Survival Outcomes in Adult Acute Lymphoblastic Leukemia at a Third-Level Hospital in Ecuador

Resultados de Supervivencia en Leucemia Linfoblástica Aguda del Adulto en un Hospital de Tercer Nivel en Ecuador

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Abstract

Background: Adult acute lymphoblastic leukemia in Latin America poses distinct clinical and epidemiological challenges, compounded by the limited availability of region-specific data. This study aimed to assess five-year overall survival and relapse-free survival in patients treated with intensive chemotherapy, to systematically characterize treatment-related complications, to identify prognostic factors associated with clinical outcomes, and to delineate the clinical and demographic profiles of the study population.
Methods: A retrospective observational study was conducted in 127 adult patients diagnosed with acute lymphoblastic leukemia who were treated with intensive chemotherapy. Demographic, clinical, cytogenetic, and treatment-related variables, as well as survival outcomes, were systematically analyzed.
Results: The median age at diagnosis was 33 years, with 63.7% of patients younger than 40 years. The complete remission rate following induction therapy was 58.5%. Induction-related mortality reached 26.7%, predominantly attributable to sepsis caused by carbapenemase-producing Klebsiella pneumoniae, which accounted for 67.4% of induction deaths. In multivariate analysis, infection with carbapenemase-producing K. pneumoniae (OR 25.1; 95% CI, 7.75–81.51), increasing age (OR 1.072 per additional year; 95% CI, 1.005–1.144), and treatment with L-asparaginase–based regimens (OR 9.58; 95% CI, 2.46–37.32) emerged as independent predictors of induction-related mortality. The estimated five-year overall survival was 17%, and only 4% of patients underwent allogeneic hematopoietic stem cell transplantation.
Discussion: Adult acute lymphoblastic leukemia in this cohort was marked by substantial induction-related mortality, largely driven by multidrug-resistant bacterial infections, in conjunction with severely limited access to allogeneic transplantation. These findings highlight an urgent need to strengthen supportive care measures, implement robust infection prevention and control strategies, and develop treatment protocols adapted to local epidemiological and resource constraints. Given the homogeneity of healthcare delivery within the national public healthcare system, these outcomes are likely representative of those observed across the country.
Conclusions: Collectively, these findings underscore the urgent need for the implementation of comprehensive health policies aimed at improving clinical outcomes in this patient population.
Keywords: Acute lymphoblastic leukemia; adult; Ecuador; survival analysis; retrospective studies; healthcare disparities; Latin America.

Resumen

Introducción: La leucemia linfoblástica aguda del adulto en América Latina plantea desafíos clínicos y epidemiológicos particulares, agravados por la limitada disponibilidad de datos específicos de la región. Este estudio tuvo como objetivo evaluar la supervivencia global a cinco años y la supervivencia libre de recaída en pacientes tratados con quimioterapia intensiva, caracterizar de manera sistemática las complicaciones relacionadas con el tratamiento, identificar factores pronósticos asociados con los desenlaces clínicos y describir los perfiles clínicos y demográficos de la población estudiada.
Métodos: Se realizó un estudio observacional retrospectivo en 127 pacientes adultos diagnosticados con leucemia linfoblástica aguda y tratados con quimioterapia intensiva. Se analizaron de forma sistemática variables demográficas, clínicas, citogenéticas y relacionadas con el tratamiento, así como los desenlaces de supervivencia.
Resultados: La mediana de edad al diagnóstico fue de 33 años, y el 63,7% de los pacientes tenía menos de 40 años. La tasa de remisión completa tras

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la terapia de inducción fue del 58,5%. La mortalidad relacionada con la inducción alcanzó el 26,7%, atribuible predominantemente a sepsis causada por Klebsiella pneumoniae productora de carbapenemasas, responsable del 67,4% de las muertes durante la inducción. En el análisis multivariado, la infección por K. pneumoniae productora de carbapenemasas (OR 25,1; IC 95%, 7,75–81,51), el aumento de la edad (OR 1,072 por cada año adicional; IC 95%, 1,005–1,144) y el tratamiento con esquemas basados en L-asparaginasa (OR 9,58; IC 95%, 2,46–37,32) emergieron como predictores independientes de mortalidad relacionada con la inducción. La supervivencia global estimada a cinco años fue del 17%, y solo el 4% de los pacientes fue sometido a trasplante alogénico de células madre hematopoyéticas.
Discusión: La leucemia linfoblástica aguda del adulto en esta cohorte se caracterizó por una elevada mortalidad relacionada con la inducción, impulsada principalmente por infecciones bacterianas multirresistentes, junto con un acceso severamente limitado al trasplante alogénico. Estos hallazgos resaltan la necesidad urgente de fortalecer las medidas de cuidado de soporte, implementar estrategias sólidas de prevención y control de infecciones y desarrollar protocolos terapéuticos adaptados a las condiciones epidemiológicas locales y a las limitaciones de recursos. Dada la homogeneidad en la provisión de servicios de salud dentro del sistema público nacional, es probable que estos resultados sean representativos de los observados a nivel nacional.
Conclusiones: En conjunto, estos hallazgos subrayan la necesidad urgente de implementar políticas de salud integrales orientadas a mejorar los resultados clínicos en esta población de pacientes.
Palabras clave: Leucemia linfoblástica aguda; adulto; Ecuador; análisis de supervivencia; estudios retrospectivos; disparidades en salud; América Latina.

Introduction

Acute lymphoblastic leukemia (ALL) is an aggressive hematologic malignancy affecting individuals across all age groups. In pediatric populations, ALL is associated with favorable outcomes, with contemporary induction chemotherapy protocols achieving high remission rates and approximately 80% five-year event-free survival. In contrast, outcomes in adults remain substantially inferior, with reported five-year event-free survival rates ranging from 30% to 45%, declining further among patients older than 40 years[1].

In Ecuador, there is a paucity of published data providing a comprehensive characterization of the clinical and cytogenetic features of patients with ALL, the therapeutic regimens employed, or the outcomes achieved. This knowledge gap is further exacerbated by limited access to cytogenetic and molecular studies, which are critical for accurate risk stratification and the selection of optimal treatment strategies. Moreover, additional contextual factors may adversely impact prognosis, including the high prevalence of multidrug-resistant bacterial infections and restricted access to hematopoietic progenitor cell transplantation (HPCT).

Within this context, the present study constitutes the first institutional retrospective analysis of survival outcomes in adult patients with ALL treated in Ecuador. Clinical data from patients who received intensive chemotherapy between 2012 and 2019 at a tertiary-care hospital within the public social security healthcare network in Quito were systematically collected and analyzed.

The objectives of this study were to evaluate five-year overall and relapse-free survival following intensive chemotherapy, to document treatment-related complications, to identify prognostic factors associated with clinical outcomes, and to describe the clinical and demographic characteristics of the study population.

Material and methods

Design and Patient Selection

An observational, retrospective, longitudinal study was conducted involving patients

diagnosed with ALL between January 2012 and December 2019. Demographic, clinical, and cytogenetic characteristics, as well as the treatment regimens administered and major clinical outcomes, were systematically collected and analyzed.

Eligible patients met the diagnostic criteria established by the fifth edition of the World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues[1]. A diagnosis of ALL was established by the presence of ≥20% blasts in peripheral blood or bone marrow. Fluorescence in situ hybridization (FISH) and reverse transcription–polymerase chain reaction (RT-PCR) assays for recurrent genetic abnormalities were not routinely available, except for testing the t(9;22) translocation or the BCR::ABL1 fusion transcript. In all cases, lymphoid precursor lineage was confirmed by flow cytometry–based immunophenotyping.

For the descriptive analysis of demographic and clinical variables, patients aged ≤14 years were excluded. For the survival analyses, additional exclusions included patients who did not receive intensive chemotherapy at the study institution, those with isolated extramedullary disease, and those diagnosed with lymphoid blast crisis. Consequently, survival analyses were restricted to patients treated with intensive chemotherapy.

Patients receiving intensive chemotherapy were treated according to one of the following protocols: BFM, Hyper-CVAD, CALGB 8811, GATLA, or PETHEMA LAL 2011. In cases of hypersensitivity reactions to asparaginase, anti-asparaginase antibody testing was not available; therefore, asparaginase administration was continued unless a severe infusion-related adverse event occurred. Monitoring of serum methotrexate levels was not performed. Patients who successfully completed the consolidation phase proceeded to maintenance therapy based on the POMP regimen, administered on a monthly schedule.

Definitions

Complete remission (CR) was defined in accordance with the criteria proposed by Cheson et al.[2] CR required <5% blasts in the bone marrow with evidence of trilineage hematopoiesis, recovery of peripheral blood counts—defined as an absolute neutrophil count >1 000/mm^3 and a platelet count >100 000/mm^3—and the absence of circulating blasts or extramedullary disease. Complete remission with incomplete hematologic recovery (CRi) was defined as fulfillment of all CR criteria except for persistent neutropenia (<1 000/mm^3) and/or thrombocytopenia (<100 000/mm^3).

Induction-related mortality was defined as death from any cause occurring within the first 30 days after diagnosis among patients who received induction chemotherapy.
Overall survival (OS) was defined as the interval from the date of diagnosis to death from any cause or last follow-up. Relapse-free survival (RFS) was assessed exclusively in patients who achieved CR and was calculated from the date of documented remission to hematologic relapse or death from any cause; patients without an event were censored at the date of last contact.

Cytogenetic risk, assessed by conventional G-banding analysis, was categorized according to the recommendations of the National Comprehensive Cancer Network (NCCN) [3]. Risk stratification for patients with BCR::ABL1–negative B-cell ALL followed the criteria established in the MRC UKALL XII/ECOG E2993 trial, which defines three risk groups: low risk (age <35 years and white blood cell count <30 × 10^9/L), intermediate risk (age ≥35 years or white blood cell count ≥30 × 10^9/L), and high risk (age ≥35 years and white blood cell count ≥30 × 10^9/L).

Objectives

The objectives of this study were to evaluate five-year overall and relapse-free survival in patients with B-cell acute lymphoblastic leukemia treated with intensive chemotherapy; to document treatment-related complications;

to identify prognostic factors associated with clinical outcomes; and to characterize the clinical and demographic features of all patients treated at the Hematology Unit of Carlos Andrade Marín Hospital between January 2012 and December 2019, with follow-up through December 31, 2021.

Statistical and ethical considerations

Descriptive statistics for clinical variables were summarized as absolute and relative frequencies. To identify factors associated with induction chemotherapy–related mortality, logistic regression analysis was conducted. Overall survival (OS) and relapse-free survival (RFS) were estimated using the Kaplan–Meier method, and intergroup differences were assessed using the log-rank test. Prognostic factors for OS and RFS were evaluated using Cox proportional hazards regression models. Variable selection for the Cox models was guided by previously documented associations with survival in the literature, and the proportional hazards assumption was assessed using Schoenfeld residuals.

All statistical analyses were carried out using R software version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria). The study protocol was approved by the Research Ethics Committee for Human Beings of the Carlos Andrade Marín Hospital. The requirement for informed consent was waived due to the retrospective nature of the study and the use of a fully anonymized database.

Table 1. Baseline Demographic and Clinical Characteristics of the Study Population

Variable		**n**	**(%)**
All Patients		285	(100)
Median age in years (range)	19 ((IQR: 9.5-42).		
Patients ≥ 15 years		178	(62.4)
Median age in years	33 (IQR: 22.7-52)		
Gender			
	Female	132	(46.3)
	Male	153	(53.7)
Region			
	Sierra	251	(88.0)
	Orient	20	(7.0)
	Coast	14	(4.9)
ALL Type		283	
	B-cell ALL	257	(90.8)
	T-cell ALL	16	(5.6)
	Ambiguous or mixed lineage	6	(2.1)
	Lymphoid Blast Crisis	4	(1.4)
B-cell all Subtype		144	(100)
	Pro B	17	(11.8)
	Common B	99	(68.7)
	Pre B (mature)	28	(19.4)
Patients evaluated for thrombosis		159	
	Deep Vein Thrombosis	5	(3.1)

ALL: Acute Lymphoblastic Leukemia; IQR: Interquartile range

Results

Patient Characteristics

Between January 2012 and December 2019, a total of 596 patients, including pediatric cases, were diagnosed with acute leukemia at our institution. The study cohort comprised 285 patients (47.8%) diagnosed with ALL. The remaining diagnoses included 260 patients (43.6%) with non-promyelocytic acute myeloid leukemia (AML) and 51 patients (8.6%) with acute promyelocytic leukemia (APL).

Among the 285 patients with ALL, the median age was 19 years (interquartile range [IQR]: 9.5–42), with 178 patients (62.4%) aged ≥15 years; 132 patients (46.3%) were female. The most prevalent geographic region of origin was the Sierra, accounting for 251 patients (88%), followed by Oriente with 20 patients (7%) and the Coast with 14 patients (4.9%).

Regarding immunophenotypic lineage, 257cases (90.8%) were of B-cell lineage, 16 (5.6%) were T-cell lineage, 6 (2.1%) were of ambiguous or mixed lineage, and 4 (1.4%) represented lymphoid blast crises secondary to chronic myeloid leukemia. Among the 144 patients with B-cell ALL whose immunophenotypic subtype was determined (primarily assessed in 15 patients younger than 15 years), 17 (11.8%) were classified as Pro-B, 99 (68.7%) as Common B, and 28 (19.4%) as Pre-B subtypes.

Of the 159 patients with available data for evaluation of associated deep vein thrombosis (DVT), 5 (3.1%) experienced this thrombotic event at any time from diagnosis onward. (***Table 1.)***

Ten patients treated with palliative intent (median age, 72.2 years) and 127 patients excluded for various reasons were not included in the analysis. Reason for exclusion included death prior to chemotherapy initiation (n=7), transfer to a pediatric oncology center (n=94), relocation to another city or institution (n=9), refusal of chemotherapy (n=4), age <15 years (n=16), and an initial misdiagnosis (n=2). Additionally, patients with ALL of ambiguous or mixed lineage and those presenting with lymphoid blast crisis were excluded.

The analysis cohort comprised 127 patients aged ≥15 years with ALL who received intensive chemotherapy, including four cases of T-cell ALL. The median age was 33 years (IQR: 22.7–52), with 81 patients (63.7%) aged ≤ 40 years. Sixty-six patients (51.9%) were female. Extramedullary infiltration (EMI) was documented in 45 patients (35.4%), predominantly central nervous system (CNS) involvement in 40 patients (31.4%). Other sites of extramedullary disease included the testis (n=1), liver (n=2), skin (n=1), and joint (n=1). Notably, lymphadenopathy and splenomegaly were not categorized as extramedullary infiltration. The mean leukocyte count at diagnosis was 51.300/mm^3, with 81 patients (63.7%) exhibiting leukocyte counts below 30 000/mm^3.

Cytogenetic data were available for 95 patients: 32 (33.6%) samples had no metaphases; 7 (7.3%) were classified as low risk; 22 (23.1%) presented high-risk cytogenetic abnormalities; 27 (28.4%) showed normal karyotypes; and 7 (7.3%) demonstrated non-clonal karyotypes.
Excluding T-cell ALL cases, 123 patients had B-cell ALL. Among 44 patients (35.7%) evaluated for the presence of t(9;22) or the BCR-ABL1 transcript, six cases (13.6%) were positive. Risk stratification was conducted using the MRC UKALL XII/ECOG criteria for patients with t(9;22)-negative B-cell ALL, independent of cytogenetic or molecular data. Of the 117 patients stratified, 28 (23.9%) were classified as high risk, 52 (44.4%) as intermediate risk, and 37 (31.6%) as low risk.

Regarding chemotherapy regimens in the 123 patients with B-cell ALL, 57 (46.3%) received HyperCVAD/MTX–ara-C, 45 (36.5%) were treated with CALGB 88/11, 13 (10.6%) received GATLA protocols, six (4.9%) received BFM regimens, and two (1.6%) were administered PETHEMA LAL protocols. All four patients with T-cell ALL were treated using the HyperCVAD/MTX–ara-C regimen.

Remission, Death, and Relapse

Among the 123 patients with B-cell ALL, CR was achieved in 72 patients (58.5%). Among those treated with chemotherapy protocols that did not include L-Asparaginase, 37 of 57 patients (71.1%) attained CR, whereas in regimens containing L-Asparaginase (CALGB 88/11, GATLA, BFM, PETHEMA), CR was achieved in 35 of 66 patients (53%).

A total of 16 patients received reinduction chemotherapy; 7 (43.7%) achieved CR, and 9 (56.3%) were refractory, representing 7.3% of all B-cell ALL patients treated with intensive chemotherapy. Combining CR rates from both first and second induction phases, a total of 79 patients (64.2%) achieved CR.

Regarding induction-related mortality, 34 deaths (26.7%) occurred among the 127 ALL patients. The predominant cause was sepsis (94%), with carbapenemase-producing *Klebsiella pneumoniae* (CPK) isolated in 21 cases (67.4%). Additionally, two deaths resulted from CNS hemorrhage and one from an ischemic cerebrovascular event. Induction-related mortality varied by treatment protocol: in patients treated with HyperCVAD/MTX–ara-C, five of 57 (8.7%) died, contrasted with L-Asparaginase-containing protocols, where 29 of 66 patients (43.9%) died. Within L-Asparaginase regimens, mortality rates were 50% with BFM, 46.6% with CALGB 88/11, and 38.4% with GATLA.

In multivariable logistic regression analysis, factors associated with induction-related mortality included isolation of CPK in blood cultures (OR, 25.14; 95% CI: 7.75–81.51; $p < 0.001$), increasing age (OR 1.072 per year; 95% CI 1.005–1.144; $p = 0.035$), and use of L-Asparaginase-containing regimens (OR 9.58; 95% CI 2.46–37.32; $p = 0.001$). No significant associations were observed with sex, residence in Pichincha province, extramedullary infiltration, adolescent and young adult (AYA) group affiliation, or initial leukocyte count.

During subsequent consolidation phases, six additional deaths occurred, bringing total treatment-related mortality to 40 patients (31.4%).

Among the 79 patients achieving CR after first or second induction, 48 (60.7%) relapsed. Another 12 patients (15.1%) died while in remission: six during intensive consolidation (including one from COVID-19), two during transplantation (procedure-related mortality), and two during late maintenance (one from pulmonary sepsis and one from COVID-19); in two cases, the cause of death was unclear. Finally, 19 patients (24%) remained in continuous remission at last follow-up **(Table 2**).

Among the 48 patients who experienced relapse, 33 received reinduction chemotherapy, of whom 13 (39.3%) achieved a second remission.

During the entire study period, 105 patients (82.6%) died. Sepsis was the leading cause of death in 63 cases (60%), with carbapenemase-producing Klebsiella pneumoniae isolated in 28 (44%) of these cases **(Table 3).**

Table 2. Patients with Loss of Response According to Chemotherapy Protocol Received

Chemotherapy Protocol	Remission (1st Induction)	Median Age (Years)	Relapsed n (%)	Relapsed <18 Months n (%)	No Relapse, Alive n (%)	Death in Remission n (%)	Documented Ph+ n (%)
HiperCVAD/ MTX–ara-C*	37	37	28(75.6)	26(70.2)	3 (8.1)	6 (16.2)	1 (2.8)
ASP-containing regimens**	35	37	16(45.7)	14(40)	14 (40)	5 (14.2)	3 (8.5)
Total	72	37	44(61.1)	40(57.1)	17(23.6)	11 (15.2)	4 (5.5)

*Protocol without L-asparaginase

**Protocols including L-asparaginase (e.g., CALGB 88/11, GATLA, BFM, PETHEMA LAL)

Table 3. Specific Cause of Death in Patients with Acute Lymphoblastic Leukemia

Cause of Death	n (105)	%
Sepsis	63	60
Sepsis of undetermined origin	33	31.1
Pulmonary sepsis	15	14.2
Gastrointestinal sepsis	8	7.6
Soft tissue sepsis	4	3.8
Perianal sepsis	3	2.8
COVID 19	2	1.9
Disease progression	27	25.7
Unknown cause	6	5.7
CNS hemorrhage	2	1.9
Intra-alveolar hemorrhage	1	0.9
Ischemic CVA	1	0.9
Gastrointestinal bleeding	1	0.9
Transplantation-related mortality*	2	1.9

*Six patients underwent allogeneic hematopoietic progenitor cell transplantation. CVA: Cerebrovascular accident; CNS: Central nervous system.

Efficacy

The median OS of patients with B-cell ALL treated with intensive chemotherapy was 10 months (95% CI: 7–13), with an IQR of 1–23 months. The 5-year OS rate was 17% (95% CI: 11%–25%). Among the 66 patients who achieved CR after first induction, the 5-year OS was 26.5%, with a median OS of 16 months (IQR: 1–24 months).

Stratified by age, the median OS was 10 months (IQR: 3.5–24) in patients under 40 years and 7.5 months (IQR: 0–21.5) in those aged ≥ 40 years, with no statistically significant difference between the age groups ($p = 0.191$).

In patients with BCR: ABL1-negative B-cell ALL, risk stratification according to the MRC UKALL XII/ECOG E2993 protocol revealed significant differences in OS (log-rank test: $p = 0.003$). Median OS was 16 months (95% CI: 10–24; IQR: 4–24) for the low-risk group,

10 months (95% CI: 6–18; IQR: 1–24) for the intermediate-risk group, and 4 months (95% CI: 1–10; IQR: 1–24) for the high-risk group **(Figure 1).** The analysis of other subgroups in relation to OS is summarized in table 4.

The median RFS in patients with B-cell ALL treated with intensive chemotherapy was 11 months, with an interquartile range of 4 to 33 months. The 5-year RFS was 25,2% (95% CI: 16.9–37.6). ***Figure 2*** presents the RFS curve for patients with B-cell ALL stratified by the chemotherapy regimen received, while table 5 provides a detailed subgroup analysis related to RFS.

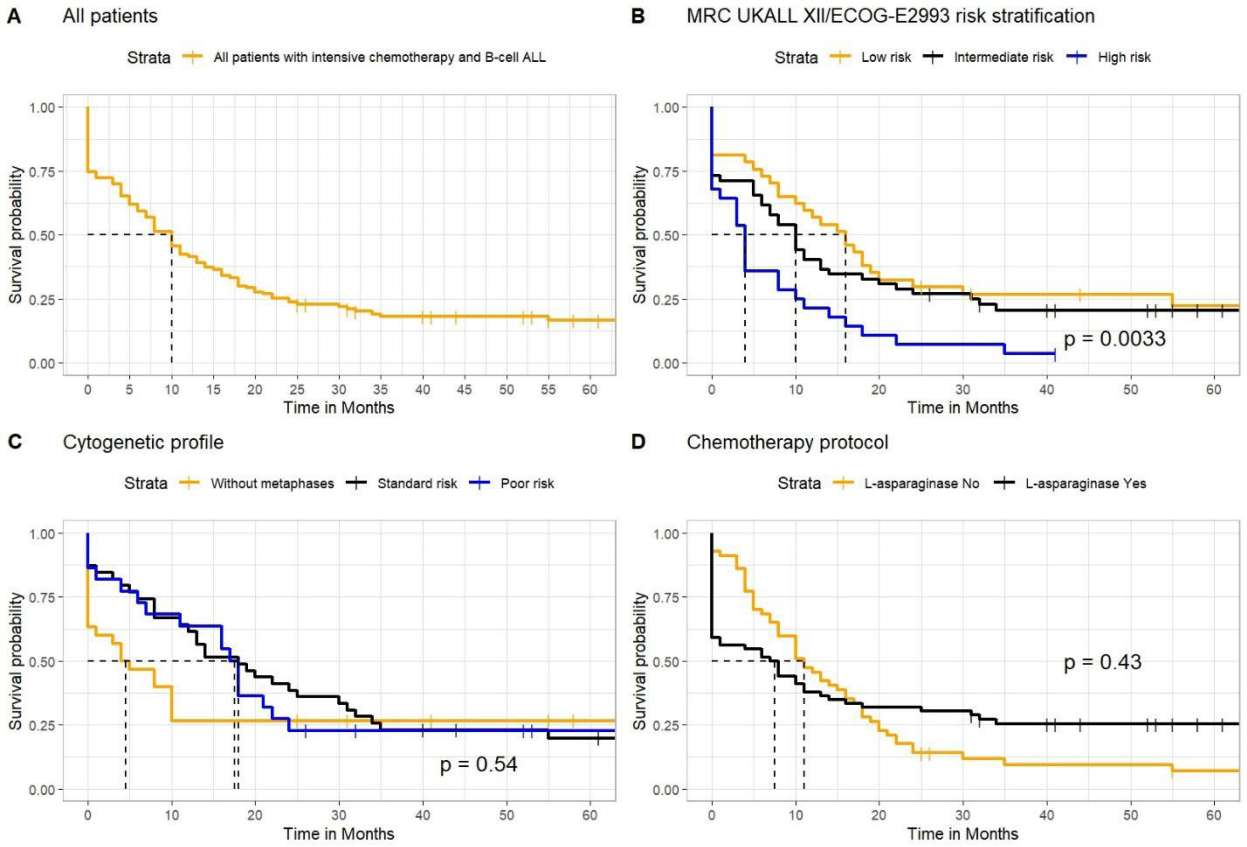

Figure 1. **(A)** Overall survival (OS) of patients with B-cell acute lymphoblastic leukemia (ALL). The 5-year OS was 17%, with a median OS of 10 months indicated by the dashed line. **(B)** OS of patients with BCR::ABL1-negative B-cell ALL stratified by MRC UKALL XII/ECOG E2993 risk groups. The 5-year OS rates were 22.3% (95% CI: 11.7–42.5) for the low-risk group, 20.5% (95% CI: 11.9–35.4) for the intermediate-risk group, and not reached in the high-risk group, with OS at 40 months of 3.5% (95% CI: 0.5–24.4). Median OS durations were 16 months, 10 months, and four months for low-, intermediate-, and high-risk groups, respectively. **(C)** OS of patients with B-cell ALL according to cytogenetic risk groups. The 5-year OS rates were 26.6% (95% CI: 15–48) for patients with no evaluable metaphases, 19.7% (95% CI: 10–37) for standard cytogenetic risk, and 22.7% (95% CI: 10–49) for poor cytogenetic risk. Median OS was 4.5 months, 18 months, and 17.5 months, respectively. **(D)** OS of patients with B-cell ALL stratified by chemotherapy regimen. The 5-year OS was 7.0% (95% CI: 3–19) for patients treated with non-L-asparaginase protocols and 25.2% (95% CI: 5–16) for those receiving L-asparaginase-containing chemotherapy. Median OS was 11 months and 7.5 months, respectively.

Table 4. Univariate Analysis of Patients Diagnosed with B-cell Acute Lymphoblastic Leukemia and Association with Overall Survival

Variable		n(%)	Median OS in months	5-year OS	p-value* for OS
Age ≤ 40 years	No	46 (37.4)	5 [95% CI: 3-16]	12,2% [95% CI: 4%-23%]	p=0.220
	Yes	77 (62.6)	10 [95% CI: 8-16]	19,2% [95% CI: 13%-34%]	
Pichincha province residents	No	61(49.5)	8 [95% CI: 4-14]	14,5% [95% CI: 7%-28%]	p=0.591
	Yes	62(50.5)	10,5 [95% CI: 8-16]	18,6% [95% CI: 10%-31%]	
Extramedullary infiltration at diagnosis	No	80(65.1)	10,5 [95% CI: 8-16]	21,5% [95% CI: 14%-33%]	p=0.154
	Yes	43(34.9)	8 [95% CI: 4-13]	11,6% [95% CI: 5%-26%]	
≥30,000 leukocytes/mm3	No	80(65)	12,5 [95% CI: 8-18]	21,6% [95% CI: 14%-33%]	p=0.033
	Yes	43(35)	6 [95% CI: 3-10]	11,1% [95% CI: 4%-26%]	
Cytogenetic profile	No evaluable metaphases	30(32.9)	4,5 [95% CI: 0-10]	26,6% [95% CI: 15%-48%]	p=0.540
	Standard risk	39(42.8)	18[95% CI: 12-31]	19,7% [95% CI: 10%-37%]	
	Poor risk	22(24.3)	17,5[95% CI: 11-24]	22,7% [95% CI: 10%-49%]	
Asparaginase-containing protocols	No	57(46.3)	11 [95% CI: 8-16]	7,0% [95% CI: 3%-19%]	p=0.433
	Yes	66(53.7)	7,5 [95% CI: 0-14]	25,2% [95% CI: 5%-16%]	
Risk Stratification†	Low	37(31.6)	16 [95% CI: 10-24]	22,3% [95% CI: 11%-42%]	p= <0.01
	Intermediate	52(44.4)	10 [95% CI: 6-18]	20,5% [95% CI: 11%-35%]	
	High	28(23.9)	4 [95% CI: 1-10]	NR‡	

*Log-rank test; †According to MRC UKALL XII/ECOG E2993 proposal; ‡Not reached at 5 years (OS at 40 months was 3,5% [95% CI: 0.5-24.4]). NR: Not reached; OS: overall survival; CI: confidence interval

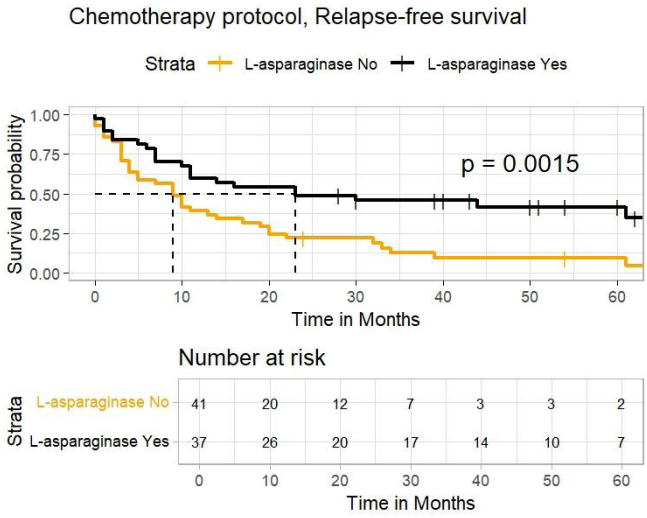

Figure 2. Patients with B-cell ALL according to chemotherapy type. Five-year progression-free survival for patients receiving non-L-asparaginase protocols: 9.4% (95% CI: 3%-26%) vs. patients receiving L-asparaginase chemotherapy: 41% (95% CI: 8%-61%). The dashed line indicates the respective median RFS times (nine months and 23 months).

Table 5. Univariate Analysis of Clinical Variables in Patients Diagnosed with B-cell Acute Lymphoblastic Leukemia and Association with Relapse-Free Survival

Variable		n(%)	Median RFS in months	5-year RFS	p-value* for RFS
Age ≤ 40 years	No	31 (39.7)	7.5 [95% IC: 9-23]	18.4% [95% IC: 8%-39%]	p=0.524
	Yes	47 (60.3)	10 [95% IC: 9-23]	29.5% [95% IC: 18.5%-39.3%]	
Residents of the province of Pichincha	No	36(46.1)	11 [95% IC: 5-23]	21.3% [95% IC: 11%-40%]	p=0.444
	Yes	42(53.9)	14 [95% IC: 7-44]	28.3% [95% IC: 16%-47%]	
Extramedullary infiltration at diagnosis	No	54(69.2)	10.5 [95% IC: 7-23]	28.7% [95% IC: 18%-44%]	p=0.841
	Yes	24(30.8)	15 [95% IC: 10-34]	18.7% [95% IC: 7%-45%]	
≥30,000 leukocytes/mm3	No	55(70.5)	11 [95% IC: 10-30]	29,6% [95% IC: 19%-45%]	p=0.269
	Yes	28(29.5)	10 [95% IC: 4-34]	14.4% [95% IC: 4%-44%]	
Cytogenetic profile	No evaluable metaphases	15(25)	44 [95% IC: 14-NA]	45.5% [95% IC: 24%-86%]	p=0.388
	Standard risk	30(50)	13.5 [95% IC: 9-34]	23.3% [95% IC: 12%-44%]	
	Poor risk	15(25)	17[95% IC: 10-NA]	32,0 % [95% IC: 15%-68%]	

Variable		n(%)	Median RFS in months	5-year RFS	p-value* for RFS
Asparaginase-containing protocols	No	41(52.5)	9 [95% IC: 5-17]	9.4% [95% IC: 3%-26%]	p= <0.01
	Yes	37(47.5)	23 [95% IC: 11-NA]	41.6% [95% IC: 27%-61%]	
Risk Stratification†	Low	27(36.5)	11 [95% IC: 7-NA]	31.7% [95% IC: 17%-56%]	p=0.449
	Intermediate	34(46.0)	11 [95% IC: 6-33]	28.6% [95% IC: 16%-49%]	
	High	13(17.5)	10 [95% IC: 3-NA]	NR‡	

*Log-rank test; †According to MRC UKALL XII/ECOG E2993 proposal; ‡Not reached at 5 years (RFS at 40 months was 15.4% [95% CI: 4.3-55]). NR: Not reached; RFS: relapse-free survival; CI: confidence interval.

In the multivariate Cox regression model for OS, age was identified as a significant factor associated with reduced survival (HR: 1.03; 95% CI: 1.00–1.06). Conversely, being aged ≤40 years was associated with a more favorable prognosis (HR: 0.46; 95% CI: 0.21–1.00). No statistically significant associations were observed between OS and white blood cell count at diagnosis, extramedullary infiltration, or risk stratification **(Figure 3).**

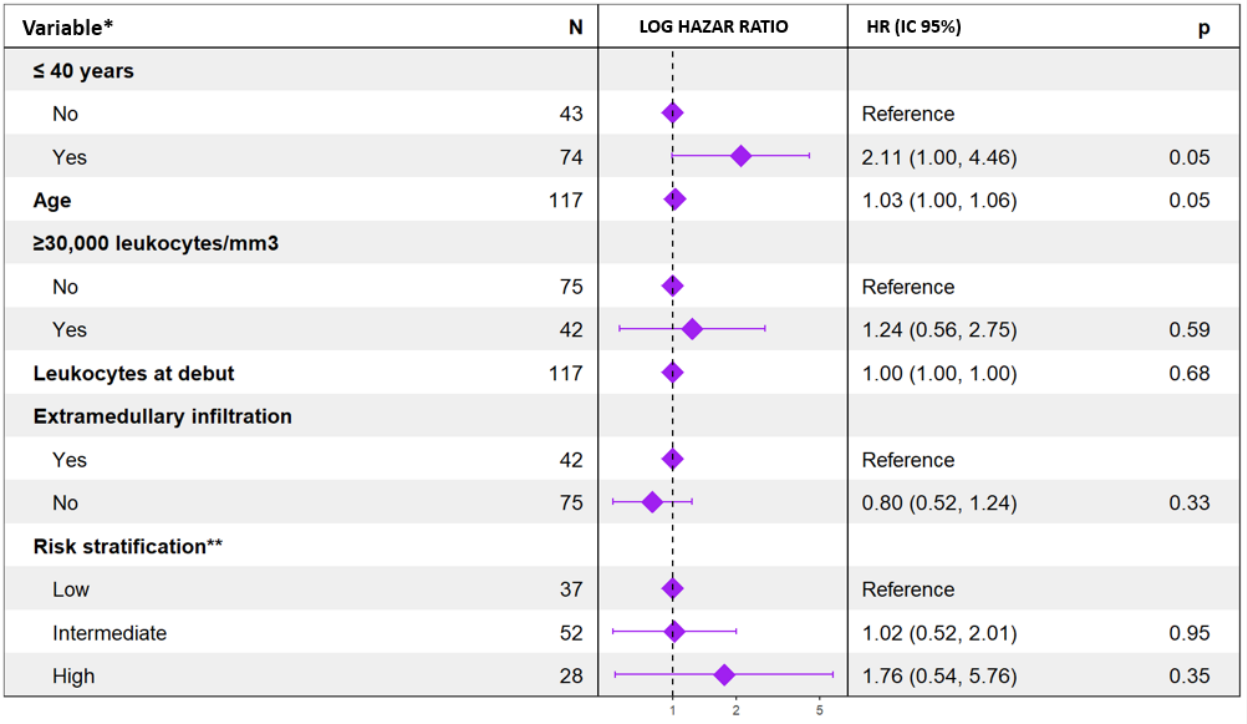

Figure 3. Multivariate analysis for overall survival in patients with B-cell acute lymphoblastic leukemia.

*From the initial multivariable model, the type of chemotherapy received was not included because the proportional hazards assumption assessment did not demonstrate linearity using the Schoenfeld approach. **According to the MRC UKALL XII/ECOG E2993 proposal. HR: Hazard Ratio.

In the multivariate regression model for relapse-free survival (RFS), the use of pediatric-inspired chemotherapy protocols containing L-asparaginase was significantly associated with improved RFS (hazard ratio [HR]: 0.40; 95% CI: 0.22–0.75). No significant associations were observed between RFS and age, being ≤ 40 years, white blood cell count at diagnosis, extramedullary infiltration, or risk stratification **(Figure 4).**

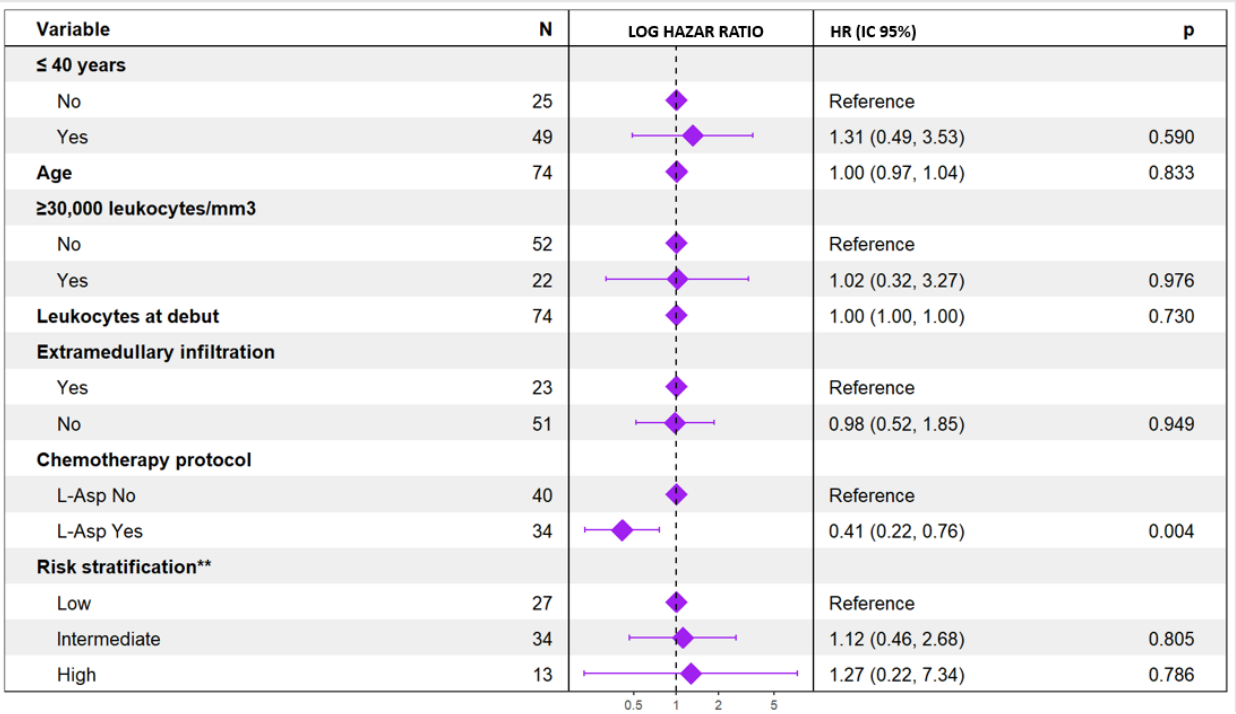

Figure 4. Multivariate analysis for event-free survival in patients with B-cell acute lymphoblastic leukemia. **According to the MRC UKALL XII/ECOG E2993 proposal. HR: Hazard Ratio.

Discussion

Consistent with the profile of ALL in Latin America, our cohort of 127 patients (aged ≥15 years) who received intensive chemotherapy was characterized by a young age distribution. The median age was 33 years (range, 15-73), with 63.7% of patients under 40. This finding is congruent with a report by Jaime-Pérez et al. from Mexico, which described an identical median age of 33 years[4].

This reality differs considerably from that observed in European and North American series; for example, the Spanish PETHEMA Group reports median ages between 44 and 50 years[5], while in the United States the mean age at diagnosis is closer to 55 years[6]. This disparity could be explained by two main factors: first, a substantially younger population pyramid in Ecuador (median age of 27,9 years[7] compared to countries like the United States (median age of 38.3 years[8]); and second, probable underdiagnosis or diagnostic delays in the older adult population, who may not access specialized hematology-oncology centers in a timely manner, thus skewing the recorded cohort toward a younger population.

In the present cohort, EMI was present in 35.4% of patients, with the CNS being the most frequently affected site (31.4%). This prevalence is considerably higher than that documented in series from high-income countries; for example, the French GRAALL group reports CNS involvement in less than 10% of young adults with ALL[9]. Our finding aligns, however, with observations from other Latin American studies. Fernandes et al. in Brazil reported a CNS infiltration rate of 29% in adults[10], while a Mexican pediatric cohort documented 30% initial CNS involvement[11]. These authors attributed the higher frequency to diagnostic delays and the presence of risk factors such as hyperleukocytosis.

Regional data support the hypothesis that the high proportion observed in our study could reflect both biological particularities of the disease and delays in healthcare access, resulting in a higher disease burden at diagnosis. It is important to note that, although

all patients in this cohort were evaluated for CNS infiltration via flow cytometry of cerebrospinal fluid —a highly sensitive technique —during the study period, clearance of peripheral blood blasts was not uniformly required before lumbar puncture. This methodological aspect introduces the possibility that some detected infiltrations might have resulted from sample contamination with peripheral blood, potentially overestimating the actual rate of CNS involvement.

Regarding leukocyte count at diagnosis, the median was 51 300/mm³, with 63.7% of patients presenting <30 000 leukocytes/mm³. This distribution is comparable to that observed in series from developed countries, where leukocytosis is a well-established prognostic marker. For example, in the multicenter cohort of the GRAALL-2003 study, approximately 70% of adults with ALL presented counts ≤ 30 000/mm³ at diagnosis, a parameter used for risk stratification and treatment guidance[12]. However, our cohort shows a slight trend toward higher mean leucocyte counts, which could be explained by potential delays in healthcare access.

The adverse prognostic value of hyperleukocytosis (>30 000/mm³) is well-established in the international literature, as demonstrated by the U.S. Surveillance, Epidemiology, and End Results Program (U.S. SEER) registry[13], the MRC UKALL XII/E2993 clinical trials[14], and studies by the Canadian Adult ALL Group[15], all of which report worse outcomes associated with this variable. This finding was corroborated in our analysis, where hyperleukocytosis >30 000/mm³ was associated with significantly inferior OS (p=0.033), reaffirming its relevance as a prognostic factor in our context.

Limited access to complex cytogenetic and molecular biology testing prevented risk stratification based on modern prognostic markers. Given this scenario, we opted to use the classic MRC UKALL XII/ECOG E2993 system, which is based exclusively on age and leukocyte count at diagnosis[14]. While it is predictable that this method might lead to an overestimation of patients in low and intermediate-risk groups by not incorporating poor prognostic markers such as the Philadelphia chromosome or complex cytogenetic abnormalities, our analysis revealed that this system effectively distinguished between risk groups, with statistically significant differences in survival observed. This finding suggests that, despite its inherent limitations, this model retains clinical utility in resource-limited settings and validates its applicability in our environment for basic prognostic risk stratification.

A critical finding of our study was the high proportion (33.6%) of samples without evaluable metaphases among the 95 patients who underwent attempted cytogenetic analysis. Only 7.3% of patients were classified as low cytogenetic risk, while 23.1% presented high-risk alterations. The overall rate of obtaining an informative karyotype in our cohort was 50.3%, a figure substantially lower than that reported in large international series, where rates between 70% and 75% are achieved[16-19]. This result, however, is comparable to the scenario described in other Latin American contexts; for example, a Mexican registry reported availability of cytogenetic data in only 54.5% of cases, attributing this limitation to lack of technical availability or failure in metaphase growth[20].

It is crucial to note that, even among karyotypes reported as “normal” (28.4% of patients), more than half did not meet the gold standard of analyzing 20 metaphases. This technical limitation, combined with the absence of statistically significant differences in survival analysis between different cytogenetic risk groups, makes it impossible to draw robust conclusions about the prognostic value of karyotype in this cohort. Our data underscore the urgent need to optimize preanalytical, culture, and analysis procedures to improve the quality and reliability of cytogenetic studies in our setting, as well as to implement complementary techniques such as FISH or next-generation sequencing (NGS) to overcome these barriers.

The frequency of Ph+ ALL (BCR::ABL1) in this cohort was 13,6%, determined primarily by RT-PCR. This percentage is notably lower than that reported internationally, where the prevalence of this alteration increases with age, affecting between 25% and 40% of adults with ALL[21, 22]. For example, in a Swedish registry with a median age of 53 years, t(9;22) was the most frequent aberration, present in 26% of cases[23]. While reported figures are variable in younger Latin American populations—such as ours—our result falls at the lower end of the spectrum. Studies from Brazil (median age: 33 years) and Mexico (median ages: 28-33 years) have documented Ph+ ALL frequencies ranging from 16.7% to 34%[4, 20, 24]. Considering that the median age of the subgroup evaluated for BCR::ABL1 in our study was 37 years—slightly higher than that of the complete cohort—a higher positivity rate would be expected. This discrepancy raises legitimate concerns about the sensitivity of the diagnostic platform used and the possibility of false-negative results. Therefore, our findings not only reflect a possible epidemiological particularity but also critically highlight the imperative need to implement internationally validated molecular detection techniques (such as multiplex quantitative RT-PCR or NGS panels) and ensure continuous training of technical staff. This is essential to guarantee diagnostic reliability, accurate risk stratification, and consequently, access to appropriate targeted therapies.

The incidence of DVT documented in this cohort was 3.1%, a frequency notably lower than those reported in the international literature, where rates typically range between 5% and 9% [25-27]. We consider that this disparity does not necessarily reflect a truly lower incidence but is more likely attributable to significant underreporting.

This underreporting could be attributed to the absence of a systematic screening protocol for thrombotic events, which would have limited the detection of asymptomatic or subclinical cases. Additionally, two other factors specific to our cohort may have contributed to this observed lower rate: the low frequency of central venous catheter placement, a well-recognized iatrogenic risk factor for DVT, and the use of treatment protocols excluding L-asparaginase in a representative subgroup of patients, a drug with a well-established thrombogenic profile in in ALL management. Therefore, the low recorded incidence should be interpreted with caution, as it is likely influenced by these methodological and practical limitations rather than representing a true difference in the thrombotic risk of the population.

The overall CR rate was 58.5% (72/123) for patients with B-lineage ALL. This finding must be interpreted in conjunction with the high early mortality rate of 26.7%, since CR is calculated based on the total population that started induction therapy, including those who died during this phase. Stratification by protocol type revealed critical differences: regimens excluding L-asparaginase (HyperCVAD/MTX–ara-C) achieved a CR of 71.1% accompanied by an acceptable early mortality rate of 8.7%. In contrast, L-asparaginase-based protocols were associated with a substantially lower CR rate (53.0%) and an alarmingly high early mortality rate (43.9%). This disparity suggests that the reduced CR observed in this group is not due to a lack of anti-leukemic efficacy of the regimen, but to fatal toxicity that prevented completion of induction therapy.

Our overall CR rate is lower than that reported in European and North American series (82-95%), in which early mortality rates are notably low (3-8%) [28-32]. Although our CR rate is closer to those observed in Latin American studies (CR: 69-76%) the early mortality rate in our study is markedly higher (26.7%), clearly exceeding the 7–17% range typically reported in the region[4,10,20].

Three interrelated factors may explain this excessive toxicity, particularly in the group receiving L-asparaginase. First, there was an unequal distribution of advanced age between treatment groups: although the median age was similar, 19% of patients treated with pediatric-inspired regimens were ≥55 years, compared with only 5% in the other group.

Doses of any drug, including L-asparaginase, were not adjusted for age these patients, thereby increasing the risk of toxicity in a more fragile population. Second, a high prevalence of KPC infections was observed, with KPC isolated in 67.4% of positive blood cultures, representing a serious infectious comorbidity. Finally, a multivariate analysis confirmed that CPK infection (OR 25.14), advanced age (OR 1.072 per year), and the use of L-asparaginase-containing regimens (OR 9.58) were significant and independent predictors early mortality. The interaction of these factors—older and more fragile patient profile, exposure to high-intensity regimens without dose adjustment, and in a context of high prevalence of multidrug-resistant pathogens—explains the catastrophic early mortality rate observed in this cohort.

The aforementioned findings suggest that the use of lower-cost generic drugs was not a determining factor in the observed CR rates. This assertion is supported by the performance of the HyperCVAD/MTX–ara-C protocol, which, despite relaying on these drugs, achieved a CR rate of 71.1% with a remarkably low treatment-related mortality (8.7%). This outcome, obtained in the context of an intensive but potentially less toxic regimen within our clinical environment, is comparable to the averages reported in other Latin American studies. Additional support for the effectiveness of the pharmacological regimens employed is provided by the primary refractoriness rate, which in our cohort was 7,3%. This figure lies within the expected range (6-20%) as documented in both international and regional literature[10, 20, 33, 34], suggesting that the intrinsic anti-leukemic efficacy of the regimens was not compromised.

In this cohort, in which only 4% of patients had access to an allogeneic-HSCT, the median OS was 10 months, with a 5-year OS of 17%. These figures are notably lower than those reported in registries from high-income countries. For example, the US National Cancer Database (2004-2016) documents a 5-year OS ranging from 30% to 40%[35], and the Spanish Network of Cancer Registries (2008-2013) reports a 5-year OS of 37%[36]. This survival gap is expected to widen further over time, given the limited access in our setting to innovative therapies—such as blinatumomab, inotuzumab ozogamicin, and chimeric antigen receptor (CAR) T-cell therapy—that are transforming the global therapeutic landscape of ALL.

The Latin American context provides a crucial framework for interpreting our results. The large Mexican registry by Crespo-Solis et al. (n=558), with equally low access to HSCT (5%), reported a 3-year OS of 22% [20], a figure comparable to the 3-year OS of 20% observed in our study. In contrast, the Brazilian registry by Fernandes da Silva et al., which showed higher access to HSCT (24%), achieved a 5-year OS of 15%[10]. These data underscore that the challenges faced in Latin America, and specifically in our country, are multifactorial. Outcomes are not determined solely by access to HSCT but rather reflect a complex problem where high rates of treatment-related mortality—documented in our study—combine with limited access to effective consolidation and salvage therapies. This combination likely accounts for the persistently poor overall survival observed across the region.

The overall 5-year RFS was 25.2%, with a median RFS of 11 months. The analysis revealed a significant improvement in RFS among patients who received protocols containing L-asparaginase compared with those who did not (5-year RFS: 41% vs. 9.4%; p = 0.004), with an HR of 0.40 (p=0.004) in favor of the L-asparaginase group. This finding indicates superior anti-leukemic efficacy and notably better long-term disease control with the use of this agent. However, this RFS benefit was drastically offset by the high early mortality rate observed with these same protocols, as previously documented.

This apparent paradox underscores a critical point: L-asparaginase-based regimens are potentially more effective in preventing relapses in our population, but their unmanageable toxicity in the current context negates this

advantage. Therefore, our results do not discourage the use of these regimens but instead highlight the urgent need to optimize their implementation. This implies more rigorous candidate selection (e.g., excluding older patients or those with significant comorbidities), the establishment of robust supportive care protocols to mitigate treatment-related toxicity (especially infection-related toxicity), and the consideration of dose adjustments based on age and/or functional status. Implementing these strategies is imperative to capitalize on the RFS benefit conferred by these regimens, thereby transforming their potential efficacy into a real and tangible improvement in OS.

The relapse rate in this cohort was high, affecting 60.7% of patients who achieved complete remission. Among these patients, only 39.3% achieved a second remission. This relapse rate is higher than that reported in other regional series, such as the study by Jaime-Pérez et al. in Mexico (2016), which documented a rate of 45% [4]. We believe this disparity can be attributed to several interrelated factors. First, the extremely limited access to allogeneic-HPCT at our center (4%)—a consolidated intervention for remission consolidation and relapse treatment—prevented an effective curative strategy for a large number of patients. Second, significant delays likely occur between consolidation and maintenance chemotherapy cycles, resulting in reduced dose intensity. This hypothesis is supported by internal data from an acute myeloid leukemia cohort from the same registry, which showed a prolonged mean interval of 50 days between cycles, a factor that can compromise treatment efficacy and favor disease recurrence. The combination of suboptimal therapeutic intensification (due to the low transplant rate) and possible reduced dose intensity (due to prolonged intervals) likely facilitated minimal residual disease persistence and ultimately contributed to the high relapse rates observed.

The multivariate analysis for OS identified advanced age as the most significant adverse prognostic factor in this cohort. The risk of death increased by 3% for each additional year of age (HR: 1.03; p=0.05), and patients older than 40 years had a significantly higher risk compared with younger patients (HR: 0.46 for ≤ 40 years; p=0.05). These findings highlight the critical need to stratify treatment not only by cytogenetic or molecular risk—which is difficult to access in our setting—but also, and primarily, by age.

Our reality necessitates the development and implementation of adapted protocols that optimize the balance between efficacy and toxicity for different age groups. A model to follow is the strategy of the Spanish PETHEMA group, which uses specific protocols like "PETHEMA old" for patients over 55 years, designed to maximize tolerability without excessively compromising anti-leukemic efficacy. Adopting a similar approach, with differentiated therapeutic guidelines for young adults (<40-55 years) and older adults (>55 years), could mitigate the high treatment-related mortality observed in older patients and improve overall outcomes in our population.

Conclusion

The analysis delineates a distinctive epidemiological profile of adult ALL in Latin America, characterized by a markedly younger patient demographic and a substantially elevated prevalence of CNS infiltration compared with cohorts from high-income countries. This profile likely reflects the interplay of a youthful population pyramid, diagnostic delays, and a correspondingly greater disease burden at initial presentation.

The classical MRC UKALL XII/ECOG E2993 risk stratification system demonstrated valid prognostic discrimination, underscoring its utility in resource-constrained settings. Nonetheless, the notably high proportion of unreliable cytogenetic findings and the relatively low frequency of Philadelphia chromosome-positive ALL underscore profound limitations in contemporary diagnostic capabilities. This diagnostic gap impedes precise molecularly based risk stratification, a challenge presumably widespread at the national level

and constituting a major obstacle to optimized therapeutic decision-making.

The observed low OS and RFS rates directly reflect two systemic failures within the healthcare infrastructure: elevated treatment-related mortality predominantly attributable to multidrug-resistant infections, and inadequate or absent access to allogeneic hematopoietic progenitor cell transplantation. This scenario likely transcends our center, representing a pervasive national reality. It is probable that other public hospitals nationwide face similar changes, including insufficient infrastructure, scarcity of specialized personnel, and constrained availability of advanced therapeutics.

Consequently, our findings may be broadly extrapolated to represent the national burden of ALL. These results strongly advocate for the development and implementation of comprehensive health policies aimed at redressing these deficiencies through coordinated, system-wide interventions.

Clarification

In the final part of the discussion, artificial intelligence writing aids (DeepSeek) were used.

Ethics committee approval and consent to participate in the study.

The Research Ethics Committee of the Carlos Andrade Marín Hospital approved the study protocol (Act 008, June 16, 2022). As the research was retrospective and utilized a fully anonymized database, informed consent was waived.

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Conflicts of interest

The authors reported not having any personal, financial, intellectual, economic or corporate conflicts of interest.

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