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Adult Acute Lymphoblastic Leukemia: Insights from Six Years of Clinical Practice in an Egyptian Tertiary Care Center

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ABSTRACT

Despite being an uncommon hematologic malignancy in adults, acute lymphoblastic leukemia (ALL) remains a highly aggressive disease, with long-term survival rates reported between 30% and 40%. A thorough understanding of the biology of the disease is essential for the effective management of ALL, enabling the application of personalized therapeutic strategies, given the heterogeneity of patient presentations. This has further facilitated the development of targeted therapies and the integration of novel therapeutic agents. This study was conducted to evaluate the overall survival, progression-free survival, and relapse patterns among patients diagnosed with acute lymphoblastic leukemia (ALL) who received treatment at the Kasr Al-Ainy Centre of Clinical Oncology and Nuclear Medicine (NEMROCK) during the period spanning January 2015 to December 2020. In this retrospective analysis, 42 adult patients newly diagnosed with ALL between January 2015 and December 2020 were evaluated at the Kasr Al-Ainy Centre of Clinical Oncology and Nuclear Medicine (NEMROCK). These patients received different treatment protocols that shared a common therapeutic foundation but differed in intensity and scheduling adjustments. Ultimately, 35 patients met the inclusion criteria for the final analysis. The median overall survival (OS) across the cohort was 14.4 months (95% CI: 11.5-17.3). Achieving a complete remission (CR) following the first induction cycle was an important prognostic factor, as patients who reached CR showed a median OS of 17.9 months, compared to 5.3 months for patients with refractory disease (P = 0.02). Among patients with B-cell ALL, those presenting with a total leukocyte count (TLC) of less than 30,000 at diagnosis experienced a significantly longer OS (P = 0.03). In addition, the median disease-free survival (DFS) was 13.3 months, with achievement of CR after the initial induction phase showing a statistically significant impact on DFS outcomes (P = 0.005). This study highlights the importance of tailoring treatment approaches based on risk stratification performed before and during the treatment course. In particular, the role of minimal residual disease (MRD) testing has emerged as a critical standard-of-care tool in the management of ALL, guiding therapeutic decisions and improving patient outcomes.

Keywords: Therapy protocols, Adult leukemias, Clinical practice, Acute lymphoblastic leukemia

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Introduction

Acute lymphoblastic leukemia (ALL) is characterized by the malignant expansion of lymphoid precursor cells, where these abnormal clones replace the normal bone marrow elements due to an early arrest in cellular differentiation. This disruption in normal hematopoiesis results in marrow failure and the suppression of healthy blood cell production [1, 2]. The leukemic process may arise from lymphoid progenitors of various lineages, giving rise to distinct subtypes such as B-cell ALL, T-cell ALL, or mixed-lineage leukemia, depending on the origin of the malignant clone [3].

ALL exhibits a high degree of biological variability, being driven by diverse genetic abnormalities that interfere with normal cell maturation and promote the unchecked proliferation of immature lymphoid precursors [4, 5].

This molecular heterogeneity plays a crucial role in determining risk categories, guiding prognosis, and shaping therapeutic decisions in clinical practice [6].

While ALL represents the most prevalent leukemia in pediatric patients—accounting for nearly 80% of childhood leukemia cases — its occurrence in adults is relatively rare, comprising approximately 20% of adult leukemia diagnoses [7, 8]. The application of intensive chemotherapy regimens in children has remarkably elevated survival rates, reaching as high as 90%, reflecting the advancements made through a deepened understanding of disease biology and treatment optimization in pediatric clinical trials [3, 9].

Adapting these pediatric treatment models to adult patients has led to improvements in achieving complete remission (CR); however, long-term disease-free survival (DFS) remains significantly lower in adults compared to children—estimated at 30-40% versus approximately 80%, respectively—highlighting the challenges and limitations of directly translating pediatric protocols to adult ALL management [10, 11].

Recent progress in the diagnostic approach to acute lymphoblastic leukemia (ALL) has been driven by advances in genomic profiling techniques, allowing for detailed biological classification of leukemic cells. This has significantly enhanced the accuracy of risk stratification and has facilitated the application of risk-oriented therapeutic strategies, incorporating optimized multi-agent chemotherapy protocols alongside targeted therapeutic agents [7, 12].

A transformative milestone in the treatment paradigm of ALL was the introduction of measurable or minimal residual disease (MRD) assessment, which has emerged as the most critical prognostic tool in determining patient outcomes and guiding treatment modifications [3, 13].

Comprehensive knowledge of the underlying molecular and cellular mechanisms of the disease has become fundamental in managing ALL, enabling clinicians to tailor treatment protocols to the individual characteristics of each patient. This personalized approach is essential because the biological behavior and therapeutic response vary widely among patients, thus laying the groundwork for the development and incorporation of targeted therapies and novel pharmacological agents [14].

The incorporation of targeted therapy into treatment regimens has notably enhanced survival outcomes in adult patients with ALL [15]. Adoption of contemporary treatment strategies has led to substantial improvements in long-term survival rates—approaching 80% in cases of Burkitt's lymphoma, approximately 50% in patients with B-cell acute lymphoblastic leukemia (B-ALL), and between 50% to 60% in those diagnosed with Philadelphia chromosome-positive ALL or T-cell ALL (T-ALL) [7]. Furthermore, employing intensified pediatric-inspired chemotherapy protocols in adolescent and young adult (AYA) ALL patients has resulted in complete remission (CR) rates of about 85-90%, with long-term event-free survival (EFS) and overall survival (OS) rates reaching 60-70% [13, 16].

Central nervous system (CNS) involvement at initial ALL diagnosis is relatively uncommon, occurring in roughly 5-10% of patients [17]. Nevertheless, without the administration of CNS prophylaxis, the likelihood of CNS relapse rises sharply, with recurrence rates ranging from 50-75% within the first year following diagnosis. In contrast, implementing CNS-directed prophylactic measures can significantly reduce this relapse risk to approximately 5-10% [16, 18-20].

This study was conducted to evaluate the overall survival, progression-free survival, and relapse patterns among patients diagnosed with acute lymphoblastic leukemia (ALL) who received treatment at the Kasr Al-Ainy Centre of Clinical Oncology and Nuclear Medicine (NEMROCK) during the period spanning January 2015 to December 2020.

The primary objectives of the study included assessing the complete remission rates and disease-free survival in adult patients with ALL, in addition to determining the distribution of different ALL subtypes within the studied population.

Secondary objectives focused on investigating the incidence of central nervous system (CNS) relapse as part of the outcome analysis.

Materials and Methods

This study retrospectively examined 42 individuals who were newly diagnosed with acute lymphoblastic leukemia (ALL) between January 2015 and December 2020. The patients were treated at the Kasr Al-Ainy Centre of Clinical Oncology and Nuclear Medicine (NEMROCK) under a variety of treatment protocols, all sharing a common foundational structure but differing in their intensity and scheduling. The diagnosis of ALL was

established by the presence of blasts in peripheral blood or more than 20% lymphoblasts in bone marrow samples. This diagnosis was further confirmed through immunophenotyping, along with cytogenetic and/or molecular analyses.

Eligibility criteria

Inclusion criteria

1. Adults aged between 18 and 60 years who have been diagnosed with acute lymphoblastic leukemia (ALL). Patients older than 60 years are excluded as they generally receive palliative care rather than curative treatment.
2. Individuals diagnosed with either B-cell or T-cell ALL.
3. Patients with stable and manageable comorbidities that permit the administration of intensive chemotherapy.
4. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status ranging from 0 to 2.

Exclusion criteria

1. Patients whose diagnostic, follow-up, or treatment outcome data is incomplete or inadequate.
2. Individuals who do not satisfy the inclusion criteria.

Treatment protocol

The majority of patients received treatment based on the "Spanish protocol" (modeled after the PETHMA ALL-96 protocol) **(Table 1)**. Other treatment approaches included APO, MRC UK ALL, Hyper-CVAD, and REZ-BFM regimens. For those who tested positive for the Philadelphia chromosome, imatinib or dasatinib was integrated into their treatment plan. Supportive care was provided to all patients throughout the follow-up phase.

Table 1. Spanish protocol

Drug	**Induction phase**
Vincristine 2 mg. IV	On days 1,8,15,22
Doxorubicin 25 mg/m2	On days 1,8,15,22
Asparaginase 10,000 IU/m2	On days 10-12, 17-19, 24-26
Cyclophosphamide 1000 mg/m2	On day 36
Prednisone 60 mg/m2	From D1 to 28
CNS prophylaxis: D1, D29 IT methotrexate 15 mg + hydrocortisone 20 mg + ARA-C 30 mg.	
Drugs	Consolidation I
6-mercaptopurin 50 mg/m2 po	From D1-D7
Methotrexate 3 gm/m2 with leucovorin rescue	On days 1,28,56
VP 16 150 mg/m2 IV	On days 14,42
ARA-C 500 mg/m2 IV	On days 14-15, 42-43
CNS prophylaxis: D1, D29 IT methotrexate 15 mg + hydrocortisone 20 mg + ARA-C 30 mg.	
Drugs	Consolidation II
Vincristine 2 mg IV	On days 1,8,15
Doxorubicin 25 mg/m2	On days 1-2, 8-9, 15
Asparaginase 10,000 IU/m2	On days 1-3, 15-17
Cyclophosphamide 600 mg/m2	On days 1, 15
Dexamethasone 10 mg/m2 then 5 mg/m2	On days d1-14, then d15-21
CNS prophylaxis: D1, D29 IT methotrexate 15 mg + hydrocortisone 20 mg + ARA-C 30 mg.	
Drugs	Maintenance

Methotrexate 20 mg/m2	Weekly from week 1-52
Mercaptopurine 50 mg/m2	Daily from weeks 1-52

Data collection

The data for this study were obtained by reviewing the electronic medical records at the Kasr Al-Ainy Centre of Clinical Oncology. Any records with incomplete information (7 patients) were excluded from the analysis. To ensure patient privacy, each record was assigned a unique identifier. All collected data were stored securely and could only be accessed by the study team. No external parties, except for the REC and health authorities, were granted access to identifiable patient data. Since the data were extracted from existing records without any direct intervention, there were no anticipated risks to patients. The data included patient demographics, medical history, physical examination results, and initial laboratory tests, such as complete blood count (CBC), bone marrow aspiration (BMA), cytogenetics, immunophenotyping, BCR-ABL1 testing, and details about the treatment regimens and follow-up information.

Follow-up

Patients were monitored regularly during treatment, either while admitted to the hospital or through outpatient visits. The assessment of treatment response included CBC and BMA, conducted according to the prescribed treatment timeline, alongside routine lab tests, physical exams, and subjective assessments of the patient's condition. Patients were followed through the various phases of treatment: induction, consolidation, and maintenance. BCR-ABL1-positive patients had specific follow-up testing, while others were monitored with CBC, BMA, and detailed history for any signs of relapse.

Treatment response

Treatment responses were evaluated at key stages throughout the treatment process.

- *Complete remission (CR)*: Defined as fewer than 5% blasts in bone marrow with no detectable blasts in the peripheral blood smear and normalization of the blood counts [21].
- *Refractory disease*: Diagnosed when complete remission was not achieved by the end of the induction phase [21].
- *Relapse*: Identified by the reappearance of blasts in peripheral blood or bone marrow, the detection of lymphoblasts in cerebrospinal fluid cytology, or the emergence of CNS symptoms indicating relapse after achieving CR [21].

Outcomes

- Primary outcomes (core measurable outcomes):
  1. Achieving complete remission (CR), as assessed by bone marrow aspirate and biopsy, and the disease-free survival rate in adults with ALL.
  2. Identifying the frequency of different subtypes of ALL.

- Secondary outcome parameters (other assessed outcomes):
  1. The occurrence rate of CNS relapse.

Statistical analysis

The analysis of data will be performed with SPSS version 22. For continuous variables such as age and BMI, results will be expressed as mean ± standard deviation, and the Student's t-test will be used for comparison. Categorical variables will be presented as counts and percentages, with the chi-square test employed for comparison. To evaluate survival, both the Log-rank test and Kaplan-Meier survival curves will be utilized. Logistic regression analysis will assess the impact of risk factors on relapse and mortality, accounting for confounding variables. A P-value less than 0.05 will be considered statistically significant.

Results and Discussion

Demographic overview of the patients

In this retrospective study, we analyzed data from 35 patients diagnosed with ALL. The average age of the participants was 33.7 ± 10.7 years, with an age range spanning from 21 to 55 years. Among them, 62.9% were under 39 years of age, categorized as adolescents and young adults (AYAs), while the remaining 37.1% were older than 39 years. The cohort consisted of 45.7% females and 54.3% males. A comprehensive breakdown of patient characteristics and their initial clinical presentation is provided in **Tables 2 and 3**.

Table 2. Patients' characteristics.

		Median/ count	SD/ percent
Age (years)		33.7	10.7
Age groups	< 39 years	22	62.9%
	≥ 39 years	13	37.1%
Comorbidities	No	27	77.1%
	Yes	8	22.9%
Type of comorbidity	None	27	77.1%
	Bronchial asthma	1	2.9%
	Diabetes	1	2.9%
	Drug addict	1	2.9%
	Down syndrome	1	2.9%
	HCV	2	5.8%
	Hypertension	1	2.9%
	Rheumatoid arthritis	1	2.9%
Virology	No	32	91.4%
	Yes	3	8.8%
Type	Free	32	91.4%
	CMV	1	2.9%
	HCV	2	5.7%

Table 3. Initial presentations among the included patients.

		Median (count)	SD (%)
Constitutional	No	8	22.9%
	Yes	27	77.1%
Initial symptoms	No associated symptoms	21	60.0%
	Dyspnea	2	5.7%
	Headache	1	2.9%
	HSM	2	5.7%
	Hypertension	1	2.9%
	Jaundice	2	5.7%
	Lymphadenopathy	4	11.4%
	Multi-organ failure	1	2.9%
	Skin lesions	1	2.9%
Extra nodal	No	28	80.0%
	Yes	7	20.0%
Site	No	28	80.0%
	Brain	1	2.9%
	GIT	1	2.9%
	Kidney	1	2.9%
	Liver	1	2.9%
	Lung	1	2.9%
	Mediastinal	1	2.9%
	Skin lesions	1	2.9%

CNS involvement	No	33	94.3%
	Yes	2	5.7%

The median total leukocyte count (TLC) observed was 22 x10^3/cc, with values ranging from 2.8 to 355 x10^3/cc. Of the 26 B-cell ALL patients, 21 had initial TLC data, with 10 of them showing levels above 30,000. Among the 9 T-cell ALL patients, initial TLC was available for 5, and only one exhibited a TLC higher than 100,000. Bone marrow aspiration and biopsy indicated that the median percentage of blasts in the bone marrow was 95%, with a range from 30% to 100%. Out of the total cohort, 74.3% (26 patients) had B-cell leukemia, while 25.7% (9 patients) had T-cell leukemia. In terms of cytogenetic findings, 65.85% (18 patients) were negative for the Philadelphia chromosome, whereas 22.9% (8 patients) tested positive. Among the B-cell ALL subgroup, 30.7% (8 patients) were BCR-ABL1 positive, and 69.2% (18 patients) were BCR-ABL1 negative.

Management and response evaluation

Induction therapy for the majority of participants (82.9%, n = 29) followed the Spanish protocol, while alternative regimens such as APO, Hyper-CVAD, MRC UK ALL, and REZ-BFM were also utilized. A total of 22 patients (62.9%) had interruptions in their treatment course; these were primarily due to infections in 8 patients, neutropenia in 4, and refractory disease in 3. Among the 8 patients with BCR-ABL1 positivity, 7 received imatinib, and 1 was treated with dasatinib. All patients underwent CNS prophylaxis through intrathecal therapy, either doublet or triplet [22].

Of the 23 patients who achieved CR, subsequent consolidation therapy was administered. The 12 patients who showed refractory disease were assigned to re-induction; however, only 3 of these patients achieved CR, bringing the total CR rate to 74.2% (26 patients) out of 35.

Relapse data

Of the 26 patients who achieved CR (either after the first or second induction), 17 (65.3%) experienced relapse. Among these, 8 (47%) had medullary relapse, 7 (41%) had both medullary and extra-medullary relapse, and 2 (11.7%) had isolated extra-medullary relapse. The median disease-free survival (DFS) for these patients was 13 months. CNS relapse occurred in 9 of the 17 relapsed patients, and 3 of these relapsed within a year from diagnosis. Six patients (23%) retained their CR, including 5 with B-cell ALL (3 of whom were Philadelphia-positive and on tyrosine kinase inhibitors) and 1 with T-cell ALL. Follow-up was not available for 3 patients.

In terms of CNS involvement, 11 patients (31.4%) developed CNS relapse. Of these, 9 had relapsed after achieving CR, and 2 developed CNS issues during refractory disease.

Survival analysis

The median overall survival (OS) was found to be 14.4 months (95% CI 11.5–17.3), significantly influenced by the achievement of CR after the first induction. Patients who achieved CR had a median OS of 17.9 months, while those who were refractory had an OS of 5.3 months, with a P-value of 0.02 **(Figure 1)**. Of the total cohort, 11 patients (31.4%) survived for 2 years or more.

Among the clinical factors examined, age, leukemia subtype, comorbidities, and both nodal and extra-nodal involvement did not significantly impact OS. The initial total leukocyte count (TLC) for B-cell ALL, however, was a significant factor for OS, though TLC in T-cell ALL did not have a statistically significant effect. For patients with initial TLC over 100,000, the median OS was 8.7 months, compared to 11.8 months for those with a TLC under 100,000, with a P-value of 0.083.

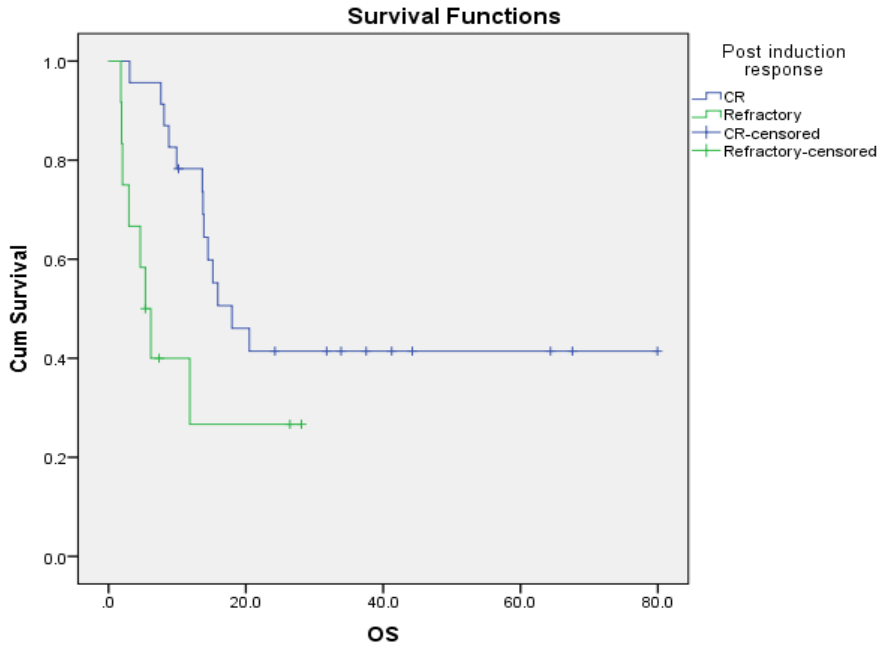

Figure 1. Kaplan Meier curve showing OS in months according to the post-induction response.

The initial total leukocyte count (TLC) in B-cell ALL patients was found to significantly influence overall survival (OS). Patients presenting with a TLC lower than 30,000 had a notably better OS, with a statistically significant P-value of 0.03 **(Figure 2)**.

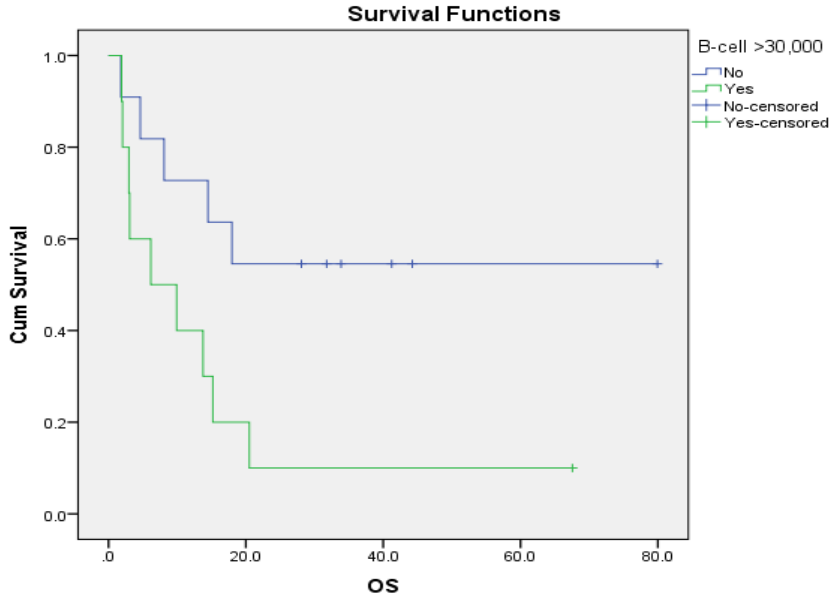

Figure 2. Kaplan Meier curve showing OS in months according to initial TLC in B-cell ALL.

There was no important difference in overall survival (OS) based on the subtype of acute lymphoblastic leukemia (ALL), with a P-value of 0.63. While patients with BCR-ABL positivity exhibited a trend toward improved OS, the difference was not statistically significant. The median OS for BCR-ABL positive patients was not reached during the study period, while BCR-ABL negative patients had a median OS of 13.6 months (P-value = 0.056). The disease-free survival (DFS) had a median value of 13.3 months and was significantly influenced by achieving complete remission (CR) following the first induction phase. Patients who reached CR had a longer DFS of 21.6 months, while those with refractory disease after induction had a much shorter DFS of 4.2 months (P-value =

0.005), **(Figure 3)**. Moreover, those who achieved two years of survival had a markedly longer DFS, with a median of 29.9 months compared to 7.7 months in patients who did not survive for two years.

Although initial total leukocyte count (TLC) did not show a significant impact on DFS across the cohort, patients with B-cell ALL presenting with TLC higher than 30,000 had a shorter median DFS of 8.5 months compared to 29.9 months in those with TLC below 30,000 (P-value = 0.070). Similarly, in T-cell ALL patients, although initial TLC did not significantly influence DFS, those with TLC greater than 100,000 had a considerably shorter DFS (2 months) compared to 13.3 months in those with TLC below this threshold (P-value = 0.083). Factors such as comorbidities, age, disease subtype, BCR-ABL status, nodal and extra-nodal involvement, and treatment interruptions during induction had no significant effect on DFS.

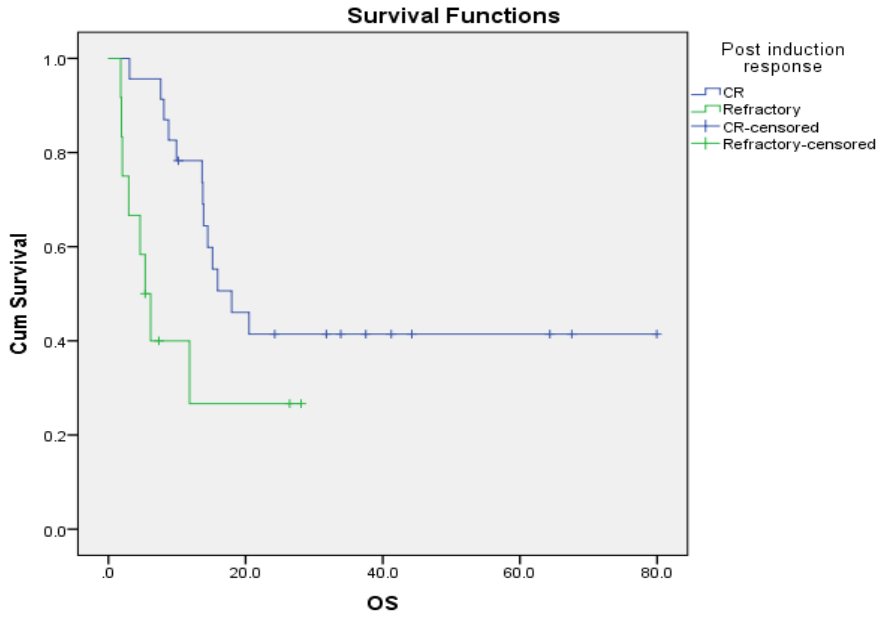

Figure 3. Kaplan Meier curve showing DFS in months according to response after induction protocol

Acute lymphoblastic leukemia (ALL) is a rare disease in adults, making up about 1% of all malignancies and around 20% of adult leukemias [21]. Despite its rarity, it remains a serious condition with long-term survival rates of only 30-40%. The adolescents and young adults (AYAs) group, aged 16 to 39 years, has garnered significant interest in recent years, as this group may have a different biological profile compared to older adults [16]. A major point of debate has been whether these patients should receive pediatric or adult treatment protocols [23]. Several studies have found that pediatric protocols tend to result in better survival rates for AYAs [24]. In a meta-analysis of 11 comparative studies, those treated with pediatric regimens had lower relapse rates, comparable non-relapse mortality, and better disease-free survival (DFS) than those who were treated with adult regimens [25].

In our study, we included 35 patients with newly diagnosed ALL. The mean age of the participants was 33.7 ± 10.7 years (ranging from 21 to 55 years), with 62.9% of them being under 39 years of age, classifying them as AYAs. The immunophenotyping revealed that 74.3% of patients had B-cell ALL, while 25.7% had T-cell ALL, which aligns with existing literature indicating that T-cell ALL is more common in adults, reaching up to 25% [13]. About 23% of patients in our study were Philadelphia chromosome-positive (Ph+), consistent with data showing that BCR-ABL1 expression is more frequent in adults, affecting 15-30% of adult B-cell ALL cases, and as much as 50% in individuals aged 50 and above [18].

Most patients in our cohort belonged to the AYA category. Of the 26 patients with available data on initial total leukocyte count (TLC), 11 exhibited high-risk TLC levels, and 8 were BCR-ABL1 positive. The treatment protocol followed was based on the PETHMA ALL-96 regimen, which was designed for standard-risk patients (SR ALL). This protocol was intended for adolescents (15-18 years) and young adults (19-30 years) with specific criteria, including a white blood cell count no greater than $30x10^9/L$ and the absence of certain chromosomal abnormalities such as t(9;22), t(1;19), t(4;11), or 11q23 rearrangements [26].

The results in our study were not as favorable as those reported in the original PETHMA ALL-96 trial, though they were similar to those observed in historical studies using adult-based regimens, which often involve lower

cumulative doses of L-asparaginase and steroids [14]. In our cohort, the complete remission (CR) rate after the first induction was 65.7%, which increased to 74.2% after the second induction. However, in the PETHMA ALL-96 trial, the CR rate was 98%. Among our patients, 65.3% relapsed, and the median overall survival (OS) was 14.4 months, compared to 4.2 years in the PETHMA study. The median disease-free survival (DFS) in our cohort was 13.3 months, compared to 6 years with 61% DFS in the PETHMA study. Two-year DFS was 42.8% and two-year OS was 60%, with these figures decreasing to 31.4% over time.

The variation in results between our study and the PETHMA trial could be attributed to differences in the risk stratification methods used in the two studies. Both studies shared the limitation of not incorporating minimal residual disease (MRD) testing, which has become a crucial prognostic factor in ALL management. MRD testing helps to identify high-risk patients who would benefit from hematopoietic stem cell transplantation (HSCT) [27]. This was highlighted in the LALA-94 and PETHMA ALL-93 trials, where patients undergoing HSCT showed better outcomes, especially those with high-risk features or poor MRD responses [26].

In our cohort, only 4 patients had matched sibling donors, and just one patient underwent HSCT. Unfortunately, the other 3 patients relapsed while awaiting transplantation [28]. Our study also highlighted that the initial TLC in B-cell ALL significantly influenced OS. Though no statistically significant differences were observed in T-cell ALL, those with lower TLC levels generally had better outcomes. This trend could be attributed to the small sample size in our study [29]. This emphasizes the importance of using initial TLC as a prognostic factor, suggesting that patients with high TLC should be classified as high-risk and treated with intensified regimens for improved survival [30, 31].

Conclusion

Although the survival rates observed in our study are somewhat aligned with historical data on adult ALL, they fall short when compared to studies employing the same treatment protocols. This difference can largely be attributed to variations in risk stratification between our cohort and those in the other studies. This highlights the need for the development of more effective strategies to improve patient outcomes. Tailoring treatment based on personalized risk assessments before and during therapy is crucial, with minimal residual disease (MRD) testing now considered a standard practice in the management of ALL. Additionally, applying more aggressive chemotherapy protocols combined with adequate supportive care could yield better results, particularly when considering the patient's age and initial risk categorization.

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