RESEARCH ARTICLE

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A Survival Analysis of Pediatric Acute Lymphoblastic Leukemia in Morocco

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Abstract

Background: As a WHO's Global Initiative for Childhood Cancer pilot site, Morocco conducted a study on the overall survival rates of the six WHO index diseases. The objectives of this study were to estimate the survival rates for childhood acute lymphoblastic leukemia (ALL) diagnosed at Moroccan Pediatric Hematology and Oncology (PHO) centers, to identify factors of treatment failure, and to explore opportunities for improvement. **Methods:** This retrospective study included children with ALL aged 0-15 years. Patients were monitored with active follow-up until March 31, 2023. The Kaplan Meier method was used to estimate survival rates, the log-rank test to compare survival, and the Cox model to identify prognostic factors. **Results:** Data included 425 patients; most were aged 1-10years (n=318, 74.9%), and males (n=239, 56.2%). The complete remission induction rate was 84%. One-, three- and five-year overall survival rates were 78.7%, 63.8% and 60.8%, respectively. In a multivariate Cox model regression, age group, phenotype, complete remission following induction and white blood cell count > 50,000/mm^3 were statistically associated with survival. Children with T-cell ALL were also more likely to die compared to those with B-cell ALL (HR=2.33 p<0.001). **Conclusion:** The 5-year survival rate in our study was 60.8%, below Morocco's 80% target by 2030. Among 203 events, 86 were relapses, 34 resulted from treatment abandonment, and 55 from treatment-related toxicity. While relapse is the leading cause of treatment failure, prioritizing the reduction of treatment abandonment and toxicity-related mortality is a more feasible first step.

Keywords: Acute Lymphoblastic Leukemia- pediatric- survival- Morocco

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Introduction

In 2018, the World Health Organization (WHO), along with key partners such as St Jude Global Pediatric Medicine and the International Society of Pediatric Oncology, launched the Global Initiative for Childhood Cancer (GICC) to provide governments with leadership and technical assistance in building and maintaining high-quality childhood cancer programs [1]. By 2030, the GICC aims to reduce suffering worldwide and increase the survival rate for all children with cancer to at least 60% [1]. Acute lymphoblastic leukemia (ALL), Burkitt's lymphoma, Hodgkin lymphoma, retinoblastoma, nephroblastoma or Wilms tumor, and low-grade gliomas

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were the six frequent index malignancies that were selected for initial focus within the GICC.

Morocco was chosen as a GICC implementation focus nation in October 2019. However, the first challenge encountered in the initiative's implementation was the absence of precise data on the epidemiology and survival of children cancer. Childhood malignancies (0–14 years old) accounted for 1.7% of all cancer cases, with an annual incidence of 12.1 per 100,000 children, according to statistics from the Rabat Cancer Registry [2]. According to data from the Grand Casablanca cancer registry, childhood malignancies had an incidence of 12.7 per 100,000 children, representing 3% of all cancers [3]. Since neither registry included survival statistics, it was challenging to establish specific goals and create a plan for 2030.

In 2020, the Ministry of Health, in collaboration with the Moroccan Society of Pediatric Hematology and Oncology (SMHOP), conducted the first national study on childhood cancer survival. Results showed an overall three-year survival rate of 68.2% and an event-free survival rate of 62.3%. The three-year survival rate for ALL was 61.5% [4].

Five-year survival rates may be analyzed thanks to the longer follow-up duration of the data from this study. Additionally, this study enables a more thorough analysis of ALL-related deaths and the variables linked to treatment failure and mortality.

The aim of this study is to estimate the survival rates for childhood ALL diagnosed at Moroccan Pediatric Hematology and Oncology (PHO) centers from January 1, 2017 to December 31, 2019 and to identify factors of treatment failure.

Materials and Methods

Study Design and Population

This retrospective study included the same population (children up to 15 years, diagnosed with ALL between January 1, 2017, and December 31, 2019, within the six Moroccan PHO units) as the initial baseline study conducted for the WHO GICC pilot [4], in addition to other pediatric ALL patients handled in Marrakech Hospital's adult hematology department. The six PHO units were referenced as Care Center numbers 1-6. Patients were monitored with active follow-up until March 31, 2023. Children were excluded if they had cancers other than ALL, were older than 15 years or diagnosed before 2017 or after 2019, or if there wasn't enough information in the patient's medical records. Duplicates patient were removed from analysis.

The diagnosis was based on morphological evaluation of wright-stained smears of bone marrow if at least 20 % lymphoblasts were present. Immunophenotyping was used to confirm the diagnosis of ALL according the WHO classification [5].

Most patients were treated according to the national protocol, "MARALL-06" (MAR: for Maroc and ALL: For acute lymphoblastic leukemia) (Supplementary figure). The stratification criteria were initial criteria at baseline. Subsequently, corticosteroid-resistant patients defined as blasts >1000 cells/mm³ in peripheral blood on day 8 were reclassified as high risk (HR) (Supplementary Table). Treatment included induction, consolidation, intensification and interphase courses (11 months) followed by maintenance (two years). The induction therapy was based on 4 drugs : vincristine, daunomycine, L-Aspa, steroids and IT-methotrexate [6] (supplementary figure). Induction lasts between 36 and 40 days. After both groups recover from aplasia, remission is evaluated starting on day 42. If a patient has a normal clinical examination, a normal blood cell count, and a rich bone marrow with blasts <5% at the medullary level, he is considered in complete morphological remission. Since Minimal Residual Disease (MRD) testing is not available in our environment, it was not included in the protocol.

Patients were systematically hospitalized during the induction phase for at least the first three weeks. Afterwards, management was adapted on a case-by-case basis, depending on treatment tolerance and the family's socio-economic profile. In collaboration with Non-Governmental Organizations (NGOs), all patients had access to a life house, a facility for parents providing lodging, food, and transportation, with a symbolic contribution.

Data Collection

Data managers were recruited and trained to extract data from eligible patient medical records. Data variables included age, gender, place of residence, the health insurance coverage, cancer type/subtype, blood test results, karyotype results, date and type of event, survival status and date of last contact. Data regarding events was collected from the medical records and the vital status information was gathered from parents over the phone when the last hospital contact date was far from the endpoint date. The date of diagnosis served as the study's start date, and February 28, 2022, was the end point date.

The place of residence was useful to calculate the distance to the care center corresponding to the distance between the city of residence and the city where the hospital is located. This distance was calculated by google maps. The threshold used to separate patients leaving near of far from the care center was 100 Km (<100Km/ ≥ 100Km).

Regarding health insurance coverage in Morocco, two basic medical coverage plans were created in 2002: the Basic Compulsory Health Insurance (CHI) and the Medical Assistance Plan (RAMED). CHI is based on the principles and techniques of social insurance benefiting employed and retired people. RAMED is based on the principles of social assistance and national solidarity with impoverished people [7].

Data Analysis

Initially, mean and standard deviation or median and interquartile range were calculated for continuous variables while the categorical variables were represented by headcount and percentage.

We considered as events deaths, disease progression, relapse, and treatment abandonment. Abandonment was defined as missing treatment for a prolonged and uninterrupted period sufficient to compromise the potential

for cure or disease control (defined as a duration of 4 weeks in pediatric oncology) including "refusal to initiate curative therapy" as an abandonment as recommended by the International Society of Paediatric Oncology (ISPO) position statement [8]. Remission is defined as the absence of cancer cells in cellular examinations, indicating a positive outcome in cancer treatment (cytological remission) [9, 10].

A survival analysis was performed considering overall survival (OS) and event-free survival. The overall survival was based on the delay between diagnosis and death due to any cause, and the event-free survival (EFS) was based on the delay between the diagnosis and the occurrence of the first event (deaths, disease progression, relapse or treatment abandonment). The Kaplan Meier method was used to estimate survival rates, a log-rank test for comparing survival curves among classes, and a Cox regression model for identifying prognostic factors. Statistical significance was defined as a p-value < 0.05. All analyses were conducted using Jamovi

Ethical Aspects

The study was approved by the ethics committee of the Faculty of Medicine and Pharmacy of Rabat Mohamed V University.

Results

Patient demographics

Data from 425 patients with ALL at the six Moroccan pediatric oncology centers and one adult hematology unit were analysed, 2 children died before treatment initiation and 423 initiated treatment (Figure 1). The majority of children were aged > 1 to < 10 years (n=318, 74.9%), most patients were under RAMED medical coverage (n=273, 65.3%) and 200 children lived at a distance greater or equal to 100 kilometers from the care center (Table 1).

Clinical Presentation

At the time of initial presentation, 303 (71.3%) children had a tumoral syndrome, 16 (3.8%) had involvement of the central nervous system, 4 (0.9%) had testicular involvement, and 382 (89.9%) children showed symptoms of bone marrow failure (pancytopenia). 127 children had a white blood cell (WBC) count greater than 50,000 cells/mm^3, according to laboratory results. Bone marrow immunophenotyping showed that B-cell ALL was more common than T-cell ALL, with 73% and 27% of cases, respectively. 172 children (40.6%) underwent karyotyping, and 63 children (43.4%) had normal results. A total of 241 children (41.8%) were identified as having high risk ALL. 265 (62.3%) children had a good prednisone response at day 8, and 315 (84.0%) children had a full remission at the end of induction (Table 1).

Survival Analysis

One-year OS was 78.7%, three-year OS 63.8% and five-year OS 60.8% (Figure 2). One year EFS was 71.6%, three years EFS was 54.3% and five years EFS was 48.7%. (Table 2). Infants aged ≤1 year had the poorest one-year OS (44.4%), compared to children aged 1–10 years, whose one-year OS was 82.7% (p = 0.001).

Among the 155 recorded deaths, 2 occurred before the initiation of treatment, and 55 were classified as treatment-related mortality (defined by an international group of expert as death occurring in the absence of progressive) [11]. Among these deaths, the primary cause of death was infection (n=25, 45.4%), followed by neurological causes (n=9), respiratory causes (n=7), hemorrhage (n=5), and metabolic syndrome (n=3).

Children with B-cell ALL had better survival rates (67.8% 5-years) compared to those with T-cell ALL (43.5% 5-years), p<0.001 (Figure 3). A good prednisone response at day 8 was also associated with better outcomes (70.4% five-year OS, p < 0.001). Similarly, children who

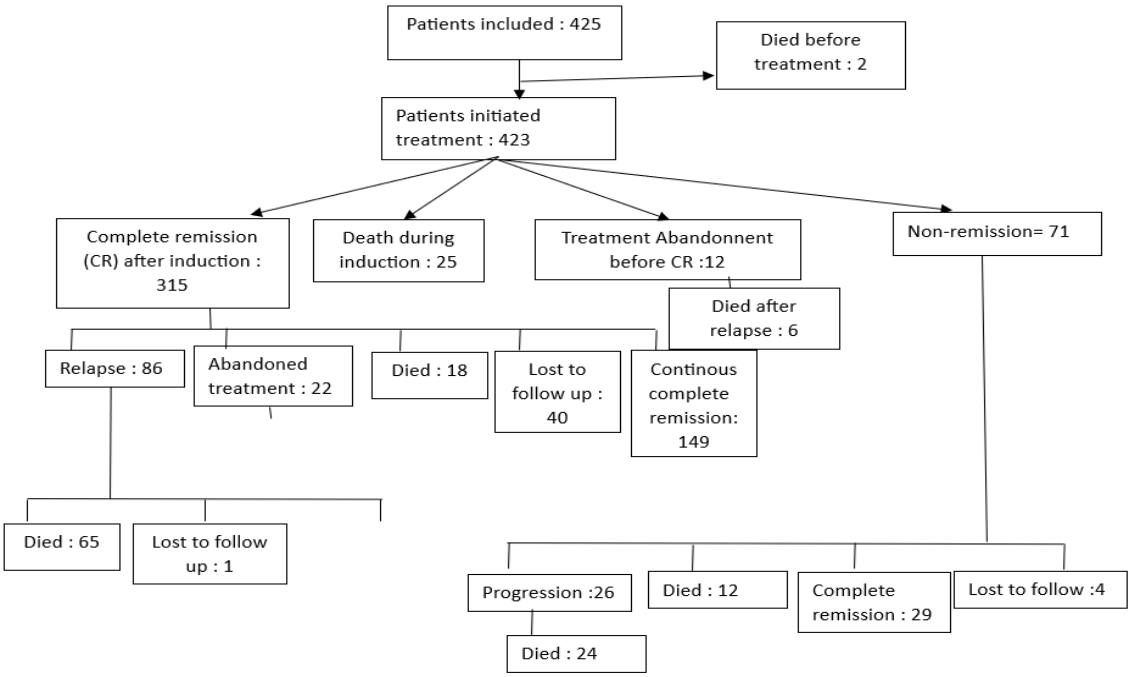

Figure 1. CONSORT Diagram for Patient Included in the Study

Table 1 . Characteristics of Children with acute Lymphoblastic Leukemia (ALL) Treated with MARALL 2006 Protocol

	N (%)
Age (Years)	
≤1	18 (04.2)
> 1 to < 10	318 (74.9)
≥ 10	89 (20.9)
Male	239 (56.2)
Medical coverage	
RAMED*	273 (65.3)
CHI**	126 (30.1)
None	19 (04.6)
Pediatric Oncology Center	
Center n°1	118(27.8)
Center n°2	73 (17.2)
Center n°3	42 (09.9)
Center n°4	77 (18.1)
Center n°5***	88 (20.7)
Center n°6	27 (06.3)
Distance from care center (Km)	
< 100	224 (52.8)
≥ 100	200 (47.2)
Pancytopenia	382 (89.9)
Tumoral syndrome	303 (71.3)
Central nervous system involvement	16 (03.8)
White blood cells ≥ 50 000/mm3	127 (30.0)
Tumor lysis syndrome	95 (22.4)
Immunophenotyping (n=412)	
ALL B	300 (73.2)
ALL T	108 (26.3)
ALL Bi-phenotypic / Undifferentiated	2 (00.5)
Protocols	
MARALL	350 (83.7)
Others	68 (16.3)
Risk groups	
Standard-risk group	173 (41.8)
High-risk group	241 (58.2)
Good prednisone response at day 8	265 (82.3)
Complete remission at end of induction	315 (84.0)

achieved complete remission at the end of induction had superior survival (69.9% five-year OS, p < 0.001) (Table 2).

In the multivariate Cox regression model, age group, phenotype, complete remission at the end of induction and WBC ≥ 50,000/mm³ were significantly associated with OS. Infants aged 1 year and below were more likely to die compared to those aged >1 to <10 (HR=4.84 p<0.001). Children with T-cell ALL were more likely to die compared to those with B cell ALL (HR=2.33 p<0.001). Conversely, a WBC count <50,000/mm³ and achievement of complete remission at the end of induction were associated with a lower risk of death (Table 3).

Table 2. Survival Analysis for Children with Acute Lymphoblastic Leukemia in Morocco 2017-2019

Characteristics	1-year survival (%)	3-year Survival (%)	5-year Survival (%)	p
Overall survival	78.7	63.8	60.8	
Event-free survival	71.6	54.3	48.7	
Age (years)				<0.001
≤1	44.4	16.7	-	
>1 to < 10	82.7	69.9	65.9	
≥ 10	70.6	51.9	51.9	
Sex				0.560
Male	78.4	62.6	58.9	
Female	78.5	65.5	63.6	
Medical coverage				0.750
RAMED*	77.7	63.1	59.8	
CHI**	80.7	66.4	63.6	
None	83.0	65.2	65.2	
Distance from care center (Km)				0.089
< 100	79.9	68.1	65.0	
≥ 100	76.8	58.8	55.9	
Phenotype				<0.001
B-cell acute l ymphoblastic leukemia	85.1	70.7	67.8	
T-cell acute lymphoblastic leukemia	64.1	47.5	43.5	
White blood cells				<0.001
< 50,000/mm³	63.4	45.2	45.2	
≥ 50,000/mm³	85.3	72.1	68.0	
Good prednisone response at day 8				<0,001
Yes	84.7	73.4	70.4	
No	69.6	43.2	-	
Complete remission at end of induction				<0,001
Yes	87.2	73.9	69.9	
No	68.9	46.1	46.1	

*RAMED, Régime d'Assistance Médicale; **CHI, Compulsory Health Insurance

Table 3. Factors Associated with Survival Analyzed Using Multivariate Cox Model

	Adjusted HR (95% CI)	p*
Age (years)		
>1 to <10	1	
≥ 10	1,18 (0.71 – 1.95)	0.525
≤1	4,84 (2.95 – 11.42)	<0001
Sex (female/male)	0.88 (0.56 – 1.39)	0.576
GB (mm³) ≥50,000	1.62 (1 .01 – 2.62)	0.046
Phenotype (T-cell/B-cell)	2.33 (1.43 – 3.78)	0.001
Complete remission at end of induction (Yes/No)	0.45 (0.27 – 0.76)	0.003
Good prednisone response at day 8 (Yes/No)	0.73 (0.43 – 1.22)	0.232

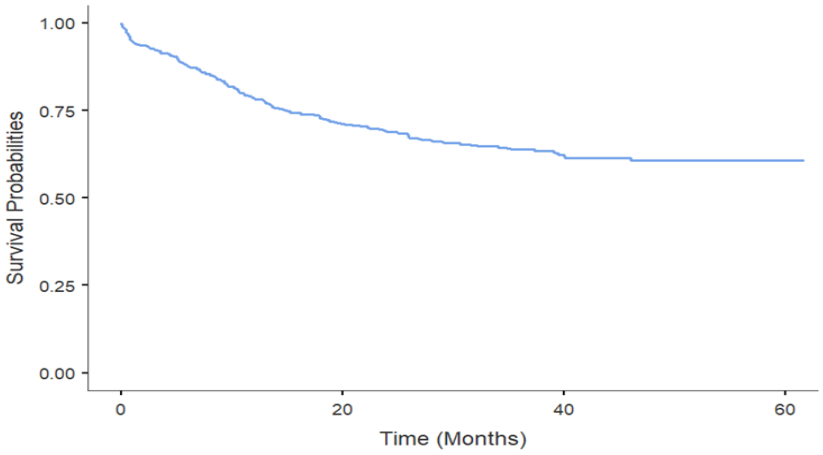

Figure 2. Overall Survival Curve for Children with Acute Lymphoblastic Leukemia in Morocco 2017-2019

Discussion

As a WHO pilot country for the GICC, Morocco should prioritize improving childhood cancer survival by conducting survival analyses of the six WHO index cancers, starting with an investigation into failure factors in ALL, the most common pediatric malignancy.

Our study included 425 cases treated at the six Moroccan pediatric oncology centers and one adult hematology department for ALL. Among the study sample, 75% of patients were aged >1 to <10 years old and patients aged 10 and over accounted for 21%. The proportion of male patients was 56% in this study with a male/female ratio of 1.28. This slight increase male/female ratio has also been reported by both high and low/middle-income countries [11-13,15].

A WBC count above 50,000/mm^3 at diagnosis was noted in 30% of the children. The proportion of children with T-cell ALL in this study was 26 %, which is still higher than reported by most low- and middle-income countries [14-17]. The prevalence of T-cell ALL has been reported to range from approximately 17.4% to 26.6% in Western European countries, the United States of America (USA) and Egypt [11,18,19].

An ALL diagnosis was based on morphological evaluation of Wright-stained bone marrow smears characterized by more than 20% blasts. Immunophenotyping was conducted with bone marrow or blood from 412 children (97%). The majority of children were treated according to the national therapy protocol MARALL 2006 (83,7%), which was adapted from the French protocol FRALLE 2000 (FRALLE = FRench Acute Lymphoblastic Leukemia) that includes SR and HR groups. Regarding the distribution of risk groups, a higher proportion of patients were allocated to the HR group (58%) than the standard risk (SR) group [11–13].

Induction failure is uncommon in the treatment of ALL, with approximately 98% of children achieving remission according to published data [11-13]. In our study, the remission rate at the end of induction was 84%, which is notably lower than rates reported in European studies, in Turkey and the USA [11,14]. This low remission rate after induction can be explained by several factors: High-risk patients (58%), poor prognosis of T-ALL that represent 26% of all patients, the lack of a specialized protocol for infants since the national protocole inadequate for children under one year old and also the treatment is not stratified based on specific cytogenetic anomalies. Moreover, in some cases, the blasts observed in the bone marrow at the end of induction may be regenerating blasts,

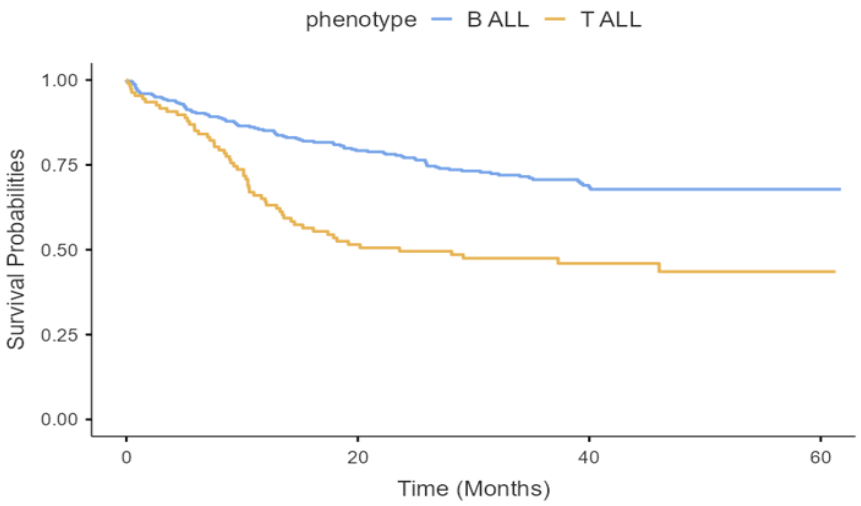

Figure 3. T and B cell ALL Survival Curves for Children with Acute Lymphoblastic Leukemia in Morocco 2017-2019

requiring immunophenotyping that was not previously performed. These results underline the importance of better stratification of risk groups by MRD, which is a more refined way of determining in vivo response at certain time points [20, 21].

In the current study, five-year EFS and OS was 48.7 and 60.8% respectively. Our results are similar to the results reported from countries with limited resources [15,16]. However, approximately 85% of patients aged 1-18 years with newly diagnosed ALL treated on current regimens in developed countries are expected to be long-term event-free survivors, with more than 90% of patients alive at five years [22].

The death rate was found to be 36,5 % in this study, which was rather high compared to those reported in well-resourced settings [11,12,17]. The most common cause of treatment-related mortality in this study was infection (n=25, 43.9%), which continues to be a major problem in countries with limited supportive care equipment and resources [13,15,16]. Significant efforts are required to reduce the high infection rate in these countries including training for specialized nurses, caregiver education, e.g., food preparation and nutritional counseling, and access to supportive care products and medications such as antifungal and antiviral.

Although more than 85% of children with ALL survive without relapse following contemporary therapies in well-resourced settings, survival following relapse is poor in Morocco and similar countries [13,15,16]. In our study, the relapse was the first cause of treatment failure (86/425), probably due to the lack of accurate risk stratification tools, such as genetic and molecular studies and MRD assessments. It is also noteworthy that, consistent with findings from other African settings, the prevalence of high-risk ALL, especially T-cell ALL, is elevated in our study [23].

The treatment of relapsed childhood ALL remains particularly challenging, as it requires high-intensity therapy to achieve and maintain a second remission. However, in our setting, further intensification of conventional chemotherapy without corresponding improvements in supportive care resources would likely lead to an increased risk of fatal treatment-related complications; therefore, novel therapies with reduced toxicity and aggressive supportive care management with existing resources are important to improve survival in relapsed childhood ALL across Morocco. Immunotherapy approaches, especially antibody therapy (with blinatumomab and inotuzumab) and the use of chimeric antigen receptor (CAR) T cells are necessary to significantly improve ALL survival [12, 24].

In Morocco, robust family support and universal healthcare coverage likely reduce the influence of factors such as geographic distance from treatment centers, which may otherwise affect outcomes. The overall treatment abandonment rate was 8%, this low rate made possible through the dedicated efforts of healthcare teams and partner organizations. Given that treatment abandonment has long been recognized as a major contributor to treatment failure in Morocco, targeted strategies have been implemented to address this issue. These include the establishment of international partnerships and improved access to supportive services such as the “Life House” [25]. As demonstrated by the study conducted in Morocco, beyond medical protocols and timely treatment, providing emotional and logistical support helps prevent treatment abandonment [26].

We can highlight some limitations of our study :

- This is a retrospective study depending on the quality of data from medical records that can be different among the 6 different units included.
- Teams from different Units/centers are with different backgrounds and varying levels of expertise
- Patients aged 15 to 18 years were not included, as they are managed in adult hematology departments
- The national protocol is not adapted for infants.
- The protocol did not take karyotyping into account neither MRD

However, the strengths of our study are the following :

- This is a nationwide study in Morocco that includes data from all hemato-oncology units/centers
- The study provides valuable insights into the five-year survival rate of children with ALL, as well as prognostic factors and causes of death in this population
- This is an African study that strengthens knowledge on ALL in Africa
- There is a limited data available in francophone countries, this study contributes to a significant knowledge gap being addressed

In conclusion, the five-year overall survival rate in our study was 60.8%, which is below Morocco’s 80% target by 2030. Among 203 events, 86 were relapses, 34 resulted from treatment abandonment, and 55 from treatment-related toxicity. While relapse was the leading cause of treatment failure, prioritizing the reduction of treatment abandonment and toxicity-related mortality is a more feasible first step. A targeted strategy should focus on addressing the most preventable factors to improve outcomes.

Author Contribution Statement

Each author has participated sufficiently in the design, or analysis and interpretation of this research. All authors have approved the final version of the paper.

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Availability of data

Due to the confidential nature of the data, the dataset is not publicly available

Conflict of interest

The authors declare no conflict of interest.

Ethical aspects

The study was approved by the ethics committee of the Faculty of Medicine and Pharmacy of Rabat Mohamed V University

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