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# Lactate Dehydrogenase and Blast Rates in the Diagnostic Phase and the Late Remission Phase of Acute Childhood Leukaemia Patients

Nelly Rosdiana[1*], Novia[1]

[1]*Department of Pediatric, Faculty of Medicine, Universitas Sumatera Utara/ H. Adam Malik Hospital, Medan, Indonesia*

***Corresponding Author**: Nelly Rosdiana, nellyrosdiana11@gmail.com

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**ABSTRACT**

**Introduction**: Leukaemia is a blood cell malignancy that manifests as young cells in the peripheral blood. In developing countries, ALL account for 80% of leukemia cases. Despite the implementation of contemporary intensive therapy, remission is attained in 98% of patients. LDH have found to have benefit in diagnosing and may be prognostic factor especially in predicting remission in ALL.

**Methods**: This observational cohort study took place at the pediatric ward of RSUP H. Adam Malik – Medan, from August 2022 to February 2023. Subjects meeting the study criteria were assessed to know the relationship between LDH between the initial phase and remission phase of ALL. Multivariate logistic regression analysis was then conducted for the combined scores.

**Results**: We found significant differences in LDH and blast levels between the initial phase and remission phase of ALL ($p<0,001$). However, the multivariate logistic regression analysis yielded statistically non-significant results ($p > 0.05$).

**Conclusion**: In this study, we found a significant differences of LDH and blast between the initial phase and remission phase of ALL. LDH and blast may be a promosing prognostic factor to assess ALL.

**Keywords**

ALL, LDH, Initial phase, Pediatric, Remission phase

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## INTRODUCTION

Leukaemia is a blood cell malignancy that manifests as young cells in the peripheral blood and is distinguished by the proliferation of white blood cells, which originate from the bone marrow.[1] Acute leukaemia is classified into two types: Acute Lymphoblastic Leukaemia (ALL) and Acute Myeloblastic Leukaemia (AML).[2] The prevalence of leukaemia fluctuates based on the spatial distribution pattern. In developing countries, more than 80% of ALL is a B-cell precursor subtype that leads to an increased incidence of leukemia in early childhood.[3] The management of childhood acute lymphoblastic leukaemia (ALL) involves the use of curative and supportive chemotherapy treatment. Nevertheless, despite the implementation of contemporary intensive therapy, remission is attained in 98% of patients. A small proportion, approximately 2-3%, of paediatric patients will experience mortality while in a state of continuous complete remission (CCR), while a larger percentage, around 25-30%, will experience a relapse.[4-5] Hence, employing additional parameters can aid in evaluating the probability of achieving remission in ALL.

Lactate dehydrogenase (LDH) is an enzyme with a chemical structure similar to pyridine that is commonly present in different types of tissues. The primary role of LDH is to enzymatically convert pyruvate into lactate. Acute leukaemia is characterised by a rapid turnover of cells, resulting in an elevated number of leukaemia cells and an increase in serum LDH levels.[6] Elevated serum LDH levels are linked to heightened cellular proliferation and turnover.[7] Numerous studies have demonstrated the correlation between serum

LDH levels and its significance in the diagnosis and prognosis of childhood leukaemia.[6-10] This study aims to highlight the significance of serum LDH as a valuable adjunctive test for assessing the diagnosis and prognosis of childhood acute leukaemia.

## METHODS

This study is an observational analytic trial designed to assess the correlation between LDH levels at diagnosis and during the induction remission phase, and blast levels at diagnosis and the end of the induction remission phase, using a prospective cohort design. The research was conducted in the pediatric ward of Haji Adam Malik Hospital in Medan over a 6-month period from August 2022 to February 2023. The study targeted children aged 1 month to 18 years diagnosed with Acute Lymphoblastic Leukemia (ALL). The sample included patients admitted to the pediatric ward of Haji Adam Malik Hospital in Medan during the study period, selected using a consecutive sampling method. Despite the potential for higher sampling bias with this method, it was the most feasible approach in our setting. The study included pediatric patients aged 1 month to 18 years diagnosed with ALL at H. Adam Malik Medan Hospital between August 2022 and February 2023. Exclusion criteria included children with ALL who had severe infection, pleural effusion, malignancy, or were taking vitamin C and E supplements.

Children diagnosed with Acute Lymphoblastic Leukaemia (ALL) will undergo a series of medical procedures to assess their condition. These procedures include the collection of blood samples for comprehensive blood tests, measurement of LDH levels, evaluation of liver function, assessment of infection markers, and examination of bone marrow. The Roche Cobas E 411 device is utilised to measure LDH levels. The test employed venous blood samples. A syringe was used to extract blood, which was then transferred into a vacuum tube without any anticoagulant. Upon receipt, the blood was stored for a duration of 20 minutes. The blood was subsequently subjected to centrifugation at a speed of 3,000 revolutions per minute for a duration of 10 minutes. The serum containing LDH was subsequently isolated and examined using the Roche Cobas E 411 instrument. Upon operating the device for approximately 20 minutes, the outcomes of the LDH examination will be generated and subsequently documented.

The blast levels will be assessed through a bone marrow aspiration examination conducted by a specialist in clinical pathology. In order to enhance the accuracy of evaluating bone marrow particles, the analysis is conducted using a technique called thin smear method on a glass substrate. The objective is to prevent the accumulation of adipose tissue or fragments of bone that could disrupt the analysis. The thin smear technique bears resemblance to the technique employed in peripheral blood smears. After the specimen is ready, staining is carried out using the May-Grünwald-Giemsa technique.

We used statistical software to analyze the data. Univariate analysis helped us understand the frequency distribution of the study groups based on their LDH and blast levels. We reported the median for non-normally distributed numerical data, and the mean and standard deviation for normally distributed data. We used Pearson correlation for normally distributed data and Spearman correlation for non-normally distributed data to examine the relationship between blast and LDH levels. Furthermore, we employed multivariate analysis to investigate how blast levels relate to ferritin.

## RESULTS

This study involved a total of 41 children with ALL who have completed the initial phase and remission and were hospitalised in the paediatric ward of Haji Adam Malik Hospital in Medan. All subjects have met the inclusion criteria. The demographic characteristics of the research subjects are displayed in detail in Table 1.

Out of the total number of children, 28 (73.2%) were male. The average age of the children was 6.82 years, ranging from 11 months to 16.5 years. The average weight of the subjects was 6.82 kg, with the minimum weight recorded as 5 kg and the maximum weight recorded as 41 kg. The average height of the participants was 113.56 cm, ranging from a minimum of 71 cm to a maximum of 164 cm.

Table 1. Demographic characteristics of this study

| Characteristics | n = 41 (%) |
|---|---|
| Sex | |
| Male | 30 (73,2) |
| Female | 11 (26,8) |
| Usia, age | |
| Mean (SD) | 6,82 (4,43) |
| Median (min – max) | 6 (0,92 – 16,5) |
| Weight, kg | |
| Mean (SD) | 20,14 (8,57) |
| Median (min – max) | 19 (5 – 41) |
| Height, cm | |
| Mean (SD) | 113,56 (21,33) |
| Median (min – max) | 110 (71 – 164) |
| Risk, n (%) | |
| Standar | 20 (48,8) |
| High | 21 (51,2) |

Table 2. Differences in LDH Levels in the Early Induction and Remission Phases of Induction

| | Early Phase | Remission Phase | p |
|---|---|---|---|
| LDH, µg/Dl | | | |
| Mean (SD) | 643 (467) | 146 (92) | <0,001* |
| (Min – Max) | (136-3083) | (34-401) | |

The median LDH value in the early induction phase was 643 U/L (136 - 3083) U/L, while in the remission phase showed a decrease with the median value being 146 U/L (34-401) U/L. Using the Wilcoxon test showed that there was a significant difference in LDH levels between the initial phase of induction and the remission phase of induction ($p<0.001$).

Table 3. Differences in Blast Levels in the Early Induction and Remission Phase of Induction

| | Early Phase | Remission Phase | P |
|---|---|---|---|
| Blast Cells, % | | | |
| Mean (SD) | 54,25 (20,89) | 0,87 (0,58) | <0,001* |
| Median (Min – Max) | 60 (1 – 93,25) | 1 (0 – 3) | |

The mean value of blast cells in the initial phase of induction was 54.25% (SD = 20.89%), while in the remission phase showed a decrease with the median value being 1% (0 - 3) %. Using the Wilcoxon test showed that there was a significant difference in blast cells between the initial phase of induction and the remission phase of induction ($p<0.001$).

Table 4. Relationship between LDH and Blast Cells in the Early Phase in Pediatric ALL Patients

| | Blast Cells in Early Phase | |
|---|---|---|
| | p* | R |
| Early Phase LDH | 0,012 | 0,389 |

*Spearman

Using the Spearman correlation test, it was found that an increase in blast was followed by a significant relationship/correlation between LDH levels and blast cells in the early induction phase of high-risk ALL

pediatric patients (p = 0.012). The correlation value obtained was 0.389, which means that there is a positive correlation with weak strength between LDH levels and blast cells in the early induction phase. The meaning of the positive correlation is that any increase in LDH values will be followed by an increase in blast cell values in the early induction phase of pediatric ALL patients.

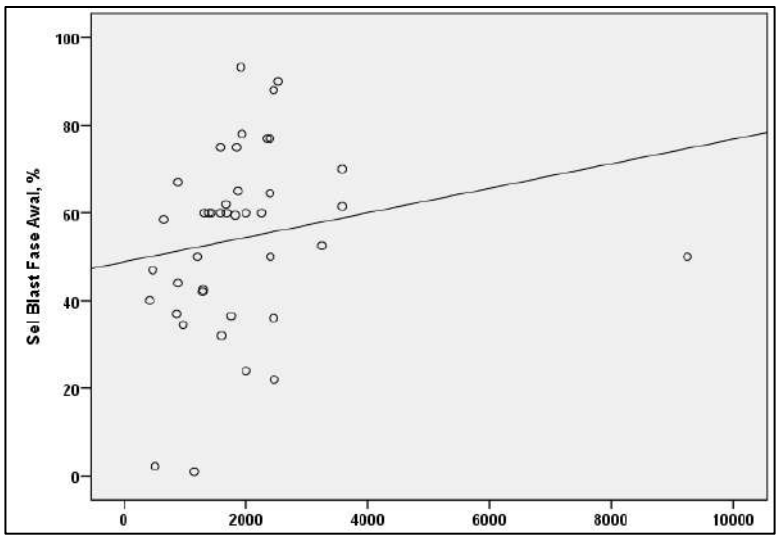


Figure 1. The Scatterplot Graph of Correlation of LDH Levels and Blast Cells in the Early Phase of Induction in Children with ALL

Table 5. Relationship between LDH and Blast Cells in Remission Phase in Pediatric ALL Patients

| | Blast Cell in Remission Phase | |
|---|---|---|
| | p* | R |
| LDH Phase Remission | 0,926 | -0,015 |

The Spearman correlation test indicated that there was no significant relationship or correlation between LDH and blast cell levels in the induction remission phase of pediatric ALL patients (p = 0.926). This means that a decrease in blast cells was not accompanied by a decrease in LDH levels.

## DISCUSSION

Multiple studies have demonstrated that cancer cells enhance their absorption of iron, disrupt iron storage, and impact iron elimination. Multiple studies have demonstrated a substantial rise in LDH levels among patients with ALL.[17] This study also reported that the median LDH levels during the initial diagnosis phase and remission phase were 643 mcg/L and 146 mcg/L, respectively. Both of these levels were higher than the normal LDH levels. LDH levels in the blood theoretically serve as an indicator of tissue damage.[11,12] Serum LDH can be used diagnostically to identify cancer by detecting tissue damage or destruction resulting from the development and growth of cancer cells. Metastatic tumours have been found to elevate LDH levels. Furthermore, elevated levels of LDH have also been documented as a prognostic marker for malignancy. This is demonstrated by the decreased survival rate of patients with elevated LDH levels prior to treatment in comparison to patients with normal LDH levels.[13-14] A separate study documented the utilisation of LDH as a cost-effective metric for aiding the assessment of ALL treatment in paediatric patients. LDH in conjunction with uric acid has been found to have the capability to identify tumour lysis syndrome in its initial phase, which is linked to the early treatment and prognosis of patients.[8]

This phenomenon was also observed in the study, where the median LDH level in the group diagnosed early was higher than the median LDH level in the group in remission. The median LDH level in the early phase ALL group was 643 mcg/L, whereas the median LDH level in the remission phase was 143 mcg/L. The Mann Whitney test revealed a statistically significant difference in LDH levels between the two study groups

($p<0.05$). Thus, LDH is a dependable and responsive tool for diagnosing deteriorating factors in patients. The synthesis rate of LDH is significantly elevated in acute leukaemia, leading to an imbalance between the production and excretion of LDH in the body. Consequently, patients with acute leukaemia experience an elevation in LDH levels.[15]

Acute leukaemia is characterised by a rapid turnover of cells, resulting in an elevated number of leukaemia cells and an increase in serum LDH levels.[6] Leukaemia cells exhibit a distinct metabolic pattern characterised by increased utilisation of glucose compared to normal tissues.[16] This is attributed to the lack of coordination between the glucose cycle and tricarboxylic acid cycle. Elevated serum LDH is positively associated with higher leukocyte count and lower platelet count.[17] Elevated serum LDH levels are linked to heightened cellular proliferation and turnover.[7] Numerous studies have demonstrated the correlation between serum LDh levels and its significance in the diagnosis and prognosis of childhood leukaemia.[6-10] Besides ALL, LDH has also been identified as a prognostic indicator in the management of patients with myelodysplasia syndrome. Additionally, there is a concomitant occurrence of thrombocytopenia and the presence of blast cells along with the observed elevation in LDH levels.[10] Consistent with the findings of this study, LDH is also linked to a 60-day mortality rate in patients with AML. Patients with LDH levels $\geqslant$ 570U/L had a higher mortality rate compared to those with LDH levels <570U/L.[9] Nevertheless, it remains imperative to conduct further research into the underlying mechanism that leads to mortality in AML during its initial stages. High levels of lactate dehydrogenase (LDH) are a result of increased activity in tumour glycolysis and the death of tumour cells caused by a lack of oxygen (hypoxia).[18-19] These events have an indirect correlation with the functioning of other organs, such as the heart, liver, and kidneys.[20] Xiao et al. documented a significant mortality rate among patients with acute myeloid leukaemia (AML) who exhibited elevated blood glucose levels, increased myoglobin levels, and decreased albumin levels.[9] Hence, it is imperative for clinical practitioners to conduct a thorough assessment of the functioning of other organs in patients with blood cancer in order to ascertain the efficacy of the treatment.

This study has several limitations, including the short sampling duration of approximately 8 weeks between the initial diagnosis phase and the remission phase, which may result in LDH levels that have not been able to modify. Increasing the sample size can yield a more comprehensive understanding of the variations in LDH observed in the study. The research on the correlation between LDH and leukaemia in children is currently quite limited. Hence, one of the strengths of this study is its ability to offer a comprehensive analysis of the variations in LDH levels during the early stages of diagnosis and the phase of remission. This study aims to demonstrate variations in LDH levels in paediatric leukaemia patients by measuring levels during the early phase and remission phase. LDH levels are anticipated to serve as a prognostic factor for evaluating the severity of the disease in the future.

## CONCLUSION

This study reports the differences in LDH values between the initial diagnostic phase and the induction remission phase in paediatric patients with leukaemia. LDH level examination can be performed as an alternative to determine the severity of ALL in paediatric patients. Subsequent research can be conducted through longer-term monitoring and utilising a larger sample size.

## DECLARATIONS

Ethics approval and consent to participate. Permission for this study was obtained from the Ethics Committee of Universitas Sumatera Utara and Haji Adam Malik General Hospital.

## CONSENT FOR PUBLICATION

The Authors agree to publication in Journal of Society Medicine.

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**COMPETING INTERESTS**
The authors declare that there is no conflict of interest in this report.

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