RESEARCH ARTICLE

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Serum Vitamin D Levels and Vitamin D Receptor Concentrations in Children with Acute Lymphoblastic Leukemia: A Cross-Sectional Study

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Abstract

Introduction: Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer, characterized by the proliferation of immature lymphoid cells. Vitamin D and its receptor (VDR) play a critical role in immune regulation and cancer progression. This study investigated serum vitamin D levels and VDR concentrations in children with ALL and their relationship with clinical risk groups. **Methods:** This cross-sectional study involved 90 children categorized into standard risk (SR), high risk (HR), and control groups at Dr. Wahidin Sudirohusodo Hospital in Makassar, Indonesia. Serum vitamin D levels and soluble VDR concentrations were measured using ELISA. Vitamin D status was classified as deficient (<20ng/mL), insufficient (20–30ng/mL), or sufficient (>30ng/mL). Statistical analysis compared the groups and examined associations with SPPS version 26. **Results:** Vitamin D deficiency was prevalent in 82.2% of ALL patients. The SR and HR groups showed significantly lower levels than controls (P<0.001). Median vitamin D levels were 13.29ng/mL (SR), 13.94ng/mL (HR), and 19.61 ng/mL (control). Median VDR concentrations were highest in the SR group (0.600ng/mL), though differences across groups were not statistically significant (P=0.163). A positive correlation between serum vitamin D levels and VDR concentrations was identified (P=0.001, r=0.342). **Conclusion:** Vitamin D deficiency is highly prevalent in children with ALL, highlighting the need for regular vitamin D screening and supplementation. Further research is necessary to explore the therapeutic potential of vitamin D and VDR in leukemia treatment.

Keywords: Acute lymphoblastic leukemia- vitamin D- receptor vitamin D, children

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Introduction

The most common pediatric malignancy is acute lymphoblastic leukemia (ALL), [1–3] Characterized by uncontrolled growth of immature lymphoid cells in bone marrow and peripheral blood [4,5]. In United States, incidence of ALL is 3.5 cases per 100,000 children. Similarly, in Indonesia, ALL is the most prevalent pediatric cancer, [6] the incidence rate is between 2.5 to 4.0 occurrences per 100,000 children and an estimated 2,000 to 3,200 new cases each year [6, 7]. Despite advancements in treatment protocols that have improved survival rates, various factors continue to influence treatment outcomes and long-term prognosis [8]. Among these, the role of vitamin D and its receptor in immune modulation and cancer progression has attracted growing attention [9].

Vitamin D is a fat-soluble vitamin. It is essential for bone health, calcium balance, and regulation of the immune system [10–12]. The active form of vitamin D, calcitriol, has been shown to exert its biological effects by binding to the vitamin D receptor (VDR), a nuclear receptor found in various tissues, including those of the immune system [13–15]. In addition to its conventional functions, vitamin D has been demonstrated to play a role in pivotal processes involved in cancer biology, such as cellular proliferation, differentiation, apoptosis, and immune regulation. A mounting body of evidence suggests a potential association between vitamin D deficiency and the development or progression of hematological malignancies, including ALL [16, 17]. Children with ALL are particularly susceptible to vitamin D deficiency due to factors such as limited sun exposure, poor nutrition, and the metabolic effects of chemotherapy [18]. Additionally, alterations in VDR expression may impact disease progression and treatment outcomes by modulating immune signalling and leukemic cell survival [17].

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This cross-sectional study aims to assess serum vitamin D levels and VDR concentrations in children with ALL. By investigating relationship between vitamin D status, VDR concentrations, and clinical parameters, the study seeks to clarify the potential role of vitamin D in the pathophysiology of ALL and its implications for therapeutic strategies. Understanding these interactions could pave the way for novel interventions, such as vitamin D supplementation, to improve treatment outcomes and enhance overall well-being in this vulnerable population.

Materials and Methods

This cross-sectional study explores correlation between serum vitamin D levels, VDR concentrations, and clinical parameters among pediatric patients diagnosed with ALL at the Haematology and Oncology Unit of DR Wahidin Sudirohusodo Hospital, Makassar, Indonesia. The inclusion criteria encompassed newly diagnosed ALL patients aged 1 to 18 years, irrespective of sex. Patients who had previously undergone chemotherapy or received vitamin D supplementation were excluded. Standard-risk (SR) group consisted of children aged 1 to 9 years with a white blood cell (WBC) count of below 50,000/μL, whereas all other patients were categorized as the high-risk (HR) [19].

Patients were stratified into standard-risk (SR) and high-risk (HR) groups based on clinical and laboratory parameters at diagnosis, following the Addendum to the Indonesian National Protocol for Childhood Acute Lymphoblastic Leukemia issued by the Indonesian Pediatric Hematology Oncology Working Group [20]. High-risk (HR) classification was assigned to patients who met one or more of the following criteria: aged <1 year or ≥ 10 years, with leucocyte count ≥ 50,000 cells/mm3 on peripheral blood smear, a mediastinal mass > 1/3 diameter of the thoracic cavity (based on chest X-ray or CT scan), central nervous system or testicular involvement, T-lineage immunophenotype, or mixed phenotype acute leukemia. Patients who did not meet any high-risk criteria, demonstrated a good response to prednisone, and achieved complete remission (M1 marrow status) by Day 35 of induction therapy (Bone Marrow Puncture, BMP) were classified as standard risk (SR).

Informed consent was acquired from the patients' relatives, the study received ethical approval from the Paediatric Department, Faculty of Medicine, Hasanuddin University. A detailed medical history and a comprehensive physical examination were performed on all participants. Furthermore, laboratory assessments were performed prior to the commencement of induction chemotherapy, including complete blood count (CBC) analysis using the Sysmex KX-21 system and the evaluation of Leishman-stained peripheral blood smears.

Serum samples were collected from the study subjects and stored at -80°C. Vitamin D (25(OH)D3) levels were quantified using an Enzyme-Linked Immunosorbent Assay (ELISA) (Catalog No. MBS2701843), following the manufacturer's guidelines. Vitamin D status was classified as normal for concentrations >30 ng/mL, insufficient for levels between 20–30 ng/mL, and deficient for levels <20 ng/mL. Soluble vitamin D receptor (VDR) levels were also assessed using the ELISA method (Catalog No. MBS268910), provided a detectable soluble form was present in the processed samples.

A bone marrow aspiration procedure was conducted, and Leishman-stained slides were analyzed to evaluate cellular morphology and immunophenotypic characteristics. Patients were divided into three categories groups based on their vitamin D status: Group 1 included individuals with vitamin D deficiency, Group 2 encompassed those with vitamin D insufficiency, and Group 3 comprised individuals with sufficient vitamin D levels. The findings were reported as quantitative measures, expressed in concentration units (e.g., ng/mL).

Statistical Analysis

Relationship between vitamin D status and patient characteristics was statistically examined using Statistical Package for the Social Sciences (SPSS) version 26. Data normality was assessed prior to analysis. Continuous variables, such as age, were reported as means ± standard deviation (SD) and medians (range). The Mann-Whitney test was applied for comparisons between 2 groups, while the Kruskal-Wallis test was used for comparing medians across multiple groups. Categorical variables were expressed as absolute frequencies (numbers) and relative frequencies (percentages), with comparisons between groups conducted using the chi-square test. Pearson correlation test was employed to assess relationship between vitamin D levels and VDR concentrations. Statistical significance is determined by a P-value less than 0.05 ($P < 0.05$), with $P < 0.001$ indicate high statistical significance (HS) and $P > 0.05$ being non-significant (NS).

Results

The result of the study showed most of the children in SR group are aged 1-5 years (64.3%), while HR group has a higher proportion of children aged >10 years (50%). Normal Risk is evenly split between age groups >5-10 years and >10 years (42.4% each). The p-value indicates a significant relationship between age and risk category, suggesting that age may influence risk classification. Age distribution significantly differs across the risk categories, with p value 0.001 (Table 1).

Distribution of males and females is relatively balanced across all categories, with a marginally greater proportion of males in the SR group and a slightly elevated proportion of females in the Normal category. No substantial gender disparity was seen among risk categories, as shown by a P-value of 0.392 ($P>0.05$) (Table 1).

Most children in the normal group exhibit good nutrition (40.7%), although the group also includes a larger proportion of children with poor nutrition (53.3%). The SR group shows a more balanced distribution of good and poor nutritional statuses. Nutritional status significantly differs across the groups, with p value 0.014 which suggests that nutrition could be linked to risk classification (Table 1).

Based on the statistical analysis, the P-value for the comparison of median and range vitamin D levels is

Table 1. Characteristics of the Study Subjects

Variable	Standard Risk (n=30)	High Risk (n=30)	Control (n=30)	Total (n=90)	P Value
Age (years)					0.001*
1-5	18 (64.3%)	9 (32.1%)	1 (3.6%)	28 (100%)	
>5-10	12 (42.4%)	4 (14.3%)	12 (42.4%)	28 (100%)	
>10	0 (0%)	17 (50%)	17 (50%)	34 (100%)	
Sex					0.392**
Male	19 (39.6%)	15 (31.3%)	14 (29.2%)	48 (100%)	
Female	11 (26.2%)	15 (35.7%)	16 (38.1%)	42 (100%)	
Nutritional status					0.014*
Good	18 (33.3%)	14 (25.9%)	22 (40.7%)	54 (100%)	
Under	1 (8.3%)	4 (33.3%)	7 (58.3%)	12 (100%)	
Over	4 (44.4%)	4 (44.4%)	1 (11.1%)	9 (100%)	
Poor	7 (46.7%)	8 (53.3%)	0 (0%)	15 (100%)	

*Fisher-Exact-Test; **Chi-Square Test; P < 0.001 : high statistical significance

Table 2. Comparison of Vitamin D Levels and Vitamin D Receptor Expression in Standard Risk, High Risk, and Normal Subjects Diagnosed with ALL

Variable	Standard Risk (n=30)	High Risk (n=30)	Normal (n=30)	P value
Vitamin D (ng/mL)				0.000*
Median	13.29	13.94	19.61	0.561**
Min-Max	10.19-22.50	10.38-20.89	14.47-23.35	0.000***
Vitamin D Receptor (ng/mL)				0.000****
Median	0.600	0.37	0.39	0.163*
Min-Max	0.10-3.35	0.03-5.77	0.03-6.63	

*Kruskal Wallis test SR-HR-Normal; **Mann Whitney test SR-HR; *** Mann Whitney test SR-Normal; **** Mann Whitney test HR-Normal; P < 0.001, high statistical significance

0.001, indicating a significant difference in vitamin D levels across the three risk groups. A notable difference in vitamin D levels is found between SR and Normal groups (P= 0.001), whereas no significant difference is observed between SR and HR groups (P= 0.561). Meanwhile, the p-value for the median VDR levels is 0.163, indicating no significant difference in median VDR expression among the groups (Table 2).

Vitamin D status significantly differed among the SR, HR, and Normal groups (p = 0.001). The prevalence of vitamin D deficiency was notably higher in the SR and HR groups compared to the Normal group. In contrast, vitamin D insufficiency was predominantly observed in the Normal group. Overall, 82.2% of children were classified as vitamin D deficient, while 17.8% were insufficient (Table 3).

Discussion

The results of this study revealed a significant difference in risk stratification based on age. Specifically, SR was more commonly observed in children aged 1–5 years (64.3%), whereas HR was more frequently identified in those older than 10 years (50%), with a p-value of 0.001. Children aged 1 to 5 years with ALL are often classified as standard risk due to the frequent presence of favorable biological features in this age group. These features include lower initial white blood cell (WBC) counts and the presence of genetic abnormalities associated with a better prognosis, such as hyper diploidy and the t(12;21) translocation (ETV6-RUNX1 fusion). In contrast, children older than 10 years are more likely to fall into the high-risk category due to factors such as higher initial WBC counts, a greater likelihood of unfavourable genetic mutations (e.g., Philadelphia chromosome or hypodiploidy), and a reduced response to treatment [21].

The significant difference in nutritional status based on risk classification in leukemia, with a p-value of 0.014, can be attributed to several physiological and clinical factors. Malnutrition is more prevalent among leukemia patients,

Table 3. Correlation Between Vitamin D Status and Risk Stratification in ALL

Variable	Standard Risk (n=30)	High Risk (n=30)	Normal (n=30)	Total (n=90)	P-value
Vitamin D (ng/mL)					0.000*
Deficiency	29 (39.2%)	29 (39.2%)	16 (21.6%)	74 (100%)	
Insufficiency	1 (6.3%)	1 (6.3%)	14 (87.5%)	16 (100%)	

*Fisher-Exact-Test; P < 0.001 : high statistical significance

particularly those in higher risk categories, compared to healthy individuals. Leukemia increases the body's metabolic demands due to the rapid proliferation of leukemic cells, which leads to higher energy consumption. This often results in a negative energy balance and malnutrition, especially in severe cases [22].

A major finding of this study is the high prevalence of vitamin D deficiency among children with ALL, especially within the SR and HR groups. These results align with the study by Atilano-Miguel et al. [23], who reported vitamin D deficiency in 61% of cases, insufficiency in 30%, and sufficiency in only 9%. This finding is in line with previous studies suggesting that vitamin D deficiency is prevalent in children with leukemia. Such deficiency may stem from a variety of factors, including decreased physical activity in children with ALL, which restricts their outdoor sunlight exposure, the primary source of vitamin D synthesis. Seasonal variations may also play a role, as lower vitamin D levels are frequently observed during the rainy season [24]. Poor nutritional status prior to diagnosis is common among children with ALL, often due to reduced dietary intake caused by symptoms such as fatigue, loss of appetite, or other systemic effects of the disease. This can lead to insufficient consumption of vitamin D-rich foods [25]. Leukemia can directly impact bone health and vitamin D metabolism by disrupting normal bone marrow function and immune regulation, both of which are closely associated with vitamin D status [26, 27]. Chronic inflammation associated with leukemia may disrupt vitamin D metabolism and elevate the body's demand for this essential nutrient [28]. Many children with leukemia may already have suboptimal vitamin D levels prior to diagnosis, reflecting global trends of vitamin D deficiency in the pediatric population. Jackman) Findings of this study differ from those reported by Norouzi A, who observed no significant difference in serum 25(OH) vitamin D levels between patients with ALL (20.42 ± 6.5 ng/mL) and healthy subjects (25.45 ± 11 ng/mL) [29].

Normal Group

Interestingly, the Normal Risk group exhibited fewer cases of vitamin D deficiency (21.6%) but a higher prevalence of vitamin D insufficiency (87.5%). This finding suggests that even in lower-risk populations, vitamin D insufficiency remains a significant concern. Vitamin D insufficiency is frequently observed in children, particularly those with inadequate dietary intake or limited limited sun exposure.

These findings highlight the critical need for routine vitamin D screening in pediatric leukemia patients, especially those in high-risk categories, and suggest that interventions such as vitamin D supplementation may be beneficial for improving treatment outcomes.

Concentration of VDR

The study also examined concentration of VDR in relation to risk categories. We found that the median VDR concentration was highest in the SR group (0.600 ng/mL), compared to the HR group (0.370 ng/mL) and the Normal group (0.390 ng/mL). Although the p-value of 0.163 for VDR concentration indicates no statistically significant differences between the groups, the observed trend suggests a possible correlation between higher VDR levels and the SR group. The VDR plays a crucial role in regulating cell proliferation, differentiation, and apoptosis, particularly in malignancies like leukemia. The SR group may demonstrate higher VDR concentrations as a compensatory mechanism in response to the disease's progression or treatment-related cellular stress [30]. The lack of statistical significance ($p = 0.163$) may be attributed to the limited sample size or high variability in VDR levels among individuals. Despite this, the observed trends are valuable for generating hypotheses and warrant further investigation through studies with larger, more homogeneous cohorts.

Our study demonstrated a positive correlation between vitamin D levels and VDR levels ($p= .001$; $r=0.342$). This correlation can be explained by several biological and molecular mechanisms. Vitamin D, particularly its active form, calcitriol (1,25-dihydroxyvitamin D), regulates the transcription of the VDR gene. Adequate vitamin D levels promote the synthesis of VDR in target cells, thereby enhancing the receptor's availability and activity. In leukemia, vitamin D may exert compensatory effects to regulate VDR expression and function in immune cells, where VDR plays a critical role in modulating cell proliferation and inflammation. brown

Implications for Treatment

These findings suggest that vitamin D status may play a crucial role in modulating immune function and the overall treatment response in children with ALL. Given high rate of deficiency in SR and HR groups, vitamin D supplementation could potentially enhance immune response, reduce inflammation, and improve treatment efficacy. Some studies indicate that maintaining adequate vitamin D levels may lead to better outcomes in cancer therapy, including a reduced risk of infection and improved overall survival [31].

In conclusion, this study conclude that vitamin D deficiency is highly prevalent in children with ALL, highlighting the need for regular vitamin D screening and supplementation. Further research is necessary to explore the therapeutic potential of vitamin D and VDR in leukemia treatment. Such research will guide the development of vitamin D-based interventions designed to improve outcomes from treatment and health in children with ALL.

Author Contribution Statement

Nadirah Rasyid Ridha: Conceptualization, formal analysis, investigation, methodology, data curation and writing the manuscript (MS); Darwati Muhadi: conceptualization, investigation, and project administration; Muh. Farid Huzein: Conceptualization, Writing-original draft; Purnamasari Natsir Putri: Investigation, formal analysis, and Writing the original draft; Bahrul Fikri: writing-review & editing; Ema Alasiry: writing-review & editing; Martira Maddeppungeng: Writing-review & editing.

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This work is an independent project and is not affiliated with any scientific body nor part of an approved student thesis.

Availability of data

The data generated and/or analyzed during the current study are not publicly available for legal/ethical reasons but are available from the corresponding author on reasonable request. This study doesn't register in any registration dataset.

Ethical Considerations

Ethical approval was obtained from the Ethics Committee of the Faculty of Medicine, Universitas Hasanuddin (Approval Number: 685/UN4.6.4.5.31/PP36/2024). Informed consent was acquired from the parents or guardians of all participants before enrolment in the study.

Conflict of Interest

There are no conflicts of interest to disclose.

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