis		4.334	0.768
Vitamin D level at diagnosis	Mean		16.681	1.6642
	95% Confidence Interval for Mean	Lower Bound	13.302	
		Upper Bound	20.059	
	5% Trimmed Mean		16.014	
	Median		14.7	
	Variance		99.7	
	Std. Deviation		9.985	
	Minimum		3.5	
	Maximum		48.7	
	Range		45.2	
	Interquartile Range		14.1	
	Skewness		1.067	0.393
	Kurtosis		1.527	0.768

Table 3a. Descriptives.

Tests of Normality						
Vitamin D Level		Kolmogorov-Smirnov[a]			Shapiro-Wilk	
	Statistic	df	Sig.	Statistic	df	Sig.
After chemotherapy	0.124	36	0.177	0.888	36	0.002
At diagnosis	0.118	36	.200[*]	0.928	36	0.021

Table 3b. Tests of Normality.

[*]. This is a lower bound of the true significance. [a]. Lilliefors Significance Correction

Paired Samples Statistics	Vitamin D Level	Mean	N	Std. Deviation	Std. Error Mean
Pair 1	At diagnosis	16.681	36	9.985	1.6642
	After chemotherapy	11.844	36	7.0638	1.1773

Table 3c. Paired Samples Statistics.

Vitamin D Level		N	Correlation	Sig.
Pair 1	At diagnosis and after induction chemotherapy	36	0.696	0

Table 3d. Paired Samples Correlations.

VitaminD Level				Paired Differences			t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	At diagnosis and after induction chemotherapy	4.8361	7.172	1.1953	2.4095	7.2628	4.046	35	0

Table 3e. Paired Samples Test.

The prevalence of vitamin D hypovitaminosis in this study was 88.8%. The incidence of hypovitaminosis D after induction phase chemotherapy is higher in high-risk ALL (100%) than in standard risk (94.4%). Tabel 3 (a-e) showed the average vitamin D level at diagnosis was 16.68±9,56 ng/ml and after induction phase chemotherapy was 11.84±7,18 ng/ml. Paired t-test was performed to obtain p value = 0.000.

Discussion

The research showed that LLA was more common in boys (52.8%). Previous research at Hasan Sadikin Hospital in Bandung in 2016 obtained the same results, namely, the majority of ALL occurred in boys, as did other studies [10-12]. A systematic review and meta-analysis conducted in Indonesia showed that ALL was more common in boys, 2.45 per 100,000 children, than in girls, 2.05 per 100,000 children [13]. Most leukemia cases occur in boy of all ages, the cause of which is still not clearly explained. A study by Jackson N et al (2009) [14] in Malaysia showed that most leukemia occurs in boys, presumably related to the type of blood group and the ABO gene on chromosome 9, which modifies the occurrence of leukemia. Williams L et al (2018) researching gender and the incidence of cancer in children, differences in genomic characteristics on the X chromosome between males and females during prenatal development and childhood determine the biological mechanisms underlying sex differences and the risk of childhood cancer [15].

The majority age at diagnosis was ≤10 years (83.3%). This research divides age into two groups. The basis for grouping is based on age stratification on the distribution of ALL types, namely standard risk or high risk. Research by Ameer K et al. found that ALL most often occurs at 5−9 years old [12].

The most frequent clinical manifestations were pallor (94.4%), fever (86.1%), hepatomegaly (72.2%),

lymphadenopathy (69.4%), splenomegaly (63.9%),bleeding (44 .4%) and bone pain (30.6%). Research conducted at Hasan Sadikin Hospital showed that the clinical manifestations that often appeared were paleness, hepatomegaly, and fever [10]. A systematic review and meta-analysis study by Clarke at al (2016) showed that the five most common symptoms in >50% of ALL children were hepatomegaly, splenomegaly, pallor, fever, and bruising [16] Meanwhile, a study in Saudi Arabia showed that the most common symptoms in ALL children were fever, fatigue, bone pain, paleness, weight loss, and decreased consciousness [17].

Laboratory results showed that when the patient was diagnosed with leukemia, most patients (41.7%) had leukocyte levels <10,000/uL. Hemoglobin level was 7−11 g/dL respectively 61.1%. Most patients had a platelet level of 20,000−99,000/uL at 52.8%. Previous research at Hasan Sadikin Hospital found that severe anemia with hemoglobin levels <7 g/dL occurred in 44.8% of cases, leukocytosis occurred in 46.9% of cases, and severe thrombocytopenia occurred in 55% of cases [10] Other studies showed that at the time of diagnosis, the median leukocytes were 7120/uL (450−600,000/uL), the median hemoglobin was 7.5 g/dL (2,4−15.3 d/dL), the median platelets were 47,400/uL (4,000−544,000 /uL). Leukocytosis occurred in 36.6% of cases, leukopenia occurred in 36.1% of cases, and anemia was found in 82.9% of cases [18].

The average vitamin D level of ALL patients at diagnosis was 16.68±9,56 ng/mL and after the induction phase of chemotherapy was 11.84±7,18 ng/ mL. The incidence of hypovitaminosis D in this study was 88.8%, and there was an increase in the number of cases of hypovitaminosis D in both standard-risk and high-risk ALL after induction phase chemotherapy. A study by Bhattacharya et al (2020) concluded that the prevalence of vitamin D deficiency in pediatric patients with ALL in India was 84.95%, and vitamin D deficiency was associated with outcomes in ALL [19].

Research by Hassanein G et al (2020) stated that vitamin D levels in pediatric acute leukemia patients were below normal, an average of 13 ng/mL, and in the control group was 21 ng/mL. If supplementation is not given, vitamin D levels will decrease after the induction phase of chemotherapy [4]. Research in West Sumatra, Indonesia [9] showed that the average vitamin D level in acute leukemia patients was 24.01 ± 7.91 ng/ml. Vitamin D status was at the level of insufficiency in 50.9% of acute leukemia patients [9]. Several risk factors contribute to Vitamin D deficiency in cancer. Cancer children are more susceptible to a lack of ultraviolet rays than healthy children. Nutritional problems can add to an existing deficiency status. Decreased vitamin D levels may be a cofactor in chemotherapy-induced mucocutaneous toxicity, and changes in the sense of taste (dysgeusia) and vitamin D supplementation may improve the condition. Other factors that

affect vitamin D levels are genetic and iatrogenic [20].

Vitamin D has anti-cancer effects through cellular mechanisms, namely suppressing cell proliferation, increasing apoptosis, reducing the incidence of metastasis and invasion, reducing angiogenesis, suppressing inflammatory processes, and enhancing the immune response [20]. Decreased levels of vitamin D in children with cancer are caused by the effects of the disease or the therapy given, one of which is chemotherapy [21]. Vitamin D receptors essentially regulate cytochrome P4503A4 (CYP3A4), cytochrome P4503A5 (CYP3A5), and p-glycoprotein (MDR1), which are involved in the metabolism of vincristine, prednisone, dexamethasone, etoposide, and daunorubicin. This chemotherapy drug is given to ALL patients, and the effects of chemotherapy can cause a decrease in RVD [22]. A systematic review of vitamin D supplementation in children with cancer recommends a standardized diet high in vitamin D and calcium and regular monitoring of 25(OH)D levels. Vitamin D and calcium supplementation are recommended in children with low vitamin D levels to maintain vitamin D levels >20 ng/mL [23] Several limitations of our study deserve comments. We did not assess the nutritional status and there was no control group. The advantage of this research is prospective research so that the data needed in this research can be obtained.

In conclusion, the prevalence of hypovitaminosis D in ALL patients is 88.8%. There are differences in vitamin D levels in leukemia patients at the time of diagnosis and after the induction phase of chemotherapy. The average vitamin D level of children with ALL at the diagnosis was 16.68 ±9.56 ng/mL which is higher than the vitamin D level after the induction phase of chemotherapy (11.84 ±7,18 ng/mL).

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Approval

It is part of an approved student thesis.

Conflict of Interest

None declared.

Ethical Declaration

Hereby, Wan Rita Mardhiya, Nur Suryawan, Budi Setiabudiawan consciously assure that for the manuscript Differences in Vitamin D Levels at Diagnosis and After Induction Phase Chemotherapy in Children with Acute Lymphoblastic Leukemia in Tertiary Hospital in West Java Indonesia the following is fulfilled:

1) This material is the authors' own original work,which has not been previously published elsewhere.

2) The paper is not currently being considered for publication elsewhere.

3) The paper reflects the authors' own research and analysis in a truthful and complete manner.

4) The paper properly credits the meaningful contributions of co-authors and co-researchers.

5) The results are appropriately placed in the context of prior and existing research.

6) All sources used are properly disclosed (correct citation). Literally copying of text must be indicated as such by using quotation marks and giving proper reference.

7) All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.

The violation of the Ethical Statement rules may result in severe consequences.

This study has obtained ethical approval from the Ethics Committee of Hasan Sadikin Hospital Bandung, No. LB. 02.01/X.6.5/252/2021.

Authors Contribution

Wan Rita Mardhiya, Nur Suryawan and Budi Setiabudiawan designed and reviewed the results, develop research method and data analysis, wrote and revised the manuscript. All authors read and approved the final version of the manuscript.

Data Availability

Study Registration: This study has obtained ethical approval from the Ethics Committee of Hasan Sadikin Hospital Bandung, No. LB. 02.01/X.6.5/252/2021.

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