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COMPARISON OF HIGH FLUORESCENCE CELL IN PEDIATRIC PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) AND INFECTION

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ABSTRACT

High Fluorescence Cell (HFC) is a cell with high nucleoplasmic and nucleic acid content, enabling it to emit a high fluorescent signal. Mind Ray Series BC 760 automated hematology analyzer uses a technology called Sheath Fluid (SF) Cube to detect these cells using the fluorescence staining method. An increase in HFC may be associated with atypical or pleomorphic lymphocytes caused by viral infection rather than immature or monomorphic lymphocytes caused by malignancy. Objective: The objective of this study is to determine the difference in high fluorescence cell in pediatric patients with Acute Lymphoblastic Leukemia (ALL) and infection at Adam Malik Hospital. Methods: This study is an observational analytical study with a prospective cohort design. The study sample was 35 people with a diagnosis of ALL of 15 people and infection of 20 people. This study was conducted on patients who came to the pediatric clinic and were hospitalized with a diagnosis of ALL and infection at Adam Malik Hospital who met the inclusion criteria and agreed to participate in this study. A high fluorescence cell blood test was performed. criteria. A complete blood test of 2 ml of blood in an EDTA vacutainer was gently homogenized. Analysis with a full blood count (FBC) test was performed using an automated hematology analyzer (Mindray BC 760) to obtain the number of lymphocytes and high fluorescence cells. Descriptive statistical analysis was used for demographic data. Statistical analysis used the Mann Whitney statistical test. The research data were analyzed statistically with the help of SPSS and the difference was considered significant if p value <0.05. Results: From the study sample of 35 people, 24 boys (68.6%) and 11 girls (31.4%), with the mean age of 6 years old. The diagnosis of ALL was 15 people (42.9%) while patients with infection were 20 people (57.1%). The median absolute HFC in ALL was 0.2 x 109/L, and the median in infection was 0.15 x 109/L. Conclusion: There was no significant difference between HFC in patients with ALL and infection (p=0.211).

Keywords: acute lymphoblastic leukemia; high fluorescence cell; infection

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INTRODUCTION

Leukemia is a heterogeneous group of hematological malignancies arising from dysfunctional proliferation of developing leukocytes. The disease is classified as acute or chronic based on the rate of proliferation and as myeloid or lymphoid based on the cell of origin (Arber DA et al., 2016). The dominant subtypes are Acute Myeloid Leukemia (AML) and Chronic Myeloid Leukemia (CML), which involve the myeloid lineage; Acute Lymphoblastic Leukemia (ALL) and Chronic Lymphocytic Leukemia (CLL), which involve the lymphoid lineage (WHO., 2010). The ALL classification according to the French-American-British (FAB) system proposes dividing it into three subtypes (L1–L3). Currently, the World Health Organization (WHO) modifies the FAB classification based on immunophenotype. Acute Lymphoblastic Leukemia (ALL) is an acute leukemia originating from the lymphoid cell lineage. ALL is characterized by the presence of lymphoblast cells >20% in blood smears or bone marrow. ALL is the most common type of

malignancy in children (Garniasih., 2020). Infection is a disease caused by pathogenic microorganisms. Infectious pathogens include viruses, bacteria, fungi, and parasites. In general, the process of disease development involves three interacting factors: the causative agent (pathogen), the host (human), and the environment. When a triggering factor such as infection is present, the number of leukocytes can increase rapidly (Erik R., 2003).

Lymphocytosis is a condition in which the absolute lymphocyte count is above 1.5–4.0 x 109/L in adults and >7.0 x 109/L in children (Matthew., 2017). In a peripheral blood smear examination, lymphocytes need to be differentiated into lymphocytes with pleomorphic or monomorphic morphology. If lymphocytes with pleomorphic morphology or varied shapes and sizes are found, suspicion is more likely to be directed toward reactive lymphocytosis. In malignant etiologies, lymphocyte shapes are more homogeneous or monomorphic (Chabot., 2014). High Fluorescence Cells (HFC) are cells with high nucleoplasmic and nucleic acid content, enabling them to emit high fluorescent signals. The HFC parameter is useful for distinguishing cells into mononuclear cells, polymorphonuclear cells, and other white blood cells. This parameter is expected to assist in the automatic analysis of samples suspected of malignancy, which were previously examined manually under a microscope (Labaere., 2015).

Mind Ray Series BC 760 automated hematology analyzer uses a technology called Sheath Fluid (SF) Cube to detect these cells using a fluorescence staining method. Cell size differences can be used to characterize forward scatter light signals, differences in intracellular particle complexity can be used to characterize side scatter light, and fluorescent signal intensity reflects the level of cell staining. The high fluorescence region is located in the upper region of lymphocytes, and cells within that region are referred to as High Fluorescence Cells (HFC) (Mindray., 2015). To date, there have been few studies comparing High Fluorescence Cell values in pediatric patients with ALL and infection. Therefore, this study aims to compare High Fluorescence Cell values in pediatric patients with ALL and infection at Adam Malik Hospital.

METHOD

This study is an observational analytical study with a prospective cohort design. The study sample was 35 people with a diagnosis of ALL of 15 people and infection of 20 people. Sampling was carried out using consecutive sampling by looking at the inclusion and exclusion criteria. Descriptive statistical analysis was used for demographic data. Statistical analysis used the Mann Whitney statistical test. The research data were analyzed statistically and the difference was considered significant if p value <0.05.

A complete blood test of 2 ml of blood in an EDTA vacutainer is gently homogenized. Analysis with a full blood count (FBC) test is performed using an automated hematology analyzer (Mindray BC 760) to obtain the number of lymphocytes and high fluorescence cells. Cytometry is used to analyze the physiological and chemical characteristics of cells and other biological particles. Flow cytometry is used to analyze these cells and particles as they pass through a very small flow cell. Flow cytometry is a method of hydro dynamic focusing that improves accuracy and repeatability for cell counting. Blood samples are aspirated and measured, dissolved into a specific ratio, and stained. A semiconductor laser light (wavelength: 633 nm) is emitted to blood cells passing through the flow cell. There are two lights, namely forward scatter and side scatter, which are captured by a photodiode, and one side fluorescent light, which is captured by an avalanche photodiode. This light is converted into an electric current so that information about the blood cells can be obtained.

RESULT

Absolute leukocyte, lymphocyte, and HFC levels were examined in 35 samples. As can be seen in Table 1 in this study found 24 boys (68.6%) and 11 girls (31.4%). The diagnosis in this study was more prevalent in infections at 57.1% compared to ALL at 42.9%. The median age of the study subjects was 6 years, with a minimum age of 1 year and a maximum age of 17 years. The median leukocyte count was 17.6 x 10^9/L, with a minimum leukocyte count of 8.5 x 10^9/L and a maximum

of 60.2 x 10^9/L. The median relative lymphocyte count was 59.6%, with a minimum value of 16.9% and a maximum value of 97.8%. Meanwhile, the median absolute lymphocyte count was 10.17 x 10^9/L, with a minimum value of 7.02 x 10^9/L and a maximum value of 27.72 x 10^9/L. Then, the median of the relative HFC count was 1.7% with a minimum value of 0.0% and a maximum value of 6.10%. Meanwhile, the median of the absolute HFC value was 0.19 x 10^9/L with a minimum value of 0.01 x 10^9/L and a maximum value of 1.05 x 10^9/L.

Table 1.
Demographic Characteristics

Variable	f (%)
Gender	
Boys	24 (68,6)
Girls	11 (31,4)
Diagnose	
ALL	15 (42,9)
Infection	20 (57,1)
Variable	Median (Min-Max)
Age	6 (1 – 17)
Leukocyte (x 10^9/L)	17,6 (8,5 – 60,2)
Relative lymphocyte count (%)	59,6 (16,9 – 97,8)
Absolute lymphocyte count (x 10^9/L)	10,17 (7,02 – 27,72)
Relative HFC count (%)	1,7 (0,0 – 6,10)
Absolute HFC count (x 10^9/L)	0,19 (0,01 – 1,05)

The median HFC value in ALL was found to be 0.2 x 109/L and in patients with infection was 0.15 x 10^9/L. The results of HFC examination in patients with ALL and infection can be seen in Table 2.

Table 2.
HFC Values in ALL and Infections

	HFC (x 10^9/L), Median (Min-Maks)	p value
ALL	0,2 (0,02 – 1,05)	0,211
Infection	0,15 (0,01 – 0,44)	

The comparison of HFC values with ALL and infection was performed using the Mann Whitney test, because the research sample data was found to be abnormally distributed. In this study, no significant difference was found between HFC values with ALL and infection (p=0.211).

DISCUSSION

This study aims to compare high fluorescence cell values in patients with ALL and infection using median-based analysis and absolute distribution. Based on the results of this study, demographic characteristic data show that the majority of subjects are male (68.6%). This is in line with the study by Garniasih et al., (2022), where data showed a higher incidence of ALL in boys, namely 2.45 per 100,000 children compared to girls, which was only 2.05 per 100,000 children. Similar to research in Syria (2020), which showed that 60.9% of 203 pediatric patients with ALL were male. This may occur because males are more susceptible to genetic changes such as certain chromosome translocations that increase the risk of ALL (Kakaje et al., 2020).

The median age of the study sample was 6 years (1–17 years). This is consistent with a study by Kakaje et al. (2020), which showed that of 203 ALL patients, 48.5% were in the 5–9 age range. This occurs because at this age, children's immune systems are developing with high activity in lymphocyte proliferation and clonal selection. Imbalances or disturbances in this process can increase the risk of malignant transformation in lymphoid cells. Children at this age are also more susceptible to exposure to environmental factors such as certain viral infections (e.g., Epstein Barr), chemicals, or radiation. This exposure can trigger genetic changes that increase the risk of ALL. The diagnosis in this study sample was more prevalent in the infection group (57.1%) than in the ALL group (42.9%). This occurred in this study because ALL samples were more difficult to obtain than those from the infection group.

The median HFC value in patients with ALL was 0.2 x 109/L, while in infection it was 0.15 x 109/L. The results of this study show that the absolute HFC value in patients with ALL is higher than in patients with infection. However, the Mann Whitney test showed that the difference in HFC values between the two groups was not statistically significant (p=0.211). This indicates that although HFC values can serve as an indicator of the presence of blast cells or atypical lymphocytes, HFC values are not strong enough to distinguish between ALL and infection.

This study shows that the median HFC value in ALL is higher than the median HFC value in infections. This is in line with the study by Saina et al., (2023) in India, which found higher absolute HFC values in malignant samples compared to non-malignant samples, with a median value of 450/µL vs. 16.40/µL. In this study, the AUC value was 0.844 for absolute HFC values, indicating a sensitivity of 82% and specificity of 81%. The study also determined the optimal cutoff value for malignancy with an absolute HFC of 15.7/µL.

Xu et al. (2017) in China also studied HFC values for screening malignant cells in body fluids and obtained similar results. The median HFC value in malignant cells was 63/µL compared to 21/µL in non-malignant cells. The AUC value = 0.707 for HFC values showed a sensitivity of 79.2% and a specificity of 55.8%. This study also determined the optimal cut-off value for malignancy with absolute HFC of 24.5/µL.46 This may be due to the nucleic acid contained in malignant cells and their larger size compared to reactive lymphocytes. This study also explained that false positives in non-malignant samples were mostly caused by the presence of mesothelial cells or macrophages that could bind more fluorescent nucleic acid dye, so that the fluorescence intensity was not detected.

Unlike the study by Hongjie et al. (2017) in China, researchers stated that an increase in HFC values was more often associated with the presence of atypical lymphocytes due to viral infection or immunological disease. The distribution of HFC in the atypical lymphocyte group had a median value of 1.8% and in the immature lymphocyte/blast group was 0.7%. The correlation coefficient (r) = 0.715 for atypical lymphocytes (good) and (r) = 0.176 for immature/blast lymphocytes (low). Flagging of atypical lymphocytes will appear if the HFC value reaches a minimum value of 0.04 x 109/L. Researchers explain that this occurs because the nucleic acid content of atypical lymphocytes is higher due to immunological activity.

Jayaram et al, (2021) in India studied the usefulness of HFLC as an early indicator for diagnosing dengue virus in acute fever infections. The results showed that HFLC values were higher in dengue cases (87.3%) compared to controls (18%). The optimal cut-off value for HFC% in dengue virus infection was 1.35% (sensitivity 82.85, specificity 87%). Atypical lymphocytes in dengue cases exhibited intense blue cytoplasm with cytoplasmic projections, reflecting high viral RNA content. The study noted that HFLC values are a useful parameter for initial screening and monitoring of patients with dengue virus infection, particularly in endemic areas with limited resources.

CONCLUSION

The comparison test results in this study showed no significant difference between HFC values in patients with ALL and infection (p=0.211).

The results of this study have important implications for clinical practice. The HFC parameter can be used as a rapid diagnostic tool to distinguish between hematological malignancies (ALL) and infections, and help speed up clinical decision-making. This is particularly relevant in the management of ALL and infections, especially in pediatric patients where early and accurate diagnosis can improve treatment outcomes.

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