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# Global survival of pediatric patients with acute lymphoblastic leukemia from a Latin American Hospital

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**Abstract**

**Background:** Acute lymphoblastic leukemia (ALL) is the most common neoplasm in pediatric and adolescent populations. Overall survival has improved in recent decades. This study aimed to assess the overall survival of patients with pediatric ALL in a Latin American hospital.

**Materials and Methods:** A longitudinal and retrospective analytical study was conducted on 31 patients less than 16 years of age diagnosed with ALL at the hematology department of a Peruvian hospital during the period 2015-2016. Overall survival at 5 years was determined using the Kaplan-Meier curve with parametric log-rank tests, and the Cox regression model was employed to ascertain the hazard ratios of significant variables.

**Results:** The average age was 6 years, and 21 (67.7%) were female. The 5-year overall survival rate was 35%, with a median survival of 33 months (95% CI = 34.078-66.861). Being 10 years or older was associated with lower survival (p = 0.002). No significant association with B-cell acute lymphoblastic leukemia was found (p = 0.057).

**Conclusion:** The overall survival rate obtained was similar to that reported in other local studies; however, several international studies have reported better survival rates compared to our findings. Age was identified as a significant factor affecting survival.

**Keywords:** Pediatric, Precursor Cell Lymphoblastic Leukemia, Survival

## Introduction

Acute leukemia is a neoplasm characterized by the clonal proliferation of hematopoietic precursor cells. According to the affected cell lineage, it can be classified into two major groups: lymphoblastic and myeloblastic (1). Acute lymphoblastic leukemia (ALL) is the most common cancer in the pediatric population, leading to significant mortality, especially among children under 6 years of age. This disease has two cellular origins: B and T lymphoid, with the latter being rarer (15-20%) (2) and associated with a poorer prognosis. Worldwide, the incidence of ALL ranges from 1 to 4.75 cases per 100,000 population (2). In the United States, an estimated 5,690 new cases and 1,580 deaths were reported in 2022 (3). In Peru, acute leukemia, predominantly ALL became the most frequent neoplasm among children and adolescents in 2013, comprising 46% of all cancer cases, with a mortality rate of 5.1 cases per 100,000 population(4). The overall survival of pediatric patients with acute lymphoblastic leukemia has significantly improved over the last five decades, with survival rates exceeding 90% at 5 years in developed countries. This improvement is attributed to timely and accurate diagnosis, better understanding of the epigenetic origins of leukemia, the introduction of minimal

residual disease testing, and advancements in therapeutic options (5-8).

However, this success has not been mirrored in Latin America, particularly in Peru. A retrospective cohort study of pediatric ALL patients covered by social insurance (EsSalud) from 2000 to 2013 reported an overall survival rate of 32.5% with a median follow-up of 27 months. Another observational study indicated a near-zero survival rate at 5 years among acute leukemia patients treated in national hospitals in Northern Peru from 2000 to 2015 (9).

Castro-Arechaga et al. identified prognostic factors such as age, leukocyte count, non-B lymphoid lineage, bone marrow relapse, and failure to receive induction treatment. These factors are part of risk stratification criteria, which also include chromosomal alterations, extramedullary involvement, and blast counts in bone marrow and peripheral blood (10).

In light of these findings, this study aimed to determine the overall survival of pediatric ALL patients in a Peruvian hospital, assess the frequency of prognostic factors affecting our population, and provide recommendations for improved management strategies.

## Materials and Methods

An analytical, longitudinal, and retrospective study was conducted involving 31 pediatric patients diagnosed with ALL at Almenara Hospital from January 2015 to December 2016. Eligible patients were under 16 years of age, with diagnoses confirmed by flow cytometry, bone marrow aspirate, and biopsy, and who began chemotherapy treatment according to institutional protocol during the study period. Patients diagnosed with mixed phenotype acute leukemia or those lacking complete data were excluded.

Variables such as age, sex, origin, leukocyte count at diagnosis, phenotype, extramedullary infiltration, cytogenetics, risk group (Table I) (11, 12), response to prednisone (positive if blast count <1000 on day 8 and negative if >=1000), and post-induction minimal residual disease (MRD) (positive if >=0.1 and negative if <0.1) were evaluated. Additionally, 5-year overall survival was measured in months from treatment initiation until death or abandonment. The treatment protocol followed the Clinical Practice Guide for Acute Lymphoblastic Leukemia of the Institute for the Evaluation of Health Technologies and Research (IETSI) of the Social Insurance of Peru (EsSalud) (13).

**Statistical analysis**

Patient records were obtained from the Statistics Office, including both physical and virtual clinical histories. Data analysis was conducted using SPSS 25.00, calculating relative and absolute frequencies of variables. For survival analysis, Kaplan-Meier curves and parametric log-rank tests were performed based on 5-year patient follow-up post-treatment initiation. A Cox regression model assessed hazard ratios for significant variables, with a 95% confidence interval applied.

**Ethical Consideration**

The study received approval from the Institutional Research Ethics Committee (LETTER N°440 GRPA-ESSALUD-2022). Data were managed exclusively by the principal investigator, ensuring confidentiality. Since data were collected from a secondary source, informed consent was not required.

## Results

Forty-one medical records of pediatric patients diagnosed with ALL between January 2015 and December 2016 were initially reviewed. Ten patients were excluded, resulting in a final sample of 31 patients. The majority of patients were aged between 2 and 9 years (67.8%), and 21 were females (67.7%).

Most patients (83.9%) were from Lima. The predominant phenotypic lineage was

common B-stage B lymphoid (64.5%). At diagnosis, 26 patients (83.8%) had a leukocyte count <100,000. The most frequent cytogenetic alteration observed was hypodiploidy (38.7%). Only 1 patient (3.2%) presented with extramedullary infiltration at the central nervous system (CNS) level upon diagnosis. The majority of patients (67.7%) were classified into the high-risk group according to criteria in Table I.

Regarding treatment response, 17 patients (54.8%) showed a good prednisone response, and 20 (64.5%) achieved negative minimal residual disease after induction chemotherapy (Table II).

Kaplan-Meier survival analysis indicated an overall survival rate of approximately 35% at 5 years of follow-up, with a median survival of 33 months (95% CI = 34.078-66.861) (Figure 1). Cox regression analysis, considering age, gender, ALL B-cell type, and response to prednisone, revealed significant associations with age and ALL B-cell type (Table III). Specifically, patients older than 10 years had significantly lower survival rates compared to younger patients. The difference in survival based on B-cell type was not statistically significant (Figure 2).

*Table I: Definition of risk groups in pediatric patients with acute lymphoblastic leukemia (11,12)*

| **Standard or Intermediate Risk group** |
|---|
| **Age at diagnose > 1 or < 9 year** |
| **B-Cell ALL leukocyte count at the beginning <50,000/mm3** |
| **Hyperdiploidy 51-81 chromosomes** |
| **Chromosome translocation 4, 10, 7 or t 12,21)** |
| **Blast count in peripheral blood at day 8 <1000/mm3** |
| **Blast count in bone marrow (BM) at day 14 <5%** |
| **Minimal residual disease (MRD) <0.1% post induction** |
| **High Risk group** |
| **Age >10 years** |
| **B-Cell ALL leukocytes count at the beginning >50,000/mm3** |
| **Pre B-Cell ALL with t(1;19)** |
| **T-Cell ALL** |
| **Hyperdiploidy 47-50 chromosomes** |
| **Hypodiploidy 30-45 chromosomes** |
| **Extramedullary involvement at diagnosis** |
| **Blast count in peripheral blood at day 8 >1000/mm3** |
| **Blast count in bone marrow (BM) at day 14 >5%** |
| **Minimal residual disease (MRD) >0.1% and <1% post induction** |
| **Very High Risk group** |
| **Age <1 year** |
| **B-Cell ALL leukocytes count at the beginning >100,000/mm3** |
| **T-Cell ALL leukocytes count at the beginning >300,000/mm3** |
| **Near haploidy 24-29 chromosomes** |
| **t(9,22) or BCR-ABL** |
| **t(4,11) or MLL** |
| **Blast count in peripheral blood at day 8 >1000/mm3 plus Pro-B ALL or blast count in bone marrow (BM) at day 14 with >25% blasts** |
| **Induction failure: Blast count in bone marrow (BM) >5% post induction, Minimal residual disease (MRD) >1% post induction** |

B-Cell ALL: B-cell Acute lymphoblastic leukemia, BM: Bone marrow, MRD: Minimal residual disease, Tcell -ALL: T-cell Acute lymphoblastic leukemia

*Table II: Epidemiological and clinical characteristics of pediatric patients with acute lymphoblastic leukemia.*

| Characteristics | Dead n=19 (%) | Alive n=12 (%) | Total n=31 (%) | p |
|---|---|---|---|---|
| **Age (years)** | | | | |
| **-<1** | 2 (40.0) | 3 (60.0) | 5 (16.1) | 0.128 |
| **-2 to 9** | 12 (57.1) | 9 (42.9) | 21 (67.8) | |
| **->=10** | 5 (100.0) | 0 | 5 (16.1) | |
| **Sex** | | | | |
| **-Female** | 12 (57.1) | 9 (42.9) | 21 (67.7) | 0.697 |
| **-Male** | 7 (70.0) | 3 (30.0) | 10 (32.3) | |
| **City of origin** | | | | |
| **-Lima** | 16 (61.5) | 10(38.5) | 26 (83.9) | 0.948 |
| **-Province** | 3 (60.0) | 2 (40.0) | 5 (16.1) | |
| **Phenotype** | | | | |
| **-ALL B common** | 12 (60.0) | 8 (40.0) | 20 (64.6) | 0.627 |
| **-ALL Pre-B** | 2 (40.0) | 3 (60.0) | 5 (16.1) | |
| **-ALL Pro-B** | 1 (100.0) | 0 | 1 (3.2) | |
| **-LLA T** | 4 (80.0) | 1 (20.0) | 5 (16.1) | |
| **Extramedullary infiltration** | | | | |
| **-Yes** | 1 (100.0) | 0 | 1 (3.2) | 0.613 |
| **-No** | 18 (60.0) | 12 (40.0) | 30 (96.8) | |
| **Leukocytes (cells/mm $^3$)** | | | | |
| **-<50,000** | 12 (54.5) | 10 | 22 (70.9) | 0.356 |
| **-50,000 to 99,999** | 3 (100.0) | 0 | 3 (9.7) | |
| **->=100,000** | 4 (66.7) | 2 (33.3) | 6 (19.4) | |
| **Cytogenetics** | | | | |
| **-Hypodiploidy** | 6 (50.0) | 6 (50.0) | 12 (38.7) | 0.871 |
| **-Normal** | 4 (50.0) | 4 (50) | 8 (25.8) | |
| **-High hyperdiploidy** | 1 (50.0) | 1 (50.0) | 2 (6.5) | |
| **-Complex** | 2 (100.0) | 0 | 2 (6.5) | |
| **-Trisomy 21** | 2 (100.0) | 0 | 2 (6.5) | |
| **-T (1,19)** | 1 (100.0) | 0 | 1 (3.2) | |
| **-Low mitotic index** | 3 (75.0) | 1 (25.0) | 4 (12.8) | |
| **Prednisone response** | | | | |
| **-Positive** | 11 (64.7) | 6 (35.3) | 17 (54.8) | 0.724 |
| **-Negative** | 8 (57.1) | 6 (42.9) | 14 (45.2) | |
| **Post Induction MRD** | | | | |
| **-MRD-** | 10 (50.0) | 10 (50.0) | 20 (64.5) | 0.128 |
| **-MRD+** | 9 (81.8) | 2 (18.2) | 11 (35.5) | |
| **Risk group** | | | | |
| **-High** | 13 (61.9) | 8 (38.1) | 21 (67.7) | 0.745 |
| **-Standard** | 3 (50.0) | 3 (50.0) | 6 (19.4) | |
| **-Very high** | 3 (75.0) | 1 (25.0) | 4 (12.9) | |

ALL: Acute lymphoblastic leukemia, MRD: Minimal residual disease

*Table III: Cox regression analysis results for overall survival based on significant factor*

| Factor | N | Coefficient | p-value | HR | 95% CI |
|---|---|---|---|---|---|
| **Age (years)** | 31 | 0.722 | 0.017 | 2.059 | 1.139 - 3.724 |
| **Female** | 21 | 0.650 | 0.540 | 1.915 | 0.240 - 15.281 |
| **ALL B** | 26 | -4.242 | 0.021 | 0.014 | 0.000 – 0.521 |
| **PPR** | 17 | 1.145 | 0.261 | 3.144 | 0.427 – 23.134 |

*ALL B: Acute lymphoblastic leukemia B-cell; PPR: Positive prednisone response; HR: Hazard ratio; CI: confidence interval*

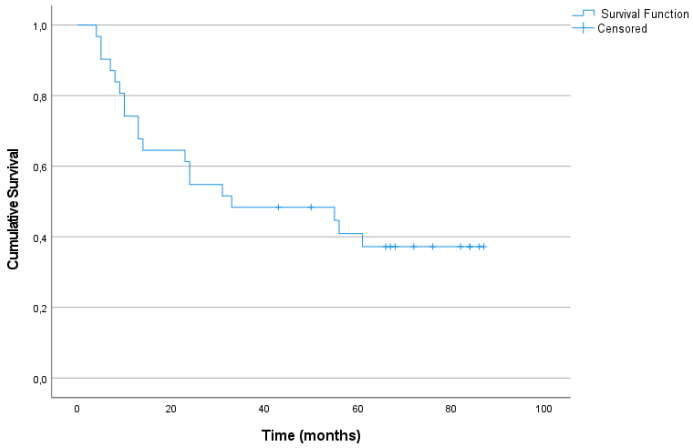


Figure 1. Kaplan-Meier curve for overall five-year survival of pediatric patients with acute lymphoblastic leukemia (OS: 35%, median survival: 33 months).

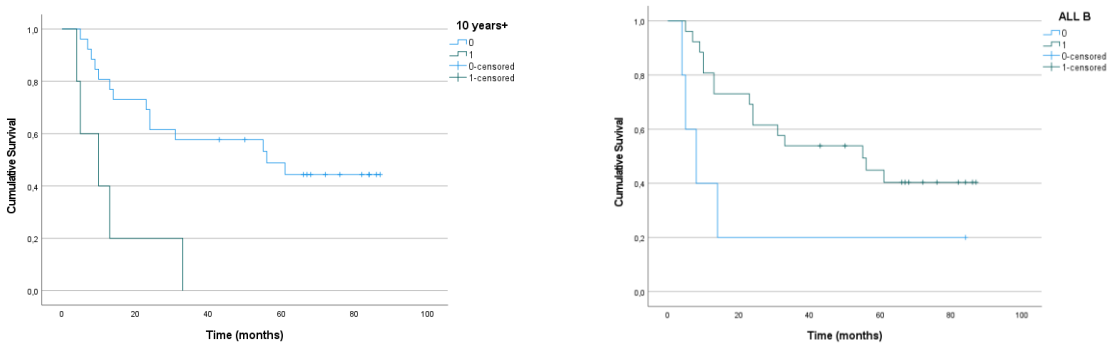


Figure 2. Kaplan-Meier curve for overall survival according to the (A) 10 or more years old (log Rank p-value = 0.002); and (B) Acute lymphoblastic leukemia B-cell (log Rank p-value = 0.057).

## Discussion

Acute lymphoblastic leukemia is the most common neoplasm among children, adolescents, and young adults (1 to 21 years of age) (11-13), and is a significant cause of death. According to the last National Cancer Registry (2010-2012), acute leukemia accounted for 40.2% prevalence among children aged 0 to 14 years, with the lymphoid lineage being the most frequent. These figures position Peru among the countries with the highest incidence of acute leukemia in South America, following Chile and Ecuador, respectively (14).

In Latin America, the predominant age group fluctuated between 1 and 9 years in Argentina and Brazil, according to the International Agency for Research on Cancer (IARC) (3,14). Jiménez de Samudio et al. reported that 67% of Paraguayan children fell within this age range (15). Similar findings were observed in our study, where the age group of 2 to 9 years (16) was most common, aligning

with risk standardization criteria per protocol.

Regarding gender, a recent literature review on ALL in children (2015-2020) found a predominant male incidence of 55% in Latin America (17). However, our study and other national studies indicated a higher incidence among females (9, 18).

Geographically, the majority of cases originated from Lima, consistent with findings from the retrospective cohort of Castro-Arechaga et al., conducted in a national social security hospital (9). Other originating departments included Huánuco, Junín, San Martín, and Amazonas

In the clinical data, the predominant phenotypic lineage considered was B lymphoid, which is globally predominant, reported at approximately 80% (2). The most common maturation stage observed was common B, consistent with findings by Mendoza and Pozo(16) The leukocyte count predominantly ranged from above 50,000 to below 100,000 cells/$mm^3$, differing from Castro-Arechaga et al.'s report where 71.8% presented with less than 50,000 leukocytes(9) The predominant cytogenetic abnormality observed was hypodiploidy, affecting 38.7% of cases. Only one case presented with extramedullary infiltration at the CNS level at initial diagnosis. Molecular studies were not included as a variable due to technical limitations at the institution during the study period

Until a few years ago, the approach and management of pediatric patients with ALL in Peruvian Social Security hospitals were based on the IETSI protocol published in 2011, a protocol with indications adjusted by risk group (16). In our study, we evaluated two treatment variables: the response to prednisone, which was positive in 54.8%—a higher percentage than that found in the cohort study of the Rebagliati hospital—and the minimal residual disease (MRD) at the end of induction, which was negative in 64.5% of our population, similar to findings reported in another national study (10).

This treatment protocol established three risk groups: standard, high, and very high risk. In our population, the high and very high-risk groups accounted for 80.6%, similar to another national study reporting 75.2% (10). In contrast to reports from non-American countries such as Turkey, where Güneş et al. found the predominant risk group was intermediate at 66%, with only 21% of patients belonging to the high-risk group according to the BFM-95 protocol (19).

One of the explanations for the improved survival of pediatric patients with ALL has been the better understanding of the disease's pathophysiology and the use of treatment protocols tailored to different risk groups. Recent reviews have highlighted high survival rates with protocols such as ALL-BFM 2009 (20) which is currently recommended for treating ALL in children and adolescents covered by Social Security (16). During our study period, the reference protocol followed the Clinical Practice Guide of Essalud(13,14). The five-year survival rate observed was approximately 40%, similar to findings from previous local studies (9, 10), but lower compared to some neighboring countries. Querol et al. reported a survival rate of 73.3% among Cuban children (21).

The prognosis of the disease is significantly affected by high and very high-risk groups, as reflected in the survival rates recorded in our study. Another contributing factor, although not discussed in this publication, is poor adherence or delays in treatment administration. For instance, Díaz Silva et al. found in a study conducted at a hospital in Lambayeque, Peru, that the waiting period for subsequent chemotherapy exceeded 30 days in some cases, far exceeding the average of seven days

typically recommended for neoplastic cell regeneration (22).

When analyzing based on the cell type of ALL, we found that the B-cell type had a better prognosis than the T-cell type (p=0.057), similar to findings reported by Castro-Arechaga et al. (10).However, no significant difference was found in the response to treatment (minimal residual disease) and prognosis, as reported by Shen S et al. in a long-term study from May 2004 to December 2015 in China, where failure of induction or positive MRD at day 35 was associated with a worse prognosis(23).

Among the limitations, we can mention that the data were obtained from a secondary source (clinical records), so it was not possible to identify all patients, and the study was conducted at a single hospital. To mitigate these biases, well-defined selection criteria and double data review were employed, although this reduced the number of participants. We believe our study contributes to understanding the landscape of ALL in our country and can guide future research.

The overall survival rate of around 35% observed in our study, consistent with earlier studies, reflects the reality of pediatric ALL in our country. However, it contrasts with international figures. One possible explanation, supported by national studies, is the predominance of high-risk groups.

Performing complete cytogenetic and molecular studies at diagnosis is crucial for accurately stratifying patients and adhering to established treatment protocols. Achieving negative minimal residual disease after induction chemotherapy is critical as it significantly impacts survival.

Finally, there is a need to standardize risk assessment criteria and establish a uniform treatment protocol across all hospitals in the country, irrespective of the healthcare provider.

## Conclusion

The overall survival rate obtained was similar to that reported in other local studies; however, several international studies have reported better survival rates compared to our findings. Age was identified as a significant factor affecting survival.

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## Authors' contribution

MAM and JAT made conception and design of the work; MAM, ESA, CDB and IPM contribute to conception of the work, participated in the acquisition, analysis, and interpretation of data, MAM and JAT wrote the main manuscript text and supervised data interpretation; All authors reviewed, approved, and accept responsibility for this manuscript.

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## Conflict of interest

The authors declare that they have no competing interests.

## Ethical considerations

The research was conducted with the approval of the Ethics Committee of Almenara Hospital (LETTER N°440 GRPA-ESSALUD-2022). All methods were performed in accordance with the relevant guidelines and regulations (Declaration of Helsinki).

## References

1. Jaime-Pérez JC, Gómez-Almaguer D. Hematología. La sangre y sus enfermedades. 4th ed. México: Mc Graw Hill Interamericana Editores 2015: 77-82.

2. Swerdlow SH, Campo E, Pileri SA, Lee N, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016; 127(20):2375-2390.
3. National Cancer Institute. Acute Lymphocytic Leukemia - Cancer Stat Facts. Surveillance, Epidemiology, and End Results Program (SEER) 2023.
4. Dirección general de epidemiología. La carga de leucemias en el Perú. Ministerio de Salud de Perú. Bol. Epidemiol (Lima) 2014; 23(32): 630-649.
5. Inaba H, Mullighan CG. Pediatric acute lymphoblastic leukemia. Haematologica 2020;105(11):2524-2539.
6. Nordlund J, Syvänen AC. Epigenetics in pediatric acute lymphoblastic leukemia. Semin Cancer Biol 2018; 51:129-138.
7. De Angelo DJ, Jabbour E, Advani A. Recent Advances in Managing Acute Lymphoblastic Leukemia. Am Soc Clin Oncol Educ Book 2020; 40:330-342.
8. Agrwal S, Sahi PK. National Comprehensive Cancer Network Guidelines for Pediatric Acute Lymphoblastic Leukemia. Indian Pediatr 2020; 57(6):561-564.
9. Tello-Vera S, Colchado-Aguilar J, Carpio-Vásquez W. Supervivencia de pacientes con leucemias agudas en dos hospitales de la seguridad social del Perú. Rev Venez de Oncol 2018; 30(1): 2-9.
10. Castro-Arechaga S, Ronceros-Salas L, Vega-Centeno S, Moreno M, Soto A. Sobrevida global y libre de enfermedad en una cohorte peruana de pacientes con leucemia linfoblástica aguda. Rev. perú. med. exp. salud pública 2018; 35(3): 416-424.
11. Stary J, Zimmermann M, Campbell M, Castillo L, Dibar E, Donska S, et al. Intensive chemotherapy for childhood acute lymphoblastic leukemia: results of the randomized intercontinental trial ALL IC-BFM 2002. J Clin Oncol 2014; 32(3):174-184.
12. Berry DA, Zhou S, Higley H, Mukundan L, Fu S, Reaman GH, et al. Association of Minimal Residual Disease With Clinical Outcome in Pediatric and Adult Acute Lymphoblastic Leukemia: A Meta-analysis. JAMA Oncol 2017; 3(7):e170580-170585.
13. Dirección de Prevención y Control de Cáncer. Plan nacional para la atención integral de la leucemia linfática aguda en pacientes de 1 a 21 años. 2017-2021. Lima: Ministerio de Salud 2017:1-26.
14. International Agency for Research on Cancer. The International Incidence of Childhood Cancer. Volumen 3. Lyon: World Health Organization; 2017.
15. Jiménez de Samudio A, Samudio M, Caniza MA. Risk Factors associated to survival in children and adolescent with Acute Lymphoblastic Leukemia. Pediatr (Asuncion) 2016;43(1):18-26.
16. Rojas N, Moreno M, Pizarro M, Aranda L, Arteta C, Eyzaguirre R, et al. Guía de Práctica Clínica para el manejo de pacientes con Leucemia Linfoblástica Aguda en el Seguro Social del Perú (EsSalud). Acta méd. Peru 2021; 38(1): 64-78.
17. Mendoza M, Pozo C. Prevalencia de Leucemia Linfoblástica Aguda en niños: Análisis citogenético y valor pronóstico. Pol. Con 2021; 6(7):346-377.
18. Morales FP, Ambulay R. Perfil clínico-hematológico y epidemiológico en los pacientes pediátricos con cáncer linfohematopoyético en un hospital de Piura-Perú, 2014-2018. Arch Med (Manizales) 2019; 20(1):62–70.
19. Güneş AM, Oren H, Baytan B, Bengoa SY, Evim MS, Gözmen S, et al. The long-term results of childhood acute lymphoblastic leukemia at two centers from Turkey: 15 years of experience with the ALL-BFM 95 protocol. Ann Hematol 2014; 93(10):1677–84.
20. Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children. N Engl J Med 2015;373(16):1541–1552.

21. Querol N, Chávez MI, Leblanch CC, Jimenez N. Caracterización clinicoepidemiológica y supervivencia de pacientes menores de 19 años con leucemia. Medisan 2021; 25 (1): 26-40.
22. Tafur-Hoyos BA, Burga-Guevara DK, Sánchez-Neira C, Díaz-Silva VH. Diferimiento y recaída post-inducción quimioterápica en niños con leucemia linfoblástica aguda en un hospital nacional de Lambayeque. Rev. Cuerpo Med. HNAAA 2022;15(1):81-85.
23. Shen S, Cai J, Chen J. Long-term results of the risk-stratified treatment of childhood acute lymphoblastic leukemia in China. Hematol Oncol 2018; 36(4):679-688.