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Article

Pediatric Patients with Acute Lymphoblastic Leukemia in Honduras: Demographic Characteristics, Clinical Features, and Laboratory Findings. Seeking a Prompt and Accurate Diagnosis for Childhood Leukemia

Pacientes Pediátricos con Leucemia Linfoblástica Aguda en Honduras: Características Demográficas, Aspectos Clínicos y Hallazgos de Laboratorio
En búsqueda de un diagnóstico rápido y eficiente de la leucemia infantil

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SUMMARY

Approximately 90% of confirmed cancer cases annually are reported in low to middle-income countries. In Honduras, the incidence of pediatric cancer has been steadily increasing, accompanied by a higher cancer mortality rate attributed to diagnostic errors, limited access to healthcare, and management challenges. Diagnostic pitfalls, such as failure to recognize signs of malignancy, inadequate assessment of persistent symptoms, and misinterpretation of diagnostic tests, significantly impede effective cancer care. This retrospective case study collected data from 68 pediatric patients diagnosed with Acute Lymphoblastic Leukemia (ALL) at the Honduran Social Security Institute in Tegucigalpa between January 2015 and December 2022. Data retrieval encompassed demographic features, clinical characteristics, and laboratory findings. We used SPSS Statistics version 29.0.2.0 to perform all statistical analysis. The cohort comprised patients of equal gender distribution, with 42.6% (N: 29) belonging to the age group of 1 to 4 years. The hospital diagnosed an average of 8.5 cases each year. Fever was the most prevalent symptom, affecting 80.9% of patients (*N:* 55). Hemoglobin levels were below 10 mg/dL in 67.6% of patients, with 33.8% exhibiting levels below 7 mg/dL (*N:* 23) and equal proportion falling within the 7-10 mg/dL range (*N:* 23). Platelet levels were below 150,000/µL, with 48.5% experiencing severe thrombocytopenia (platelet levels <50,000/µL). Additionally, most patients presented phosphorus levels exceeding 4.5 mg/dl (*N:* 33, 48.5%), along with elevated LDH levels surpassing 500 U/l (*N:* 34, *P:* 50%). The presence of persistent fever should trigger suspicion of cancer, necessitating thorough assessment. Implementing guidelines outlining common symptoms and referral protocols could significantly reduce mortality in Honduran children with ALL.

Keywords: Pediatrics; acute lymphoblastic leukemia; low-income population

1. Introduction

Cancer continues to pose a significant threat to pediatric populations worldwide. The World Health Organization (WHO) estimates 400,000 confirmed cases of cancer annually among children and adolescents aged 0 to 19 years (WHO, 2021). Since 1975, there has been a steady annual increase of 0.8% in cancer incidence, with leukemia emerging as the most frequently diagnosed type, closely followed by brain and nervous system tumors (Siegel, *et al.*, 2022; Howlader, *et al.*, 2018).

Approximately 90% of confirmed annual cancer cases occur in low to middle-income countries (WHO, 2021). In Honduras, between 2007 and 2016, the incidence rate stood at 10.6 per 100,000 inhabitants under 15 years old, with leukemia accounting for the highest number of diagnoses and a national survival rate of 58% (PAHO, 2016). By 2021, this incidence had risen, with a pediatric cancer rate of 41.5 per million inhabitants under 18 years old (OMS, 2021).

Among pediatric cancers, acute lymphoblastic leukemia (ALL) reigns as the most prevalent type. Despite a global 5-year survival rate surpassing 70%, this percentage reduces in low to middle-income countries due to many challenges, including diagnostic errors, limited access to medical care, treatment discontinuation, toxicity, and relapses (WHO, 2021).

Diagnostic setbacks in ALL patients pose a universal challenge, particularly prevalent in low to middle-income countries (Carberry, *et al.*, 2017). These delays in diagnosis stem from numerous factors, such as insufficient awareness of childhood cancer, limited referral networks, and obstacles in accessing specialized care facilities (WHO, 2021). A simulation-based analysis in 2019 projected a staggering 6.7 million childhood cancer cases worldwide between 2015 and 2030. Worryingly, under the current healthcare framework, an estimated 2.9 million cases are expected to go undiagnosed (Ward, *et al.*, 2019). Common diagnostic pitfalls often include inadequate assessment of persistent symptoms, failure to recognize signs indicative of malignancy, and misinterpretation of diagnostic tests (Carberry, *et al.*, 2017).

More research and publications are needed in Honduras to address leukemia's clinical and laboratory manifestations. The need for more local studies limits our ability to identify unique patterns and characteristics of leukemia in Honduran children and adolescents, as well as to draw comparisons with global data. Moreover, standardized protocols need to be improved for a better system for referral, diagnosis, and appropriate treatment of patients.

2. Material and Method

This retrospective case study collected data from 68 patients diagnosed at the Honduran Social Security Institute in Tegucigalpa, Honduras. These patients have a confirmed diagnosis of ALL by bone marrow biopsy, ages 0 to 18 years. Data collection spanned from January 2015 to December 2022. All included patients had not received prior antineoplastic treatment. Two physicians retrieved data from digital and physical medical records, encompassing demographic features, clinical characteristics, and laboratory findings. We conducted descriptive statistical analysis to summarize epidemiological trends, clinical characteristics, and laboratory parameters of pediatric patients diagnosed with ALL. Data was summarized using frequency tables and percentages to describe demographic variables, clinical characteristics, and laboratory parameters. We used SPSS Statistics version 29.0.2.0 to perform all statistical analysis.

3. Results

Gender did not show any significant discrepancy in the diagnosis of ALL, with equal prevalence observed among both male and female patients. A notable proportion of diagnosed patients fell within the age range of 1 to 4 years (*N*: 29, *P:* 42.6%), followed by those aged 5 to 11 (*N:* 21, *P:* 30.9%). Most cases originated from the Francisco Morazán department (*N:* 47, *P:* 69.1%), followed by Choluteca (*N:* 6, *P:* 8.8%) and Comayagua (*N:* 4, *P:* 5.9%). Over the observation period, an average of 8.5 cases were diagnosed annually, with the highest number of cases diagnosed in 2019 (*N:* 11, *P:* 16.2%). *(Table I)*

Table I: Demographic Characteristics of Pediatric Patients with ALL Diagnosed in the Honduran Social Security Institute, Tegucigalpa, Honduras.

Gender	*N*	*P*
Male	34	50.0
Female	34	50.0
Age		
0 to 1	1	1.5
1 to 4	29	42.6
5 to 11	21	30.9
12 to 18	17	25.0
Origin		
Francisco Morazan	47	69.1
Choluteca	6	8.8
Comayagua	4	5.9
La Paz	3	4.4
El Paraiso	3	4.4
Valle	2	2.9

Olancho	1	1.5
Intibucá	1	1.5
Copán	1	1.5
Year	*N*	*P*
2015	8	11.8
2016	6	8.8
2017	10	14.7
2018	3	4.4
2019	11	16.2
2020	10	14.7
2021	10	14.7
2022	10	14.7
Status		
Treatment	29	42.6
Surveillance	16	23.5
Relapse	5	7.4
Deceased	18	26.5

Currently, patients are undergoing treatment (*N*: 29, *P:* 42.6%), under surveillance (*N*: 16, *P:* 23.5%), have experienced relapse (*N*: 5, *P:* 7.4%), or are deceased (*N*: 18, *P:* 26.5%). Immunophenotyping revealed that among the 68 patients, Pre-B was the most frequent immunophenotype (*N*: 61, *P:* 89.7%), followed by T cells (*N*: 4, *P:* 5.9%) and B cells (*N*: 3, *P:* 4.4%). Fever was the most prevalent symptom (*N*: 55, *P:* 80.9%), followed by pallor (*N*: 39, *P:* 57.4%), adynamia (*N*: 36, *P:* 52.9%), hepatomegaly (*N*: 35, *P:* 51.5%), and anorexia (*N*: 31, *P:* 45.6%). *(Table II)*

Table II: Clinical Features of Pediatric Patients with ALL Diagnosed in the Honduran Social Security Institute, Tegucigalpa, Honduras.

Clinical Manifestation	*N*	*P*
Fever	55	80.9
Pallor	39	57.4
Adynamia	36	52.9
Hepatomegaly	35	51.5
Anorexia	31	45.6
Tachycardia	30	44.1
Lymphadenopathy	29	42.6
Splenomegaly	24	35.3
Ecchymosis	16	23.5
Heart murmur	12	17.6
Weight loss	12	17.6
Petechiae	10	14.7
Bone pain	8	11.8
Epistaxis	7	10.3
Transvaginal bleeding	2	2.9
Gingival bleeding	1	1.5

Regarding laboratory characteristics, most ALL patients exhibited low hemoglobin levels below 10 mg/dl. Leukocyte counts showed patients with counts less than 10,000/µL (*N*: 34, *P:* 50%), followed by patients falling within the 10,000-50,000/µL (*N*: 21, *P:* 30.9%). Lymphocytes predominated among the leukocyte population, with neutrophil counts below 500/µL (*N*: 35, *P:* 51.5%). Most of the population had platelet levels less than 150,000/µL, with 48.5% experiencing severe thrombocytopenia with platelet levels less than 50,000/µL. Additionally, most patients presented phosphorus levels exceeding 4.5 mg/dl (*N*: 33, *P:* 48.5%), along with elevated LDH levels surpassing 500 U/l (*N*:34, *P:* 50%). *(Table III)*

Table III: Laboratory Findings of Pediatric Patients with ALL Diagnosed in the Honduran Social Security Institute, Tegucigalpa, Honduras.

Hemoglobin (mg/dL)	*N*	*P*
<7	23	33.8
7-10	23	33.8
>10	22	32.4
Leucocytes (/µL)		
<10,000	34	50.0
10,000-50,000	21	30.9
50,000-100,000	6	8.8
>100,000	7	10.3
Lymphocytes (/µL)		
<10,000	34	50.0
10,000-50,000	21	30.9
50,000-100,000	6	8.8
>100,000	7	10.3
Neutrophils (/µL)		
<500	35	51.5
500-1,000	10	14.7
1,000-1,500	3	4.4
>1,500	20	29.4
Platelets (/µL)		
<20,000	16	23.5
20,000-50,000	17	25.0
50,000-100,000	13	19.1
100,000-150,000	6	8.8
>150,000	16	23.5
Blasts*		
Positive	52	76.5
Negative	16	23.5
BUN (mg/dL)		
<10	34	50.0
10-20	33	48.5
>20	1	1.5
Creatinine (mg/dL)		
<0.5	34	50.0
0.5-1	30	44.1
>1	4	5.9

Phosphorus (mg/dL)		
<2.5	4	5.9
2.5-4.5	26	38.2
>4.5	33	48.5
N/D	5	7.4
Potassium (mEq/L)		
<3.5	3	4.4
3.5-4.5	51	75.0
4.5-6.5	2	2.9
>6.5	11	16.2
N/D	1	1.5
Calcium (mg/dL)		
<8	6	8.8
8-10	51	75.0
>10	9	13.2
N/D	2	2.9
LDH (u/L)		
<150	2	2.9
150-500	27	39.7
500-1,000	16	23.5
>1,000	18	26.5
N/D	5	7.4
Uric Acid (mg/dL)		
<5	30	44.1
5-8	19	27.9
>8	10	14.7
N/D	9	13.2

*Considered positive with the presence >20% of blasts in peripheral blood smear.

4. Discussion

Demographic Characteristics

In this study, no gender predominance was observed, with an equal distribution between males and females, each comprising 50% of the population. While global statistics indicate a slight prevalence of male children over females, as observed in both the US, Latin, and regional populations (American Cancer Society, 2023; Rivera, 2016; Tábora, 2017), our findings contrast with previous studies.

The age distribution analysis revealed that the highest number of cases occurred within the age range of 1 to 4 years, accounting for 42.6% of the total cases, followed by the age group of 5 to 11 years, comprising 30.9% of cases. This pattern is consistent with local and global literature, which suggests a higher frequency of cases occurring between the ages of 2 and 5 years (American Cancer Society, 2024; Lassaletta, 2016; Raetz, 2014; Alas, *et al.*, 2022). The distribution is similar to a study conducted at the Pontifical Catholic University of Ecuador, where the age group of 1 to 4 years also exhibited the highest number of cases, followed by the 5 to 12 years age group (Bonilla, 2019).

In Honduras, the survival rate for childhood leukemia in 2021 stood at 58% (PAHO, 2016). Our sample revealed a mortality rate of 26.5%, similar to the mortality rate between 25-29.5% previously seen in Hospital Mario Catarino Rivas in standard, intermediate, and high-risk patients (Alas, *et al.*, 2022). The primary causes of mortality seem to be linked to infectious complications, as evidenced by a study conducted at Hospital Escuela, where 75% of patients experienced such complications (Miralda, 2021; Toquica, *et al.*, 2016).

Misdiagnosis remains a significant concern in childhood leukemia, with estimates suggesting that 50% of cases may go undiagnosed and less than 20% will achieve a cure. This issue was reflected in our population by previous instances where healthcare workers treated some children with persistent fever for possible infectious conditions before confirming a leukemia diagnosis. Furthermore, referred children from outside Tegucigalpa faced additional hurdles, such as traveling independently due to unclear referral systems or protocols, exacerbating the delay in receiving appropriate medical attention.

Clinical Features

Clarke et al. highlighted that fever, pallor, and anorexia/weight loss are more commonly observed symptoms in low-income/moderate-income settings compared to high-income settings (Clarke, *et al.*, 2016). In this study, fever emerged as the most frequently observed clinical manifestation (*N*: 55, *P:* 80.9%). Notably, fever has been documented as one of the most common symptoms in Latin America, ranking second at the University Clinic of Colombia and the Department of Pediatric Hemato-oncology at the Faculty of Medical Sciences, National University of Asunción (Jimenez, et al., 2016; Toquica, *et al.*, 2016).

Pallor emerged as the second most prevalent symptom (*N*: 39, *P:* 57.4%). Prior research found pallor to be the most frequent symptom in 83.6% of patients across six hospitals in Bogotá and Bucaramanga, Colombia (Castro, *et al.*, 2015). Similarly, the anemic syndrome emerged as the most frequent clinical presentation in 80% of cases in a hospital in Piura, Peru (Morales, *et al.*, 2020).

Visceral enlargement was frequently found in physical examination, particularly hepatomegaly (*N*: 35, *P:* 51.5%). International literature suggests hepatomegaly presents in up to 68% of cases, and over 50% of children diagnosed with leukemia display palpable livers upon diagnosis (Clarke, *et al.*, 2016; Margolin, *et al.*, 2021). A report from Hospital Escuela in Tegucigalpa, Honduras, from 2015 to 2017 described hepatosplenomegaly as a common finding in patients experiencing ALL relapses (Medina, *et al.*, 2020).

Lymphadenopathy was a frequently reported finding (*N*: 29, *P:* 42.6%), and it is considered a high indicator of leukemia in pediatric patients, particularly noted in the neck and axilla lymph node chains (Castro, *et al.*, 2015).

Laboratory Findings

A significant portion, comprising 67.6% of the patient cohort, exhibited hemoglobin levels below 10 mg/dL, closely mirroring percentages observed at Hospital Mario Catarino Rivas (84.1%) and Hospital Infantil de Morelia (87.4%) (Alas, *et al.*, 2022; Rivera, 2016). Moreover, severe anemia was apparent in 33.8% of patients with hemoglobin below 7 mg/dL. This reflects the prevalence noted among pediatric cases at Hospital Escuela, where 34.8% exhibited hemoglobin levels below 7 mg/dL (Medina, *et al.*, 2020).

80.9% of the patients displayed leukocyte counts below 50,000/µL. Patients with a high total WBC count are classified as high-risk cases, with a count of 50,000/µL, a cutoff point to consider a worse prognosis. (Layton, 2015) A minority, constituting 10.3%, demonstrated counts exceeding 100,000/

µL. These findings closely align with those observed at Hospital Mario Catarino Rivas, where only 13.2% of the sample exhibited leukocytosis exceeding 100,000/µL (Alas, *et al.*, 2022). More than half of the patients showcased severe neutropenia (<500/µL) at a rate of 51.5%. Severe neutropenia has been identified as a contributing factor to the deterioration of oncological patients, as evidenced by cases observed at Hospital Escuela, where severe neutropenia was present in up to 34.1% of the patients (Miralda, 2021).

Most exhibited thrombocytopenia, a common finding previously documented in patients at Hospital Escuela (Miralda, 2021). Platelet distribution mirrored the results observed at Hospital Mario Catarino Rivas, with platelet values below 50,000/µL detected in 48.5% of our sample and 57.9% at this hospital (Alas, *et al.*, 2022). Additionally, there is a 23.4% incidence of platelet counts below 20,000/µL, a condition previously regarded as unfavorable and predisposing to central nervous system infiltration in patients at Hospital Escuela (Medina, *et al.,* 2020).

Parameters indicative of tumor lysis syndrome were evident, with 8.8% of patients exhibiting calcium concentration below 8 mg/dL, 14.7% showing uric acid levels exceeding 8 mg/dL, and 16.2% displaying potassium levels surpassing 6.5 mEq/L. There are comparable occurrences at Hospital Infantil de Morelia, Mexico, with hyperuricemia at 15.6% and hyperkalemia at 9.8% of their population (Rivera, 2016). Notably, our patients exhibited markedly elevated phosphate values, with over 48.5% registering levels above 4.5 mEq/L, contrasting with previously reported findings. Additionally, elevated LDH levels were observed in more than 50% of patients, exceeding 500 u/L. This elevation in LDH is associated with a high tumor burden and leukocyte count >50,000/µL (Rivera, 2016).

In peripheral blood smears, blasts tested positive in 76% of cases and negative in 24% of cases, mirroring the trend seen at Hospital Infantil de Morelia, where the positivity rate stood at 86.2% and the negativity rate at 13.7% (Rivera, 2016). As for immunophenotype analysis, most cases, constituting 90%, were identified as early pre-B-cell acute lymphoblastic leukemia (ALL), followed by 6% diagnosed as T-cell ALL and 4% as B-cell ALL. These findings closely align with global and regional incidence rates (Alas, *et al.*, 2022; Medina, *et al.,* 2020; Reyes, *et al.*, 2021).

5. Conclusion

When faced with persistent fever in children, leukemia should be among the possible diagnoses considered. A complete blood count can unveil significant hemoglobin, leukocytes, and platelet irregularities to aid early detection. Moreover, conducting a thorough physical examination to detect lymphadenopathies and hepatosplenomegaly is crucial. It is concerning that only 20% of countries globally have established early detection programs or guidelines for childhood cancer symptoms in primary care settings (WHO, 2020). Hence, formulating comprehensive guidelines outlining vital clinical indicators and establishing clear referral protocols for primary healthcare providers in Honduras could mitigate mortality resulting from diagnostic delays.

Ethical Considerations

This study was approved by the Ethics Committee of the Honduran Social Security Institute on March 13, 2024, under Record 006-CB-HE-2023, with data retrieval authorized by the Medical Management Department.

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Disclosure

All authors have declared no conflicts of interest.

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RESUMEN

Aproximadamente el 90% de los casos confirmados de cáncer anualmente se reportan en países de ingresos bajos a medios. En Honduras, la incidencia de cáncer pediátrico ha aumentado, con una mayor mortalidad atribuida a errores de diagnóstico, acceso limitado a la atención médica y desafíos en el manejo. Los errores diagnósticos, como no reconocer signos de malignidad, evaluación inadecuada de síntomas persistentes e interpretación errónea de pruebas diagnósticas, dificultan la atención efectiva del cáncer. Este estudio retrospectivo comprende una muestra de 68 pacientes pediátricos diagnosticados con Leucemia Linfoblástica Aguda (LLA) en el Instituto Hondureño de Seguridad Social en Tegucigalpa entre enero de 2015 y diciembre de 2022. La recopilación de datos incluyó características demográficas, clínicas y hallazgos de laboratorio; con análisis estadístico utilizando SPSS Statistics versión 29.0.2.0. La cohorte comprendía pacientes de igual distribución por género, con el 42.6% (N: 29) perteneciendo al grupo de edad de 1 a 4 años. El hospital diagnosticó un promedio de 8.5 casos cada año. La fiebre fue el síntoma más prevalente, afectando al 80.9% de los pacientes (N: 55). Los niveles de hemoglobina fueron inferiores a 10 mg/dL en el 67.6% de los pacientes, con el 33.8% por debajo de 7 mg/dL (N: 23) y una proporción igual dentro del rango de 7-10 mg/dL (N: 23). Los niveles de plaquetas fueron inferiores a 150,000/µL, con el 48.5% experimentando trombocitopenia severa (niveles de plaquetas <50,000/µL). Además, la mayoría de los pacientes presentaron niveles de fósforo superiores a 4.5 mg/dL (N: 33, 48.5%) y niveles elevados de LDH que superaban los 500 U/L (N: 34, P: 50%). La presencia de fiebre persistente debe despertar sospechas de cáncer, requiriendo una evaluación exhaustiva. La implementación de guías que delineen síntomas comunes y protocolos de referencia podría reducir significativamente la mortalidad en niños hondureños con LLA.

Palabras clave: Pediatría; leucemia linfoblástica aguda; población de bajos ingresos