

RISK FACTORS AND OUTCOMES OF HYPERLEUKOCYTOSIS IN PEDIATRIC ACUTE LEUKEMIA: A FIVE-YEAR RETROSPECTIVE CASE-CONTROL STUDY AT TIKUR ANBESA SPECIALIZED HOSPITAL, ADDIS ABABA, ETHIOPIA.

A RESEARCH THESIS TO BE SUBMITTED TO ADDIS ABABA UNIVERSITY, COLLEGE OF HEALTH SCIENCES; PEDIATRICS AND CHILD HEALTH DEPARTMENT IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE SPECIALTY CERTIFICATE PROGRAM IN PEDIATRICS AND CHILD HEALTH

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Acronyms and abbreviations

WBC – White Blood Cell

RBC- Red blood cell

ANC- Absolute Neutrophil Count.

ALL - Acute Lymphoblastic Leukemia

Acute Myeloid Leukemia (AML)

APML-Acute Promyelocytic Leukemia

CML - Chronic Myeloid Leukemia

LDH - Lactate Dehydrogenase

LAP-Lymphadenopathy

HSM- Hepatospleenomegally

CNS- Central Nervous System

TLS- Tumor Lysis Syndrome

TASH_ Tikur Anbessa Specialized Hospital

PI- main investigator

SES- Socio-Economic Status

LMIC – Low and medium income countries

BMA-Bone marrow aspirate

IHC-Immuno histochemistry

WHO – World health organization

COG Children's Oncology Group

RFT- Renal function test

BUN – Blood Urea Nitrogen

Cr- Creatine

UA- Uric Acid

CXR - chest x-ray

SPSS—Statistical Package for Social Sciences

SPNN-Southern Peoples Nations Nationalities

ATRA- All trans-retinoic acid

Abstract

Background:

Hyperleukocytosis is a pediatric oncologic emergency in acute leukemia associated with leukostasis, tumor lysis syndrome, and early mortality. Despite its clinical importance, the data on risk factors and outcomes of hyperleukocytosis in children with acute leukemia are limited in low-resource settings.

Objective:

To identify risk factors and early outcomes of hyperleukocytosis among pediatric acute leukemia patients at Tikur Anbesa Specialized Hospital, Addis Ababa, Ethiopia.

Methods:

A five-year case-control study took place at the pediatric hematology-oncology unit of Tikur Anbesa Specialized Hospital from April 1, 2020, to March 31, 2025. The study included children under 18 years with newly diagnosed acute leukemia. Cases were patients with hyperleukocytosis (white blood cell count ≥100,000/μL) at diagnosis, and controls were patients without hyperleukocytosis in a 1:2 ratio. Researchers collected data using a structured checklist and analyzed it with SPSS version 29. They calculated descriptive statistics and made comparisons between groups using chi-square and Mann-Whitney U tests. They used multivariable logistic regression analysis to find independent risk factors and predictors of early mortality. The study reported adjusted odds ratios (AOR) with 95% confidence intervals, and a p-value of less than 0.05 was considered statistically significant.

Results:

A study of 153 patients diagnosed with pediatric acute leukemia indicated that 51 of these patients presented with hyperleukocytosis and the remaining 102 served as the control group for this study. The association between hyperleukocytosis at the time of presentation and respiratory symptoms, peripheral blast percentage, uric acid concentration, and leukemia subclass was found to be statistically significant. Multivariate analysis demonstrated that respiratory symptoms (AOR = 5.74), acute myeloid leukemia (AOR = 4.23), peripheral blast percentage (AOR = 1.045), and uric acid level (AOR = 1.213) were independent risk factors for hyperleukocytosis. Patients with hyperleukocytosis had significantly more complications than patients without hyperleukocytosis (88.2% vs 57.8%) and greater than the patients without hyperleukocytosis (25.5% vs 5.9%). Our study further demonstrated that hyperleukocytosis (AOR = 19.31), respiratory symptoms (AOR = 10.37), low platelet count (AOR = 0.942), and elevated uric acid (AOR = 1.302) were independent predictors of early mortality.

Conclusion:

Pediatric acute leukemia patients who have hyperleukocytosis, have a much higher risk of developing

complications and dying shortly thereafter. The factors that independently predict response to treatment in these patients include respiratory symptoms, AML type, high number of peripheral blasts in the blood, and the presence of elevated uric acid levels. To reduce mortality in any sub-group of high-risk patients, they need to be identified early, and appropriate supportive care should be started quickly.

Keywords: Hyperleukocytosis, Pediatric acute leukemia, Case-control study, Risk factors, Early mortality, Ethiopia.

1. Introduction

1.1 Background

Globally, children and adolescents compose nearly 25% of the world's population, with an estimated 85 percent living in low to very-low countries. (1) As of 2030, UNICEF predicts that 47 percent of the entire African population will be aged 18 years old and younger. The total number of these populations are projected to continue to increase until approximately 2.53 billion by the year 2026. This is particularly relevant to low- or middle-income countries where access to health services designed specifically for children and adolescents is severely limited. Ensuring that children and adolescents are developing in a healthy manner (both physically and emotionally) is essential to their success as they represent not only the greatest resource any society has, but also the future of that society; their development will have a significant effect on that society's overall development. (2)

Annually, approximately 400,000 children receive a diagnosis of cancer. In developed nations where most of their citizens have access to comprehensive health services, 80% of children diagnosed with a form of cancer have been successfully treated. In lesser developed countries that cannot provide access to similar services, only 30% of children diagnosed with some form of cancer have received any type of successful treatment. (WHO) In 2020, leukemia was responsible for about 2.5% of the total number of new cancer cases globally, which resulted in approximately 3.1% of all global deaths due to cancers. (3)
Pediatric oncological emergencies contribute substantially to the mortality and morbidity associated with pediatric oncology, especially in low- and middle-income countries (LMICS). Hyperleukocytosis, which occurs when the white blood cell count exceeds 100,000 cells/μL, represents one of the most common oncologic emergencies in pediatrics, and it can be prevented. Hyperleukocytosis most often occurs in children with cancer, and more specifically in children with acute leukemia. Additionally, hyperleukocytosis significantly increases the frequency of complications which can occur as a direct result of elevated systemic WBC counts (leukostasis, tumor lysis syndrome, disseminated intravascular coagulation). Without prompt treatment, complications are likely to negatively impact the clinical outcomes for these children. The majority of the childhood (pediatric) cancers that are associated with hyperleukocytosis are represented by both acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). The increased accumulation of leukemic blasts leads to poor microcirculation and, as a result, significant end-organ damage to major organs, such as the brain, lungs, and kidneys. Management of these complications will require not only aggressive and timely intervention but also a combination of both both leukoneutralization (leukapheresis, cytoreductive therapy and supportive care.(4)

Even with improvements in managing cancer, hyperleukocytosis remains a very important prognostic factor affecting survival in children with cancers.(7) There are many factors that can affect the outcome of

treatment including the malignancy that the patient has, the patient's age, additional diseases the patient has at the time of diagnosis, and how quickly that patient can be treated. In addition to these factors the results from lab tests including the WBC count, the percentage of blasts in the WBC and the presence of tumor lysis syndrome, can all assist in determining the severity of hyperleukocytosis and assist in determining how to treat the patient.(8) Understanding the extent of hyperleukocytosis and the other factors associated with hyperleukocytosis is critical to achieving the best treatment and ensuring that more children survive these types of cancers.(4) While previous research has studied hyperleukocytosis in adult cancer patients, there is limited information on children and still less in low-resource environments.

1.2 Statement of the problem

There is inadequate data available on hyperleukocytosis in Ethiopia, which hinders the ability of clinicians and policymakers to provide effective strategies for the early diagnosis, timely treatment and adequate supportive care needed for children diagnosed with pediatric cancers. Therefore, in order to improve the quality of life and survival rate of children who have been diagnosed with cancer, it is important that healthcare professionals address hyperleukocytosis and determine what influence(s) affect treatment outcomes. Understanding the number of occurrences of hyperleukocytosis as well as the factors associated with treatment outcomes can help clinicians make better clinical decisions, use resources more efficiently and create contextually appropriate, evidence-based interventions for hyperleukocytosis in children diagnosed with pediatric acute leukemia.

1.3 significance of the study

Through understanding its impact on treatment response and survival will provide risk stratification information that can aid efficient allocation of resources, develop an evidence-based management protocol, and ultimately improve the survival and quality of life for children with leukemia by providing prognostic information. Identifying the fulcrum and influences of the local population will also promote early identification of high-risk patients, provide guidance for prompt and appropriate supportive and cytoreductive treatment, and give clinicians an opportunity to anticipate negative outcomes from induction therapy.

2. Literature Review

The highest prevalence of leukemia among children is found in both boys (29.1%) and girls (26.8%) and are sub-classified as: acute lymphocytic leukemia (ALL) (60-80%) and acute myeloid leukemia (AML) (20-40%) (19).

Despite significant advancements being made to improve the overall cure rates of leukemia among pediatric patients, oncologic emergencies remain a key contributor to the totality of their overall outcomes.

A review of 690 pediatric patients diagnosed with acute leukemia between 1998 and 2017 indicated that 16.6% of patients diagnosed with ALL and 20.3% of patients diagnosed with AML presented with hyperleukocytosis at diagnosis (9).

Similarly, up to 18% of AML patients may present with white blood cell (WBC) counts of > 100,000/μL at diagnosis (10).

A study conducted in Uganda demonstrated that pediatric cancer patients admitted with hyperleukocytosis had significantly higher rates of early mortality compared to control group cancer patients due to complications related to leukostasis and tumor lysis syndrome (16).

In addition, although direct evidence is limited regarding the causal effect of socioeconomic status on white blood cell count at diagnosis, there is a plethora of evidence documenting the association of lower SES (poor to low parental educational attainment, remote or rural residency) with delayed presentation, complications, and poor outcomes (11).

Acute Myeloid Leukemia (AML) and Acute Lymphoblastic Leukemia (ALL) patients from low socio-economic status (SES) neighborhoods were more likely to present with higher acuity of illness at their first presentation with disease than those from higher SES neighborhoods. (12)

The findings of hyperleukocytosis heavily depended on the clinical and laboratory presentations of the patients. A large number of deaths occurred in all children with ALL, and a number of risk factors associated with men, older than 10 years, elevated LDH, sepsis, an elevated percentage of peripheral blasts, and low platelet count. (5)

A study conducted in Nigeria showed that hyperleukocytic pediatric cancer patients' prognosis was significantly worsened by other conditions, such as infection, and malnutrition, that they also experienced. (17)

In Ethiopia, a combination of low SES, delayed access to health care, and lack of knowledge of childhood cancers has often contributed to late presentations of disease, thus increasing the risk of developing hyperleukocytosis by a significant factor. (20)

Mortality rates following hyperleukocytosis vary greatly. However, hyperleukocytosis is also associated with severe complications such as leukostasis and tumor lysis syndrome, and is considered to be a medical emergency.

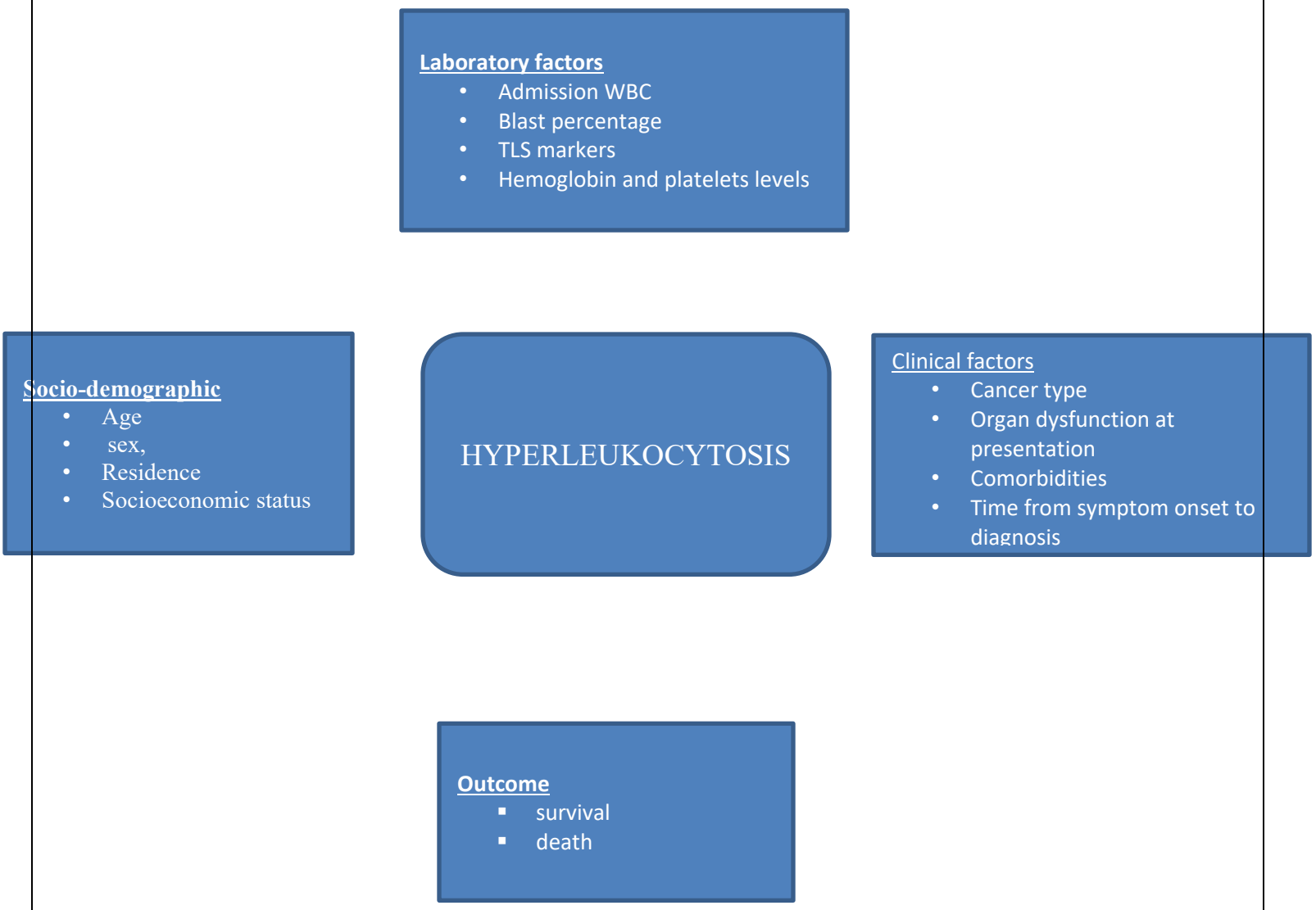
Survival rates following leukocytosis in non-Hispanic Black children are generally not very good; one study of children with hyperleukocytosis and acute lymphoblastic leukemia (ALL) showed a 5-year survival rate of 36% as opposed to 70.2% in children with ALL without hyperleukocytosis (13).

The same study also found that early deaths occurred in 29.3% of kids with acute myeloid leukemia (AML) and that the 1-year survival rate was only 28.2% (14).

The higher rate of hyperleukocytosis among children with cancer from sub-Saharan Africa is attributed to late diagnoses and to the greater number of children who present with advanced stage cancers compared to children from higher socioeconomic regions (15).

Recent advances in management, such as supportive care, have greatly reduced the incidence of early deaths in children with AML and hyperleukocytosis (18).

3. Conceptual framework



4. Objectives of the Study

4.1 General Objective

- To identify risk factors and assess outcomes of hyperleukocytosis among pediatric acute leukemia patients admitted to Tikur Anbesa Specialized Hospital, Addis Ababa, Ethiopia.

4.2 Specific Objectives

- To compare sociodemographic characteristics of children with acute leukemia who do or do not have hyperleukocytosis
- To compare clinical and laboratory characteristics in children with acute leukemia who do or do not have hyperleukocytosis
- To determine independent risk factors for hyperleukocytosis among children with acute leukemia
- To evaluate early outcomes (complications and early mortality) for children with acute leukemia who have hyperleukocytosis versus those who do not have hyperleukocytosis

5. MATERIALS AND METHODS

5.1 Study Area

This study was carried out in the Pediatric Hematology and Oncology unit of the Department of Pediatrics and Child Health at Kasa micro-specialized hospital of health sciences at Addis Ababa University in Addis Ababa, Ethiopia. This hospital is the largest tertiary referral and teaching hospital in Ethiopia where undergraduates, graduates and specialty trainees receive training and also it serves as a site for research. The hematology and oncology units contain a total of 42 inpatient beds and 16 emergency stay beds. The unit has four staff members who are specialized hematologist-oncologists. In addition to the staff members, the unit is supported by residents, interns, nurses and allied health personnel that are trained to provide holistic care to pediatric oncology patients.

5.2 Study Population

5.2.1 Source Population

All pediatric (under age 18) patients admitted to TASH Hematology Oncology Unit with a diagnosis of acute leukemia that met eligibility requirements during the time frame of this study were included as potential study participants.

5.2.2 Study units

The study units were pediatric acute leukemia patients meeting eligibility requirements and were divided into two groups:

- Cases: Patients with hyperleukocytosis at the time of their initial diagnosis.

- Controls: Patients without hyperleukocytosis at the time of their initial diagnosis.

5.3 Study Design

A retrospective case-control study was conducted to gather and analyze the data for this study in order to find differences between groups based on the variables being studied.

5.4 Study period

The data for this study were collected over a five-year period from April 1, 2020 to March 31, 2025.

5.5 Determination of the Sample Size

All eligible hyperleukocytosis cases identified during the study were included in the study, with each case being matched to two controls that did not meet the criteria of hyperleukocytosis, providing a ratio of one case to two controls.

5.6 Sampling Technique

We performed census-based sampling with all cases that qualified for the study included. For cases of acute leukemia with no hyperleukocytosis controls were taken from the same population of patients using a simple random sample, yielding a ratio of 1:2 cases to controls.

5.7 Eligibility Criteria

5.7.1 Inclusive Criteria

• Age <18 years

• Acute leukemia (new diagnosis)

• Admitted in the study observation period

• Complete medical records available

5.7.2 Exclusion Criteria

• Age ≥18 years

• Acute relapsed leukemia

• Chronic or non-acute leukemia

• Incomplete or missing medical records

• Discharged against medical advice

5.8 Study Variables

5.8.1 Dependent Variables

• Case vs. control based on hyperleukocytosis status

• Morbidity during the first month post-diagnosis:

o TLS (tumor lysis syndrome)/leukostasis

o Early death (30–42 days from diagnosis)

5.8.2 Independent Variables

• Demographics: age, sex, residence

• Clinical: presenting symptoms (e.g., respiratory), CNS status/comorbidities

• Related to disease: type of leukemia (ALL/AML)

• Laboratory: WBC count, % of peripheral blasts, hemoglobin, platelets, lactate dehydrogenase, uric acid and electrolytes.

5.9 Data Collection Methods and Tools

To extract information from patients' Hospital Management Information System data (HMIS) and medical records, a standardised data collection form was used. The standardised data extraction form was adapted from previous studies. For training, data collectors received training before collecting data, and the process of data collection was monitored by the principal investigator. The checklist contained demographic and clinical data: where they had been living, their clinical presentation, laboratory results, complications, and outcome results. Before starting the actual data collection, the data collection instrument was pre-test, and each day the data collected were reviewed for completeness and consistency. Any discrepancies were corrected through an assessment of the original documents.

5.10 Data Processing and Analysis

The data were initially entered into Kobo Tool Box and later exported to SPSS version 29 for analysis. Cleaning and validation of collected data preceded analysis. Descriptive statistics were used to describe the collected data using means, medians, count, and percentages (as appropriate). The differences between the cases and controls were tested using the Chi-Square test for categorical and the Mann-Whitney U test for non-normal distributions of continuous measurements. A multivariable logistic regression analysis identified independent risk factors for hyperleukocytosis and early mortality predictors. The analysis is reported as adjusted odds ratios (AOR) with 95% confidence intervals. A p-value of less than 0.05 was considered statistically significant.

6. Ethical considerations

The Pediatrics & Child Health department's research committee at the College of Health Sciences, Addis Ababa University's school of medicine granted me ethical approval to carry out this research. All aspects related e.g., confidentiality maintained during stages involved in collecting data, analyzing collected data, & publishing final results.

7. Dissemination of findings

The study will be submitted for partial requirement of pediatric and child health specialty certificate at Addis Ababa University, College of Health Sciences, School of Medicine, Department of Pediatrics and Child Health. Other concerned bodies will also be informed and the results of the study will be submitted for publication in peer-reviewed journals.

8. Operational definitions

A pediatric patient is defined as any cancer patient aged 0-18 years at diagnosis (WHO definition),

Hyperleukocytosis refers to a total white blood cell (WBC) count of greater than or equal to 100,000 cells/microliter at the initial diagnosis of cancer.

Symptomatic hyperleukocytosis is defined as leukostasis, which is hyperleukocytosis combined with clinical signs of microvascular compromise or tissue hypoxia. Classic examples of affected organs include those that are typically involved, but the pulmonary and neurological systems, as well as the kidneys, can also be affected.

Tumor lysis syndrome (TLS) is defined based on the Cairo-Bishop criteria.

Laboratory TLS is defined as the presence of two or more metabolic derangements listed below occurring within a defined period (3 days before and 7 days after therapy):

¬ Uric Acid (UA): >8mg/dl or increased by 25%

¬ Potassium: >6mEq/L or increased by 25%

¬ Phosphate: >4.5mg/dl or increased by 25%

¬ Calcium: <7mg/dl or decreased by 25%.

Clinical TLS is classified as laboratory TLS plus one or more of the following:

¬ Increased creatinine (>1.5 X upper limit).

¬ Cardiac arrhythmias or sudden cardiac death.

¬ Seizures.

Early death/induction death (COG) is defined as death that occurs within 30-42 days of diagnosis (21).

9. Results

9.1 Socio-Demographic Characteristics

Of the 153 acute leukemia patients included in the cohort, 51 (33.3%) developed hyperleukocytosis (WBC ≥100 $\times 10^9$/L), while 102 (66.7%) did not. The majority of hyperleukocytosis cases occurred in children aged 2–9 years (44/51, 86.3%), followed by infants under 1 year (6/51, 11.8%), with only a single case observed in children aged ≥10 years (1/51, 2.0%). Age at diagnosis was significantly associated with hyperleukocytosis ($p < 0.001$).

Regarding sex, males accounted for two-thirds of hyperleukocytosis cases (34/51, 66.7%), compared to 33.3% in females (17/51), and this difference was statistically significant ($p = 0.029$).

Hyperleukocytosis was slightly more frequent among patients from urban areas (27/51, 52.9%) than rural areas (24/51, 47.1%), although the difference was not statistically significant ($p = 0.423$).

Analysis by region showed that patients from Oromia had the highest proportion of hyperleukocytosis (18/51, 35.3%), followed by Amhara (9/51, 17.6%), SNNPR (8/51, 15.7%), Addis Ababa (8/51, 15.7%), Dire Dawa (4/51, 7.8%), Somali (3/51, 5.9%), and other regions (1/51, 2.0%). No statistically significant association was observed between region and hyperleukocytosis ($p = 0.658$)

Table1 : Sociodemographic Characteristics of Acute Leukemia Patients by Hyperleukocytosis Status (n=153) at pediatrics hematology and oncology unit, Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

Variable	HL (n=51)	Non-HL (n=102)	Total (n=153)	p-value
Age group				0.0001
<1 year	6 (11.8%)	0 (0.0%)	6 (3.9%)	
2–9.9 years	44 (86.3%)	74 (72.5%)	118 (77.1%)	
≥10 years	1 (2.0%)	28 (27.5%)	29 (19.0%)	
Sex				0.029
Male	34 (66.7%)	49 (48.0%)	83 (54.2%)	

Female	17 (33.3%)	53 (52.0%)	70 (45.8%)	
Residency				0.423
Urban	27 (52.9%)	47 (46.1%)	74 (48.4%)	
Rural	24 (47.1%)	55 (53.9%)	79 (51.6%)	
Region				0.658
Oromia	18 (35.3%)	32 (31.4%)	50 (32.7%)	
Amhara	9 (17.6%)	17 (16.7%)	26 (17.0%)	
SNNPR	8 (15.7%)	26 (25.5%)	34 (22.2%)	
Addis Abeba	8 (15.7%)	19 (18.6%)	27 (17.6%)	
Somali	3 (5.9%)	4 (3.9%)	7 (4.6%)	
Dire Dawa	4 (7.8%)	3 (2.9%)	7 (4.6%)	
Other	1 (2.0%)	1 (1.0%)	2 (1.3%)	

9.2. Clinical & Laboratory Characteristic

Among the 153 patients included in the study, 51 (33.3%) had hyperleukocytosis (WBC ≥100 $\times 10^9$/L), while 102 (66.7%) did not.

Regarding nutritional status, 88 (57.5%) patients had normal nutritional status, 41 (26.8%) had moderate acute malnutrition, 18 (11.8%) had severe acute malnutrition, and 6 (3.9%) were not assessed. Hyperleukocytosis occurred in 32 (62.7%) of patients with normal nutritional status, 11 (21.6%) with moderate malnutrition, and 8 (15.7%) with severe malnutrition. However, there was no statistically significant association between nutritional status and hyperleukocytosis ($p = 0.162$).

In terms of leukemia type, hyperleukocytosis was most common among ALL_HR patients (36, 70.6%), followed by AML (15, 29.5%). This association was statistically significant ($p < 0.001$).

For CNS status, hyperleukocytosis was observed in 3 (5.9%) of CNS-positive patients, 29 (56.9%) of CNS-negative patients, and 19 (37.3%) among those with missing CNS status. There was a statistically significant association between CNS status and hyperleukocytosis ($p = 0.011$).

Regarding CXR presentations, 47 (92.2%) of patients with hyperleukocytosis had CXR findings at presentation compared to only 4 (7.8%) without. This association was highly significant ($p < 0.001$).

Similarly, for CXR findings, 33 (64.7%) of patients with hyperleukocytosis had normal CXR findings, while 18 (35.3%) had abnormal findings. A significant association was observed between CXR findings and hyperleukocytosis (, $p < 0.001$).

Table 2: Clinical and Disease Characteristics Associated with Hyperleukocytosis (n = 153)

Variable	Category	No Hyperleukocytosis(WBC <100 $\times 10^9$/L) n (%)	Hyperleukocytosis (WBC ≥100 $\times 10^9$/L) n (%)	Total n (%)	p-value
Nutritional Status	Not assessed	6 (5.9%)	0 (0.0%)	6 (3.9%)	0.162
	Normal	56 (54.9%)	32 (62.7%)	88 (57.5%)	
	Moderate acute malnutrition	30 (29.4%)	11 (21.6%)	41 (26.8%)	
	Severe acute malnutrition	10 (9.8%)	8 (15.7%)	18 (11.8%)	
Leukemia Type	ALL_SR	52(51%)	0(0.0%)	52(34%)	<0.001
	ALL_HR	32 (31.4%)	36 (70.6%)	68(44.4%)	
	AML	18 (17.6%)	15 (29.4%)	33(21.6%)	
CNS Status	Positive	1 (1.0%)	3 (5.9%)	4 (2.6%)	0.011
	Negative	80 (78.4%)	29 (56.9%)	109 (71.2%)	
	NA	21 (20.6%)	19 (37.3%)	40 (26.1%)	
CXR at Presentation	No	62 (60.8%)	4 (7.8%)	66 (43.1%)	<0.001
	Yes	40 (39.2%)	47 (92.2%)	87 (56.9%)	
CXR Findings	Normal	32 (31.4%)	33 (64.7%)	65 (42.5%)	<0.001
	Abnormal	70 (68.6%)	18 (35.3%)	88 (57.5%)	
Total		**102 (100%)**	**51 (100%)**	**153 (100%)**	

Among the 153 acute leukemia patients, clinical symptoms at presentation were compared between those with hyperleukocytosis (HL, n=51) and those without (Non-HL, n=102). Fever was the most common symptom, occurring in 66.7% of HL patients and 70.6% of Non-HL patients (p = 0.62). Fatigability and weight loss were reported in 58.8% vs 62.7% and 43.1% vs 40.2% of HL and Non-HL patients, respectively, with no statistically significant differences. Respiratory symptoms were significantly more frequent among HL patients (54.9% vs 24.5%, p < 0.001), while bone pain was less common in HL (3.9% vs 16.7%, p = 0.024). Other symptoms, including bleeding, lymphadenopathy, hepatomegaly, splenomegaly, pallor, neurological symptoms, and edema, did not differ significantly between the two groups.

Table 3: Clinical Features by Hyperleukocytosis Status at pediatrics hematology and oncology unit, Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

Symptom	HL (n=51)	Non-HL (n=102)	Total (n=153)	p-value
Fever	34 (66.7%)	72 (70.6%)	106 (69.3%)	0.62
Fatigability	30 (58.8%)	64 (62.7%)	94 (61.4%)	0.64
Bleeding	15 (29.4%)	30 (29.4%)	45 (29.4%)	1.00
Weight loss	22 (43.1%)	41 (40.2%)	63 (41.2%)	0.73
Respiratory symptoms	28 (54.9%)	25 (24.5%)	53 (34.6%)	<0.001
Bone pain	2 (3.9%)	17 (16.7%)	19 (12.4%)	0.024
Lymphadenopathy	32 (62.7%)	63 (61.8%)	95 (62.1%)	0.91
Hepatomegaly	33 (64.7%)	61 (59.8%)	94 (61.4%)	0.56
Splenomegaly	32 (62.7%)	51 (50.0%)	83 (54.2%)	0.14
Pallor	23 (45.1%)	38 (37.3%)	61 (39.9%)	0.35
Neurological symptoms	2 (3.9%)	1 (1.0%)	3 (2.0%)	0.22
Edema	6 (11.8%)	6 (5.9%)	12 (7.8%)	0.20

The laboratory characteristics of children with hyperleukocytosis (WBC $\geq 100 \times 10^9$/L) were compared with those without hyperleukocytosis (WBC $< 100 \times 10^9$/L). Median values with interquartile ranges (IQR) and the results of the Mann–Whitney U test are summarized in Table 4.X.

Children with hyperleukocytosis had a significantly higher peripheral blast percentage (median 68%, IQR: 42–82) compared to those without hyperleukocytosis (median 44.5%, IQR: 29–65; $p < 0.001$). Similarly, LDH levels were elevated in the hyperleukocytosis group (median 1098 U/L, IQR: 679–2040) relative to the non-hyperleukocytosis group (median 642 U/L, IQR: 316–1428; $p < 0.001$).

Significant differences were also observed for hemoglobin, platelet count, and uric acid. Children with hyperleukocytosis had lower median hemoglobin levels (5.9 g/dL, IQR: 4.1–7.9 vs. 6.75 g/dL, IQR: 5–8.83; p = 0.036) and higher platelet counts (30 $\times 10^9$/L, IQR: 15–56 vs. 18 $\times 10^9$/L, IQR: 10–33; p = 0.004). Median uric acid was higher in the hyperleukocytosis group (7.9 mg/dL, IQR: 4.9–9.8) compared to the non-hyperleukocytosis group (6 mg/dL, IQR: 4.55–8.5; p = 0.030).No statistically significant differences were noted for phosphorus, potassium, calcium, or creatinine between the two groups (p > 0.05).

Table 4: Comparison of Laboratory Parameters Between Hyperleukocytosis and Non-Hyperleukocytosis Patients at pediatrics hematology and oncology unit, Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

Laboratory Parameter	Non-Hyperleukocytosis Median (IQR)	Hyperleukocytosis Median (IQR)	p-value (Mann-Whitney U)
Peripheral Blast (%)	44.5 (29–65)	68 (42–82)	0.001
Hemoglobin (g/dL)	6.75 (5–8.83)	5.9 (4.1–7.9)	0.036
Platelet count (10^9/L)	18 (10–33)	30 (15–56)	0.004
LDH (U/L)	642 (316–1428)	1098 (679–2040)	0.001
Uric acid (mg/dL)	6 (4.55–8.5)	7.9 (4.9–9.8)	0.03
Phosphorus (mg/dL)	3.95 (3–4.23)	4 (3–4.1)	0.933
Potassium (mmol/L)	3.9 (3.6–4.22)	3.89 (3.5–4.2)	0.433
Calcium (mg/dL)	9 (8–9)	9 (8–9)	0.691
Creatinine (mg/dL)	0.4 (0.3–0.6)	0.4 (0.3–0.6)	0.566

Among the cohort of 153 patients, hyperleukocytosis was significantly associated with a higher proportion of complications: 88.2% of hyperleukocytosis patients experienced at least one complication compared to 57.8% of non-hyperleukocytosis patients (p=0.000).

All hyperleukocytosis patients received hydration and allopurinol, which was significantly higher than the non-hyperleukocytosis group (p=0.000 for both). Hydroxyurea use was also significantly more common in the hyperleukocytosis group (23.5% vs 0%; p=0.000). Steroid use was lower in the hyperleukocytosis group (3.9% vs 26.5%; p=0.001).

Blood transfusion (64.7% vs 43.1%, p=0.012) and antibiotic use (47.1% vs 23.5%, p=0.003) were also significantly higher among hyperleukocytosis patients.

Cytoreduction, platelet transfusion, Atra, and other medications showed no statistically significant differences between groups ($p > 0.05$).

Table 5: Complications and Management by Hyperleukocytosis Status at pediatrics hematology and oncology unit, Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

Variable	**Hyperleukocytosis (WBC ≥100×10⁹/L) n=51**	**Non-HL (WBC <100×10⁹/L) n=102**	**p-value (Pearson Chi-square)**
Any Complications	45 (88.2%)	59 (57.8%)	0.000
Hydration	51 (100%)	53 (52%)	0.000
Allopurinol	51 (100%)	51 (50%)	0.000
Hydroxyurea	12 (23.5%)	0 (0%)	0.000
Steroid	2 (3.9%)	27 (26.5%)	0.001
Cytoreduction	1 (2%)	0 (0%)	0.156
Platelet transfusion	34 (66.7%)	56 (54.9%)	0.163
Blood transfusion	33 (64.7%)	44 (43.1%)	0.012
Antibiotics	24 (47.1%)	24 (23.5%)	0.003
Atra	1 (2%)	5 (4.9%)	0.377
Other medications	0 (0%)	2 (2%)	0.314

9.3 Early Outcomes

Early mortality was significantly higher among patients with hyperleukocytosis (25.5%) compared to non-hyperleukocytosis patients (5.9%, p=0.001).

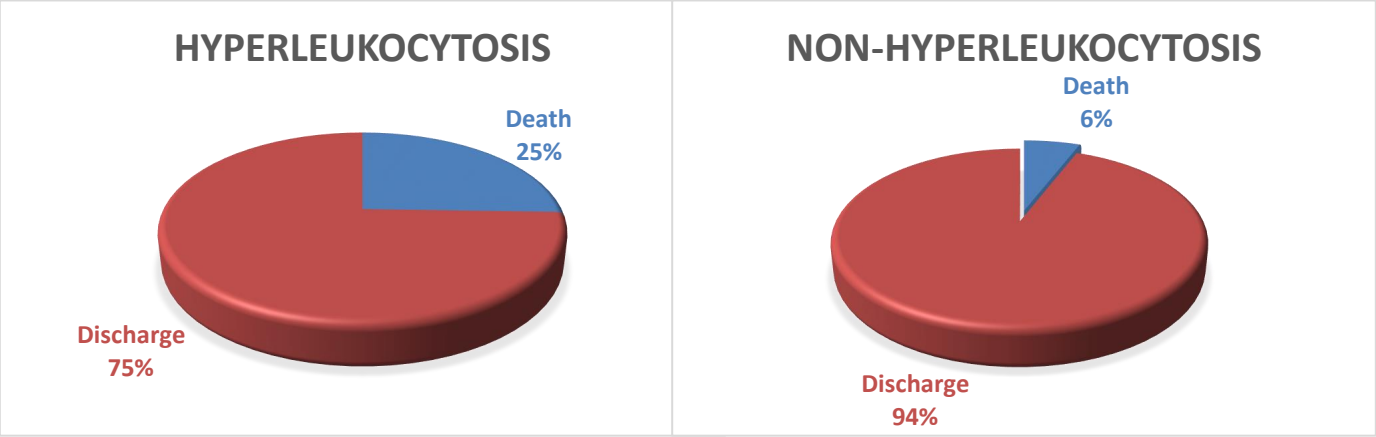


Fig 2 Early outcomes of hyperleukocytosis and non-hyperleukocytosis patients at pediatrics hematology and oncology unit, Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

Deaths in hyperleukocytosis occurred predominantly within the first week (61.5%), whereas non-hyperleukocytosis deaths occurred later. The most common causes of death in hyperleukocytosis patients were leukostatic lung injury (38.5%) and septic shock (30.8%).

Table 6 Early Outcomes by Hyperleukocytosis Status at pediatrics hematology and oncology unit, Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

Early Outcome	Hyperleukocytosis n=51 (%)	Non-HL n=102 (%)	p-value
Death	13 (25.5)	6 (5.9)	0.001
Discharge	38 (74.5)	96 (94.1)	—
Deaths within first week	8 (61.5% of HL deaths)	1 (16.7% of Non-HL deaths)	—
Leading cause of death – Leukostatic lung injury	5 (38.5% of HL deaths)	1 (16.7% of Non-HL deaths)	—
Leading cause of death – Septic shock	4 (30.8% of HL deaths)	1 (16.7% of Non-HL deaths)	—

9.4 Factors Associated with Hyperleukocytosis

In the multivariable logistic regression analysis, peripheral blast percentage, leukemia type, chest X-ray (CXR) findings, respiratory symptoms, and uric acid level were independently associated with hyperleukocytosis. Each one-unit increase in peripheral blast percentage was associated with a 4.5% increase in the odds of hyperleukocytosis (AOR = 1.045; 95% CI: 1.019–1.071; p = 0.001). Children diagnosed with AML had significantly higher odds of hyperleukocytosis compared to those with ALL (AOR = 4.23; 95% CI: 1.285–13.925; p = 0.018). Abnormal CXR findings were associated with significantly reduced odds of hyperleukocytosis (AOR = 0.231; 95% CI: 0.071–0.759; p = 0.016), whereas the presence of respiratory symptoms increased the odds nearly sixfold (AOR = 5.737; 95% CI: 1.818–18.101; p = 0.003). In addition, higher uric acid levels were significantly associated with hyperleukocytosis, with each unit increase corresponding to a 21.3% increase in odds (AOR = 1.213; 95% CI: 1.009–1.457; p = 0.040). Age at diagnosis, sex, CNS status, hemoglobin level, platelet count, and LDH level did not show statistically significant associations with hyperleukocytosis after adjustment ($p > 0.05$).

The logistic regression model was evaluated for goodness-of-fit and explanatory power. The Hosmer-Lemeshow test indicated that the model fits the data well ($\chi^2 = 7.86$, df = 8, p = 0.447), suggesting no significant difference between observed and predicted outcomes.

Table 7: Multivariable Logistic Regression for Hyperleukocytosis

Variable	Category	Hyperleukocytosis No n (%)	Hyperleukocytosis Yes n (%)	AOR	95% CI	P-value
Age at diagnosis	<1 yr (ref)	0 (0.0%)	6 (11.8%)	1	–	–
	2–9 yr	74 (72.5%)	44 (86.3%)	0	0.000 – –	0.999
	≥10 yr	28 (27.5%)	1 (2.0%)	0	0.000 – –	0.999
Sex	Male (ref)	49 (48.0%)	34 (66.7%)	1	–	–
	Female	53 (52.0%)	17 (33.3%)	0.894	0.269 – 2.970	0.855
Peripheral blasts (%)	Continuous	44.5 (29–65) *	68 (42–82) *	1.045	1.019 – 1.071	**0.001**
Leukemia type	ALL (ref)	84 (82.4%)	36 (70.6%)	1	–	–
	AML	18 (17.6%)	15 (29.4%)	4.23	1.285 – 13.925	**0.018**
CNS status	Positive (ref)	1 (1.0%)	3 (5.9%)	1	–	–
	Negative	80 (78.4%)	29 (56.9%)	0.977	0.070 – 13.603	0.986
	NA	21 (20.6%)	19 (37.3%)	0.903	0.046 – 17.817	0.947
CXR findings	Normal (ref)	32 (31.4%)	33 (64.7%)	1	–	–
	Abnormal	70 (68.6%)	18 (35.3%)	0.231	0.071 – 0.759	**0.016**
Respiratory symptoms	No (ref)	77 (75.5%)	23 (45.1%)	1	–	–
	Yes	25 (24.5%)	28 (54.9%)	5.737	1.818 – 18.101	**0.003**
Hemoglobin (g/dl)	Continuous	6.75 (5–8.83)*	5.9 (4.1–7.9)*	0.986	0.785 – 1.238	0.902
Platelet (10^9/L)	Continuous	18 (10–33)*	30 (15–56)*	1.013	0.999 – 1.027	0.074
LDH (U/L)	Continuous	642 (316–1428)*	1098 (679–2040)*	1	1.000 – 1.000	0.51
Uric acid (mg/dl)	Continuous	6 (4.55–8.5)*	7.9 (4.9–9.8)*	1.213	1.009 – 1.457	**0.04**

*Continuous variables presented as Median (IQR)

9.5 Factor Associated Early outcome

In this study of 189 pediatric leukemia patients, most were aged 2–9 years and diagnosed with Acute Lymphoblastic Leukemia. Among the patients, 134 were discharged while 19 died during the early treatment period. On univariate analysis, hyperleukocytosis and respiratory symptoms were strongly associated with mortality. Patients who died had higher median peripheral blast counts, lower hemoglobin and platelet levels, and higher uric acid levels compared to those discharged.

In multivariable analysis, independent predictors of early death included hyperleukocytosis (AOR=19.31; 95% CI: 2.76–135.01; p=0.003), respiratory symptoms at presentation (AOR=10.37; 95% CI: 1.74–61.74; p=0.010), low platelet count (AOR=0.942 per 10^9/L; 95% CI: 0.896–0.991; p=0.021), and elevated uric acid (AOR=1.302 per mg/dL; 95% CI: 1.055–1.607; p=0.014). Other factors, including age, sex, leukemia type, hemoglobin, peripheral blasts, LDH, and CXR findings, were not independently associated with early mortality.

The model showed good fit, with a Nagelkerke R^2 of 0.629 and a non-significant Hosmer-Lemeshow test (Chi-square=1.594, p=0.991), indicating that the model adequately explained the variability in early mortality among pediatric leukemia patients.

Tabel 8 Clinical and Laboratory Predictors of Early Outcomes in Pediatric Leukemia Patients

Variable	Category	Discharge	Death	COR (95% CI)	AOR (95% CI)	P-value
Age at diagnosis	<1 yr (ref)	4 (3.0%)	2 (10.5%)	1	1	–
	2–9 yr	102 (76.1%)	16 (84.2%)	0.31 (0.05–1.86)	0.47 (0.04–5.63)	0.552
	≥10 yr	28 (20.9%)	1 (5.3%)	0.07 (0.01–0.98)	1.06 (0.03–33.24)	0.973
Sex	Male (ref)	75 (56.0%)	8 (42.1%)	1 –	–	–
	Female	59 (44.0%)	11 (57.9%)	1.75 (0.66–4.62)	4.64 (0.92–23.38)	0.063
Leukemia type	ALL (ref)	108 (80.6%)	12 (63.2%)	1 –	–	–
	AML	26 (19.4%)	7 (36.8%)	2.42 (0.87–6.76)	2.45 (0.43–14.13)	0.316
Hyperleukocytosis	No (ref)	96 (71.6%)	6 (31.6%)	1	1	–
	Yes	38 (28.4%)	13 (68.4%)	5.47 (1.94–15.45)	19.31 (2.76–135.01)	0.003*
Respiratory symptoms	No (ref)	95 (70.9%)	5 (26.3%)	1	1	–
	Yes	39 (29.1%)	14 (73.7%)	6.82 (2.30–20.23)	10.36 (1.74–61.74)	0.010*
CXR findings	Normal (ref)	61 (45.5%)	4 (21.1%)	1	1	–
	Abnormal	73 (54.5%)	15 (78.9%)	3.13 (0.99–9.94)	5.10 (0.87–29.85)	0.07
Peripheral Blast (%)	Median (IQR)	51.0 (32–72)	62.0 (34–70)	1.01 (0.98–1.03)	1.02 (0.99–1.06)	0.26
Hemoglobin (g/dL)	Mean ± SD	6.77 ± 2.49	5.55 ± 1.65	0.79 (0.64–0.99)	0.79 (0.55–1.14)	0.207
Platelet (10^9/L)	Median (IQR)	22.5 (12–43.3)	12.0 (8–16)	0.97 (0.94–1.00)	0.94 (0.90–0.99)	0.021*
LDH (U/L)	Median (IQR)	876.5 (356–1587)	883.0 (563–1160)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	0.075
Uric acid (mg/dL)	Median (IQR)	6.2 (4.68–8.8)	9.0 (5.9–11.9)	1.15 (1.01–1.30)	1.30 (1.06–1.61)	0.014*

*Continuous variables presented as Median (IQR) and Mean SD

10.DISCUSSION

This study assessed the risk factors and outcomes of hyperleukocytosis among pediatric acute leukemia patients admitted to Tikur Anbesa Specialized Hospital. The findings demonstrate that hyperleukocytosis is strongly associated with specific clinical and laboratory parameters and is a major determinant of early complications and mortality.

10.1 Socio-demographic Characteristics

Hyperleukocytosis was most common in children aged between 2 to 9 years in this study which corresponds to the relative prevalence of acute lymphocytic leukemia (ALL) in this age group where most childhood leukaemias occur world wide (19). Hyperleukocytosis was predominantly seen in males resulting in accordance to global epidemiological studies indicating an increased incidence of pediatric leukaemia in boys (19); however, the role of gender as an independent factor has yielded inconsistent data in the literature. Geographic location and/or regional distribution did not show a significant association with hyperleukocytosis in this study, however, previous studies have shown that low socioeconomic status (SES) and living in rural areas are associated with children presenting at a significantly later time, and with significantly worse outcomes (11 & 20). Children who come from disadvantaged backgrounds present with a higher degree of disease burden and have more complicated cases (12).

10.2 Clinical and Disease Characteristics

There was a significant association found between hyperleukocytosis and the type of leukemia, with hyperleukocytosis being more prevalent in the high-risk subtypes of acute lymphoblastic leukaemia and acute myeloid leukaemia. Previous literature has estimated that approximately 16.6% of patients with acute lymphoblastic leukaemia (ALL) and 20.3% of patients with acute myeloid leukaemia (AML) will present with hyperleukocytosis at the time of diagnosis(9), with up to 18% of cases of AML having white blood cell (WBC) counts greater than 100,000/μL(10). Hyperleukocytosis was associated with respiratory symptoms at a significantly higher frequency. This finding suggests that hyperleukocytosis can contribute to leukostasis, a well-known complication of high leukaemic blast counts that can lead to microvascular obstruction, especially in the lung and central nervous systems; this has been demonstrated in numerous studies that have also reported that respiratory distress is associated with an adverse prognosis.(16) This study has not demonstrated a significant correlation between nutritional status and hyperleukocytosis. However, studies conducted in Nigeria and other low-resource settings have reported that malnutrition and infectious co-morbid conditions can impair the prognosis of paediatric oncology patients.(17)

10.3 Laboratory Characteristics

Children with hyperleukocytosis exhibited markedly elevated levels of peripheral blast cell percentages, serum LDH, and uric acid, signifying both an increased tumor burden as well as rapid cellular proliferation. Results were consistent with previous studies that found elevated LDH and uric acid to be important indicators of tumor lysis syndrome and/or poor clinical prognosis (5). An increasing percentage of peripheral blasts has also been identified as a major risk factor for the development of hyperleukocytosis and adverse clinical outcomes (5). These laboratory findings are a reflection of an aggressive biological behavior of the disease and consequently represent an increased risk of complications.

10.4 Complications and Management

This study found that hyperleukocytosis is associated with greater complication rates. In similar research done in Uganda, pediatric patients with hyperleukocytosis also had significantly higher complication rates (such as leukostasis and tumor lysis syndrome) resulting in a greater risk of death (16). Standard treatment regimens to decrease tumor burden and prevent complications were utilized more in this study with the increased use of hydration, allopurinol, and cytoreductive therapy being reflective of these treatment regimens. Improved supportive care has been reported to be associated with reduced early mortality for patients with hyperleukocytosis (18).

10.5 Early Outcomes

Compared to patients without hyperleukocytosis, hyperleukocytosis was associated with a greater risk of early death. Previous systematic reviews have described early deaths from leukemia of up to 29.3% in children with acute myelogenous leukaemias (AML) (14). The five-year survival rates in one study showed that the outcomes in patients with hyperleukocytosis were worse than those without hyperleukocytosis (36% vs. 70.2%) (13). The majority of deaths in this study took place within the first week after diagnosis emphasising the need for early intervention. The leading causes of death (e.g. leukostatic lung injury, septic shock) were consistent with studies from other low-income countries (16).

10.6 Factors Associated with Hyperleukocytosis

There were three independent predictors identified by multivariate analysis of hyperleukocytosis based on peripheral blast percentage, leukemia subtype, and respiratory symptomatology. Leukemia subtype and high peripheral blast count have both been identified in prior studies as major risk factors (5,9). The identification of respiratory symptoms as an independent predictor supports the role leukostasis has in the pathophysiology of hyperleukocytosis. Demographic factors (e.g., age, sex) did not remain independently associated after adjustment, supporting the established literature that disease-specific characteristics are more significant in determining hyperleukocytosis than demographic factors.

10.7 Clinical Implications

In conclusion, hyperleukocytosis has been identified by our study as one of the major risk factors for early death among children with acute leukemia. Children in sub-Saharan Africa experience significantly higher rates of hyperleukocytosis compared to children living in higher-income countries, partly due to delays in diagnosis and advanced disease presentation (15). To enhance survival outcomes for children with acute leukemia in resource-constrained environments, the development of better strategies for early diagnosis, improved supportive care, and timely intervention will be necessary.

10.8 Summary of Key Findings

• High levels of white blood cells present with large amounts of disease and considerable severity (5,9).

• Symptoms in the respiratory system reflect the presence of white cells in blood vessels and predict poor prognosis (16).

• Hyperleucocytosis has been associated with an increase in severe medical problems and premature death (14,16).

• Most patients who die prior to the end of their treatment do so within the first week.

• Patients who present later in low-or-resource settings have poor prognosis and worse outcomes from their disease (15,20).

11.CONCLUSION AND RECOMMENDATIONS

11.1 Conclusion

This article provided an overview of the main risk factors, as well as an early outcome of hyperleukocytosis in pediatric patients diagnosed with acute leukemia at the Tikur Anbesa Specialized Hospital. It was noted that hyperleukocytosis has been found to be associated with several markers indicating a high tumor load (e.g., high peripheral blood blast proportion, increased lactate dehydrogenase, and hyperuricemia) and also manifested clinically as respiratory symptoms (due to leukostasis). Patients with hyperleukocytosis had a higher incidence of complications and early mortality than those who did not exhibit hyperleukocytosis. The majority of deaths were found during the first week of diagnosis, with the most common clinical cause of death being leukostatic lung injury or septic shock. The multivariable analysis indicated that peripheral blood blast percentage, high-risk leukemia subtype, and respiratory symptoms were all independent predictors of hyperleukocytosis. Hyperleukocytosis was shown to be a strong predictor of early mortality. Overall, hyperleukocytosis is indicative of severity of disease and a predictor of poor early outcomes in patients with pediatric acute leukemia. Early identification and prompt intervention are essential for survival improvement.

11.2 Recommendations

As demonstrated in this research study, the need to recognize hyperleukocytosis in children with acute leukemia when they are diagnosed is paramount. Special recognition needs to be given to children who have respiratory distress, a very elevated peripheral blast count and an aggressive form of leukemia as those children are at highest risk for developing serious complications or dying due to hyperleukocytosis. Encouragement to begin supportive management (e.g., aggressive hydration, allopurinol and cytoreductive treatment) upon diagnosis is critical in order to establish early supportive management and reduce the occurrence of early complications and death. Developing a strengthened referral system for patients diagnosed with acute leukemia and improving access to specialized pediatric oncology services is necessary to reduce delays in the diagnosis and treatment. Additionally, increasing the availability of essential medications and supportive care resources in tertiary hospitals will be necessary to improve survival. Furthermore, initiatives to increase public awareness of the early warning signs of childhood cancer may help improve early healthcare access. Finally, additional prospective multicenter studies are needed to assess long term outcomes and provide evidence based recommendations for the reduction of mortality due to hyperleukocytosis in low resource settings.

12. Limitations

The study's retrospective nature leaves it vulnerable to gaps in data and also its limited ability to establish causal linkages. Furthermore, this investigation was carried out in a single tertiary centre, which impairs the extent to which the results can be generalized to other sites. In addition, the study was limited to looking at only early outcomes and will not provide information on long-term survival or quality of life. Thus, it will not contribute to the decision making process for pediatric patients with leukemia.

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