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Unveiling the Survival Gap: Addressing the Challenges of Acute Lymphoblastic Leukemia in Adolescents

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ABSTRACT

Background: Acute Lymphoblastic Leukemia (ALL) remains the most common pediatric cancer, yet survival outcomes vary widely across age groups. In Indonesia, comprehensive data on ALL survival rates are sparse, particularly for adolescents who often fare worse than younger children. The underlying factors contributing to the difference in adolescent survival rates still need to be fully understood. This study aimed to evaluate and compare the survival rates of children and adolescents with ALL treated at Dharmais Cancer Hospital.

Method: We conducted a retrospective cohort analysis of 94 ALL patients, including 37 adolescent patients and 71 patients with B-lineage ALL. All patients with ALL from 2021 to 2023 were identified. Children aged 1–18 years, diagnosed with ALL based on bone marrow results and not yet treated, are included in the study. Patients were stratified by risk stratification (Standard Risk [SR] vs. High Risk [HR]), lineage (B-lineage vs. T-lineage), and age group (children under 10 vs. adolescents 10 years and above). The survival curve was analyzed using the Kaplan-Meier method, and the log-rank test was used to assess and compare survival across groups.

Results: The overall survival (OS) rate for ALL patients was 49.5%. Adolescents had a significantly lower OS rate of 23.2% compared to children. SR patients exhibited an OS rate of 95.7%, while HR patients had a 33.3%. B-cell lineage had a higher OS rate (59.8%) than T-cell lineage (15.9%). In B-cell ALL, OS was 61.4% in children but only 28.1% in adolescents.

Conclusion: The survival rate for adolescents with acute lymphoblastic leukemia (ALL) is significantly lower than that of children, influenced by risk stratification, lineage, and age. Further research is needed to identify these risk factors through genetic and molecular analyses.

INTRODUCTION

Ovarian cancer is a deadly gynecological cancer that appears in ovarian tissue. According to Global Cancer Statistics in 2020, ovarian cancer was included in the top 10 most common cancers in women [1]. In Indonesia, of 109,813 deaths caused by cancer in women, ovarian cancer ranks 4th with 7% of cases [2]. Acute lymphoblastic leukemia (ALL) is the leading cause of cancer-related mortality in individuals under 20 years old [1]. This disease is an onco-hematologic condition characterized by genetic alterations that disrupt lymphocyte differentiation and proliferation, with the infiltration of neoplastic hematopoietic cells into the bone marrow, blood, and

various tissues [2]. The pathophysiology of ALL includes chromosomal abnormalities and genetic changes that affect the development of lymphoid precursor cells, particularly from the B, T, and NK lineages [3]. Genetic factors significantly influence the occurrence of ALL in children; for instance, individuals with trisomy 21 (Down syndrome) have a 10- to 20-fold increased risk of developing leukemia compared to the general pediatric population. Additionally, exposure to environmental factors such as radiation and toxic chemicals may contribute to the development of acute leukemia [4].

The incidence of acute lymphoblastic leukemia (ALL) is significantly higher in males than in females, with males tending to have a poorer prognosis. Leukemia ranks as the tenth leading cause of cancer-related deaths, accounting for over 305,000 deaths out of 487,294 reported cases [5]. In Indonesia, the incidence of acute lymphoblastic leukemia (ALL) in children is estimated to range from 2.5 to 4.0 cases per 100,000 children, translating to approximately 2,000 to 3,200 new cases each year [6]. Data from Dharmais Cancer Hospital between 1993 and 2020 show an increasing number of pediatric cancer cases over five-year periods. Between 2003 and 2007, leukemia was the most common childhood cancer, followed by lymphoma and other malignant epithelial neoplasms [7].

Globally, the five-year survival rate for patients with acute lymphoblastic leukemia (ALL) has shown remarkable improvement over time. For children under 15 years old, the survival rate has increased from 60% to approximately 90%. Similarly, for adolescents aged 15 to 19, the survival rate has risen from 28% to more than 75% [8–10]. However, survival rate improvement in adolescents is not as significant as in children, as there is a “survival cliff” in adolescent ALL survival. This difference is associated with various biological factors that play a crucial role in treatment outcomes, particularly in adolescents with acute lymphoblastic leukemia (ALL).

The biological factors influencing adolescent survival rates in ALL include significant genetic variations and mutations, as well as minimal residual disease (MRD) expression after therapy. Mutations such as IKZF1, TP53, and ETV6-RUNX1 are recognized as critical prognostic indicators. For instance, studies have shown that IKZF1 mutations are specifically associated with poorer prognoses in ALL patients [11]. Additionally, chromosomal abnormalities such as hyperdiploidy and hypodiploidy have prognostic implications, indicating that children and adolescents with ALL exhibit genetic variations that can lead to significantly different clinical outcomes [12].

From a clinical perspective, treatment response in adolescents with ALL is crucial. Many patients exhibit resistance to standard therapies such as steroids and asparaginase-based regimens, contributing to poorer outcomes [11]. Treatment response is often assessed by evaluating MRD expression after induction therapy, which serves as a critical prognostic factor. High MRD levels indicate the persistence of residual cancer cells post-treatment, which is strongly correlated with a higher likelihood of relapse and poorer outcomes [13–14]. Recent research suggests that MRD resurgence not only reflects the effectiveness of therapy but may also indicate genetic shifts in cancer cell profiles, thereby influencing long-term survival [14–15].

Treatment-related complications, including infections and chemotherapy-induced toxicities, also significantly impact survival rates. Studies indicate that adolescent patients experiencing severe medical complications due to treatment tend to have worse prognoses compared to those undergoing therapy without complications [11]. Acute lymphoblastic leukemia can also be categorized based on cell lineage subtypes, which fundamentally influence prognosis. For instance, T-lineage ALL (T-ALL) is generally associated with worse outcomes compared to B-lineage ALL (B-ALL) [16]. Resistance to conventional therapies in T-ALL remains a major challenge in clinical management, increasing relapse risk and lowering overall survival rates [12,17].

Socioeconomic and environmental factors also play a role in ALL prognosis. Delayed diagnosis and limited access to quality treatment significantly impact treatment outcomes. Studies show that children (including adolescents) in developing countries often experience substantial delays in diagnosis, which is reflected in lower survival rates compared to children in high-income countries [17,18]. Timely and high-quality access to treatment can be a major determinant of adolescent ALL survival rates, emphasizing the critical role of healthcare policies and medical education in improving treatment outcomes [12]. On the other hand, adolescents often perceive themselves as a healthy population, making them less likely to seek medical check-ups or participate in clinical research. This contributes to delayed diagnosis and complicates treatment.

Data on ALL survival rates in specific age groups in Indonesia remain limited, highlighting the need for further research. More in-depth studies can help identify unique challenges in ALL management in Indonesia [18]. The above factors provide the foundation for the importance of studying adolescents with ALL. Therefore, this study aims to evaluate and compare survival rates in children and adolescents diagnosed with acute lymphoblastic leukemia (ALL) at Dharmais Cancer Hospital.

METHODS

A total of 94 ALL patients were identified during the period from 2021 to 2023 at Dharmais Cancer Hospital. Children aged 1 to 18 years, diagnosed with ALL based on bone marrow results and not yet treated, are included in the study. The data collection was

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patients' demographics, clinical characteristics, risk stratification, and outcome. All the results were identified in the medical records.

The primary endpoint of this study was overall survival (OS), defined as the time from the patient's hospital admission to the date of death. The parameter for assessing patient survival was based on the time of the last recorded follow-up visit. The follow-up period lasts 3 years. We did stratification analysis in this study. Stratification was performed according to age (children under 10 years vs. adolescents 10 years and older), risk stratification (standard risk vs. high risk), and lineage (B-lineage vs. T-lineage). Statistical analysis was performed using SPSS version 25. The survival curve was analyzed using the Kaplan-Meier method, and the log-rank test was used to assess and compare survival across groups. All analyses were two-sided, and the significance level was set at $p < 0.05$.

RESULTS

In the cohort data from 2021 to 2023, patients with Acute Lymphoblastic Leukemia (ALL) were more prevalent compared to children aged 10 years and above. We calculated that the average age at diagnosis was 7.85 years, ranging from 1 to 17 years. Based on lineage, 75.5% of ALL patients had B-lineage, and 75.5% were classified as high-risk. The outcomes reveal that 35.1% of ALL patients did not survive. This study was conducted over three years, with an average observation period of 12.6 months, ranging from 0 to 40 months **(Table 1).**

The 3-year overall survival (OS) rate for ALL patients was 74.8%. The follow-up period was extended to assess long-term survival trends in this cohort. The extended follow-up revealed a median survival time of 29 months for ALL patients **(Figure 1)**.

By lineage, the OS rate was 59.8% for B-lineage and 15.9% for T-lineage, with mean survival times of 28 months and 11 months, respectively **(Figure 2a)**. Based on risk stratification, nearly all patients survived for 3 years, with an OS rate of 95.7%. However, high-risk patients had a 33.3% OS rate and a median survival of 20 months **(Figure 2b)**. Regarding age, patients aged 10 and older had a 23.2% survival rate with a mean survival of 15 months, while those younger than 10 had a 67.7% survival rate with a mean survival of 31 months **(Figure 2c)**. The log-rank test results show a significant difference in survival probability among ALL patients based on age, lineage, and risk stratification (p-value < 0.05). These results suggest that adolescents have a lower overall survival (OS) compared to younger children.

Table 1. Characteristics of acute lymphoblastic leukemia (ALL) patients 2021–2023

Variables	n	%
Age		
< 10 years	57	60.6
≥ 10 years	37	39.4
Lineage		
B-lineage	71	75.5
T-lineage	23	24.5
Risk stratification		
Standard risk	23	24.5
High risk	71	75.5
Outcome		
Life	45	47.9
Abandonment	16	17.0
Dead	33	35.1

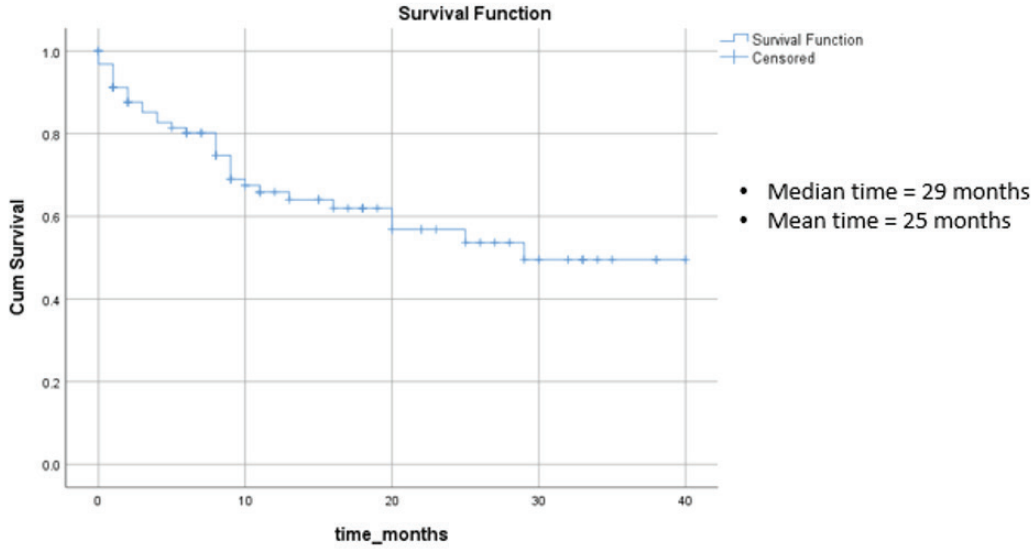
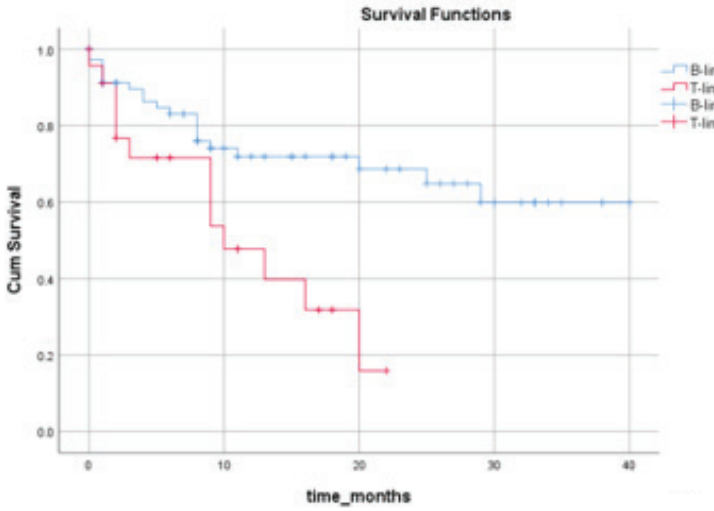


Figure 1. Overall survival function of patients with acute lymphoblastic leukemia (ALL)



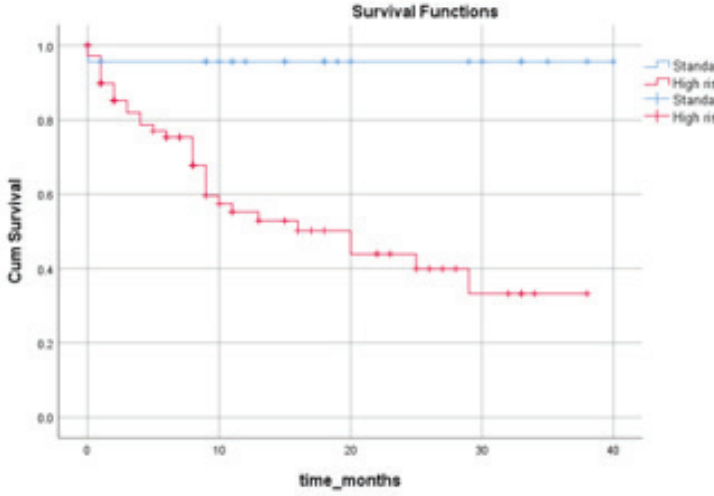
- Survival B-lineage: 59.8%
- Survival T-lineage: 15.9%
- Mean time B-lineage = 28 months
- Mean time T-lineage = 11 months

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	8.386	1	.004

Test of equality of survival distributions for the different levels of Lineage.

(a)



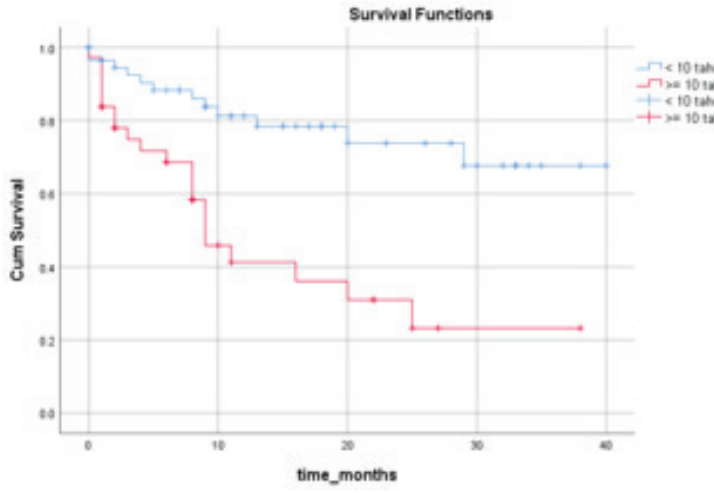
- Survival standard risk: 95.7%
- Survival high risk: 33.3%
- Mean time standard risk = 38 months
- Mean time T-lineage = 20 months

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	12.466	1	.000

Test of equality of survival distributions for the different levels of Stratifikasi.

(b)



- P-value = <0.001
- Survival ≥ 10 years old : 23.2%
- Survival < 10 years old :67.7%
- Mean time ≥ 10 years old = 15 months
- Mean time < 10 years old = 31 months

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	15.236	1	.000

Test of equality of survival distributions for the different levels of usia_kat.

(c)

Figure 2. Kaplan-Meier curves for overall survival (OS) in ALL patients based on lineage (a), risk category (b), and age (c). The OS outcomes were compared using the log-rank test with $p < 0.05$.

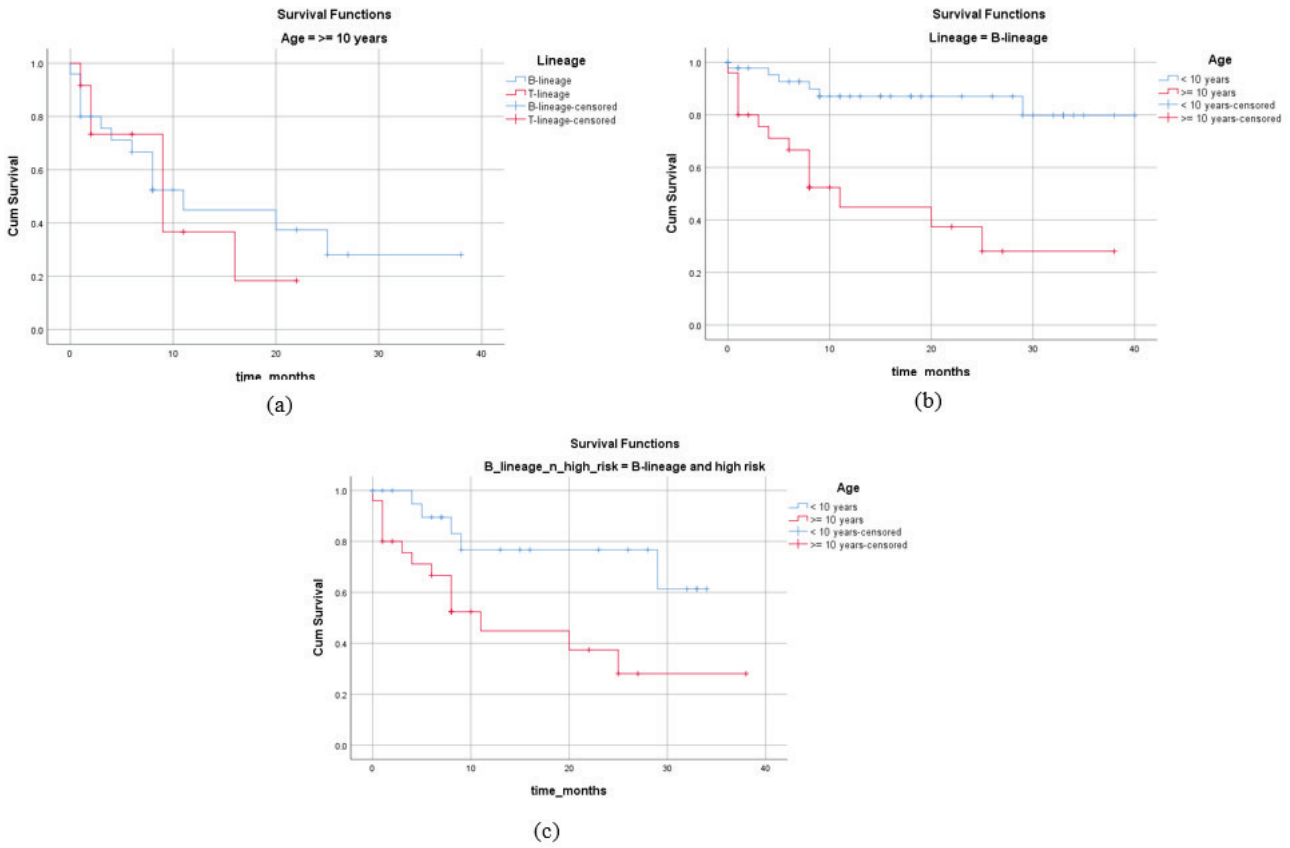


Figure 3. Survival function of Acute Lymphoblastic Leukemia (ALL) patients with age ≥ 10 years based on lineage (a), with B-lineage based on age (b), and with B-lineage and high risk based on age (c)

We stratified patients based on age, risk, and lineage. By age, the OS rate was higher in adolescents with B-lineage than in those with T-lineage (28.1% vs 18.3%) (**Figure 3a**). By B-lineage, patients under 10 years had a higher OS rate than adolescents (79.8% vs 18.3%) (**Figure 3b**). Among high-risk patients with B-lineage, those under 10 years had a higher OS rate than adolescents (61.4% vs. 28.1%) (**Figure 3c**).

We conducted stratification based on age, leukemia lineage, and established risk classification systems. Among adolescent patients, the median survival times for B-lineage and T-lineage leukemia were 11 months and 9 months, respectively, with no statistically significant difference ($p > 0.05$). This lack of significance suggests that lineage alone does not fully account for survival differences within this age group, implying the presence of additional biological, genetic, or treatment-related determinants affecting prognosis.

Further stratification within the B-lineage cohort revealed a significant difference in survival outcomes between adolescents and children, with mean survival times of 17 months and 34 months, respectively ($p < 0.05$). This suggests that age-related factors, potentially including variations in leukemia biology, treatment response, or host-related variables such as pharmacokinetics, immune microenvironment, and therapy-related toxicities, contribute to inferior survival outcomes in adolescents compared to younger children. Additionally, when stratifying patients with both B-lineage and high-risk classification, the median survival for adolescents remained at 11 months, indicating a persistently poor prognosis despite standard risk-adapted therapy.

DISCUSSION

Acute lymphoblastic leukemia (ALL) predominantly affects children under the age of 10, but a significant number of cases are diagnosed in adolescents, indicating an urgent need for tailored treatment strategies targeting this age group. Adolescents encounter distinct biological and psychosocial challenges that differentiate them from their younger counterparts, necessitating age-specific treatment protocols to optimize health outcomes.

Adolescents often struggle with treatment adherence, which can significantly impact event-free survival (EFS) and overall survival (OS). Psychosocial barriers, including transitioning from parental supervision to self-management, pose challenges in maintaining medication adherence [19,20]. The complexity of the treatment regimen for ALL, combined with the developmental stage of adolescence, often leads to decreased adherence

rates. Factors contributing to non-adherence include treatment-related toxicities such as pancreatitis, osteonecrosis, and neurocognitive impairment due to corticosteroid and asparaginase therapies [20,21].

Acute lymphoblastic leukemia (ALL) primarily affects the B-cell lineage, accounting for approximately 75.5%. B-cell lineage acute lymphoblastic leukemia (B-ALL) is the most common form, comprising 85% of all cases [14]. In adults, about 75–80% of ALL cases are B-cell lineage, while 20–25% are T-cell lineage [15]. A separate study shows that 85% of ALL cases in children are B-lineage (B-cell ALL), while 10–15% are T-lineage ALL. B-lineage ALL causes abnormalities in B lymphocyte cells [4].

The 3-year overall survival (OS) rate for ALL patients was 74.8%. A study in Malaysia found that the 3-year OS was 72.2%. In a study in Iran, the 3-year OS was 75.10%. The differences in 3-year overall survival (OS) rates across studies may reflect variations in patient demographics, treatment protocols, healthcare infrastructure, and genetic factors. While our study reported a 3-year OS of 74.8%, similar to the study in Iran (75.1%), the slightly lower OS rate in Malaysia (72.2%) could indicate differences in disease management, access to advanced therapies, or population characteristics [21].

The cumulative survival rate is higher for patients under 10 years old compared to those aged 10 and older. The lower survival rate in adolescents compared to children suggests biological and clinical challenges that require further investigation. Adolescents with ALL often present unique clinical and biological characteristics that influence their prognosis. One notable feature is the higher prevalence of T-cell lineage ALL, which is associated with a worse prognosis compared to the more common B-cell lineage ALL. This is a crucial factor since T-cell lineage ALL tends to be more refractory to conventional therapies, and its aggressive nature necessitates more intensive treatment approaches [21]. Additionally, older adolescents are at an increased risk for high-risk genetic mutations such as Philadelphia chromosome-positive ALL or IKZF1 deletions. These mutations typically require targeted therapies, including tyrosine kinase inhibitors (TKIs) such as imatinib, which are not always part of standard treatment regimens for younger patients [21].

We did the stratification in this study. the median survival for patients aged ≥10 years is reported as 11 months; however, the survival data for those under 10 years is absent, making direct comparisons difficult. The log-rank p-value of 0.777 indicates that survival differences between these age groups are not statistically significant. These findings highlight a critical gap in current stratification models, suggesting that conventional risk classification systems may not adequately capture the unique biological and clinical characteristics of adolescent leukemia.

Given these findings, the integration of advanced molecular diagnostics is imperative to refine prognostication and therapeutic stratification in this population. Emerging evidence suggests that adolescent leukemia may harbor distinct mutational landscapes and cytogenetic abnormalities that influence disease progression and treatment resistance. Multiplex Ligation-dependent Probe Amplification (MLPA), in conjunction with next-generation sequencing (NGS), minimal residual disease (MRD) assessment, and transcriptomic profiling, could provide deeper insights into the genomic alterations and copy number variations (CNVs) associated with high-risk leukemia in adolescents. MLPA is particularly valuable for detecting recurrent deletions and amplifications in leukemia-associated genes, including those affecting the IKZF1, PAX5, and CDKN2A/B loci, which have been linked to poor outcomes in B-ALL [21].

By incorporating these molecular techniques, a more refined and biologically informed risk stratification model can be developed, allowing for targeted therapeutic interventions and potentially improving survival outcomes in adolescent leukemia. Future studies should focus on integrating MLPA-based CNV analysis with other genomic and transcriptomic approaches to identify novel biomarkers and therapeutic targets tailored to the adolescent leukemia population [22].

Survival based on lineage classification offers more definite insights. Although patients diagnosed with T-lineage ALL do not have a reported median survival in the studied cohort, the p-value of 0.000 highlights a highly significant difference between B-lineage and T-lineage ALL outcomes. This finding reaffirms established knowledge that T-lineage ALL is associated with poorer survival rates compared to B-lineage ALL, supported by evidence of higher initial leukocyte counts, increased resistance to chemotherapy, and a greater tendency for central nervous system (CNS) involvement at diagnosis [23–24].

Among B-lineage ALL patients, those classified as high-risk have a median survival of 11 months, with a lower p-value of 0.013 indicating a significant impact of high-risk status on survival outcomes. This highlights the necessity for risk-adapted therapy, ensuring that high-risk patients receive intensified treatment regimens, including novel approaches such as targeted immunotherapy or tyrosine kinase inhibitors for Philadelphia chromosome-positive (Ph+) ALL [25–26].

Simultaneously, results for high-risk B-lineage patients suggest a need for enhanced monitoring of minimal residual disease (MRD) and the earlier use of advanced therapies like Blinatumomab for persistent MRD post-induction [26]. Improved patient education regarding treatment adherence, especially in older children and adolescents facing psychosocial barriers, is essential for optimizing clinical outcomes.

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The impressive survival rates in patients with acute lymphoblastic leukemia (ALL) are a result of advanced chemotherapy protocols developed over the past seventy years. Understanding the risk level of ALL is essential for tailoring effective treatment strategies. Molecular markers play a key role in identifying high-risk genetic mutations and chromosomal abnormalities associated with a poor prognosis. This information helps determine the intensity and duration of treatment while providing patients and families with valuable insights into their journey. While traditional karyotyping has long been used to detect genetic abnormalities in young ALL patients, recent advancements in genomic studies are expanding our ability to diagnose and assess risks more accurately than ever. This progress not only improves treatment but also offers hope for a brighter, healthier future for those affected [17,27,28].

Integrating genetic and molecular factors into risk stratification enhances the understanding of various health conditions. Equally important, tailoring interventions to adolescents' unique needs improves treatment effectiveness. This study has several limitations. Its retrospective design introduces potential selection bias and limits control over confounding variables. Missing or incomplete data, particularly on treatment adherence and genetic profiles, may affect the accuracy of survival estimates. With only 94 patients, the study may not fully represent the heterogeneity of ALL in adolescents. The absence of detailed molecular markers, such as MLPA and next-generation sequencing, prevents a comprehensive assessment of genetic risk factors influencing survival. Variations in chemotherapy intensity, supportive care, and access to immunotherapy may also impact survival outcomes but remain unaddressed. Larger multicenter studies with molecular profiling are needed to validate these findings and refine risk stratification in adolescent ALL.

CONCLUSIONS

The survival rate for adolescents with acute lymphoblastic leukemia (ALL) is significantly lower than that of children, with outcomes strongly influenced by risk stratification, lineage, and age. There are factors in adolescents that cannot yet be explained by the current risk stratification, including differences in lineage. This is supported by data showing that the OS of patients with B-lineage and high-risk stratification remains lower than that of children. Therefore, further research is needed to identify these risk factors through genetic and molecular analyses. This step is crucial to support more precise treatments and improve the survival rates of ALL patients in Indonesia, particularly among adolescents.

DECLARATIONS

Competing interest

The authors declare no competing conflicts of interest in this study.

Ethics approval

This study was approved by the Ethical Committee of the Dharmais Cancer Centre Hospital (No. 244/ KEPK/X/2022) and the Faculty of Medicine of Universitas Indonesia (KET-1201/UN2.F1/ETIK/PPM.00.02/2022).

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