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Assessing Pancytopenia in Leukemia Patients through flow Cytometry and ELISA to Evaluate the Complete Blood Counts and Cluster of Differentiation Markers

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ABSTRACT

To diagnose cases involving pancytopenia or leukopenia, a comprehensive assessment of various factors is necessary, including blood count, peripheral blood, and bone marrow analysis, immunophenotyping, and cytogenetics. This study aims to examine the complete blood count parameters and CD markers in Sudanese patients with leukemia and pancytopenia, utilizing flow cytometry and ELISA techniques. This study is a laboratory-based addressing the assessment of the target population (acute Leukaemia with pancytopenia) by complete blood count, flow cytometry, and ELISA techniques. The research group was comprised of patients who were diagnosed with acute leukemia and had pancytopenia before undergoing treatment. Another group of patients with acute leukemia but without pancytopenia was also included. In addition, there was a control group consisting of healthy individuals who volunteered for the study. Essentially, the control group was made up of healthy individuals who were not affected by acute leukemia or pancytopenia. In our study, we enrolled a total of 150 participants, comprising three groups: 50 cases of acute leukemia, 50 patients with acute leukemia who subsequently developed pancytopenia, and 50 healthy volunteers. The majority of participants were female, constituting 56% of the sample (84 individuals), while the most prevalent age group represented was individuals aged 65, accounting for 43.3% of the participants. Our analysis revealed a statistically significant correlation between age and both leukemia and leukemia with pancytopenia, with a p-value of 0.00. Furthermore, the presence of either AML or ALL also exhibited a substantial association with the disease, indicated by a p-value of 0.00. Specifically, the use of a flow cytometer allowed us to identify the presence of CD3 with a p-value of 0.00 and CD4 with a slightly higher p-value of 0.04. Improvement of patient management by introducing effective tools for predicting prognosis is the key to success in managing diseases. We recommend that flowcytometry be used routinely to diagnose leukemia and leukemia with cytopenia in patients at all stages of the disease.

Keywords: CBC, CD markers, Leukemia, Pancytopenia, Flowcytometry, ELISA, and Sudan.

INTRODUCTION:

Leukemia is a heterogeneous group of hematological malignancies characterized by the uncontrolled proliferation of the abnormal white blood cells (WBCs) within the bone marrow (Hussen Ebrahim *et al.,* 2022). Pancytopenia, a condition characterized by low levels of red blood cells (RBCs), WBCs, and platelets in the peripheral blood, is often observed in the leukemia patients (Ware, 2020; Geissler, 2021). Evaluating the complete blood count (CBC) and cluster of differentiation markers (CD) provides crucial information for diagnosing and monitoring

leukemia patients with pancy topenia (Ware, 2020; Geissler, 2021; Langroudi, 2023).

Flow cytometry and enzyme-linked immunosorbent assay (ELISA) are two commonly used techniques for analyzing CD markers in hematological disorders (Guan L *et al.,* 2022). Flow cytometry allows for the rapid and accurate identification of cell populations based on their specific CD markers, providing essential information about the lineage & maturation stage of the leukemic cells (Weeda V *et al.,* 2022). ELISA, on the other hand, quantitatively measures the concentration of specific CD markers in the blood serum, thereby offering valuable insights into disease progression & treatment response (Butreddy A *et al.,* 2021; and van Dijk AD, 2020). Flow cytometry is a powerful technique that has revolutionized the field of the cell analysis and is widely utilized in research, diagnostics, and clinical settings. However, the application of the flow cytometry in resource-limited settings poses unique challenges due to the constraints of infrastructure, availability of specialized equipment, and limited access to sophisticated reagents (Li Z. *et al.,* 2020; Gucluer S, 2023; and Jeon H *et al.,* 2020). Despite these obstacles, the use of flow cytometry in low resource settings is of great importance, as it enables the identification, quantification, and characterization of different cell populations, providing the valuable insights into various diseases and health conditions (Hartmann *et al.,* 2020 & Hu Z *et al.,* 2022). In low resource settings, where laboratories may have limited funding and infrastructure, the ability to the accurately and efficiently analyze cell populations can be a significant asset for disease diagnosis, monitoring treatment efficacy, and understanding the underlying mechanisms of diseases (Cantera JL *et al.,* 2019). Flow cytometry offers a range of the capabilities, including the assessment of cell surface markers, intracellular antigens, DNA content, and functional assays (Drescher H *et al.,* 2021; Manohar SM, 2021). As such, it is essential to explore strategies that make flow cytometry more accessible, affordable, and feasible for laboratories operating in low resource settings.

In routine clinical practice, the control and utilization of tumor markers has been lacking oversight (Taube JM *et al.,* 2020). There are limited criteria or the guidelines available for the use of these markers. TNF-alpha, a protein associated with the development of leukemia and myelodysplastic syndrome, has not been studied in Sudanese leukemias before and its prognostic significance is still unknown. To address this knowledge gap, a study was conducted to explore the impact of TNF-alpha on the development of pancytopenia in the patients with acute leukemia. By analyzing the complete blood count parameters and CD markers using flow cytometry and ELISA, researchers aimed to acquire valuable tumor marker data. These findings should aid in making informed decisions for the improved clinical outcomes, including longer overall survival, extended disease-free survival, and enhanced quality of life for patients. The objective of this study is to evaluate the utility of flow cytometry and ELISA in assessing the CBC and CD markers in leukemia patients presenting with pancytopenia. By correlating CBC parameters such as RBC count, WBC count, and platelet count with the expression levels of CD markers, we aim to the identify valuable diagnostic and prognostic indicators. In addition, we will analyze the relationship between these parameters and the clinical outcomes of patients, including survival rates and response to therapy.

METHODOLOGY:

Study design

Case-Control Laboratory-Based Study on the Acute Leukemia with Pancytopenia

Settings

The study involved three institutions, namely the Khartoum Centre for Flow Cytometry, the Faculty of Medical Laboratories at the University of Khartoum, and the Al Rayan Laboratory Centre. The technical aspects of complete blood count and CD marker analysis were conducted at these institutions.

Study Population

The study group consisted of patients diagnosed with acute leukemia and pancytopenia before receiving treatment. Additionally, a group of the patients with acute leukemia but without pancytopenia, as well as a control group of the healthy individuals without leukemia or other chronic diseases, were included. Inclusion criteria required patients to be diagnosed with acute leukemia and pancytopenia, and both patients and healthy controls had to the provide informed consent. Patients with chronic leukemia who already began treatment, refused to provide consent, or individuals with chronic diseases were excluded.

Sample Size

The sample size was determined using a formula at a confidence level of 95% and a precision degree of 0.04. In total, the study included 150 participants, distributed as follows: 50 cases with acute leukemia, 50 patients with acute leukemia and pancytopenia, and 50 healthy volunteers.

Data Collection and Technical Procedures

The lead researcher gathered venous blood and bone marrow samples from the each participant. These samples underwent processing, with a particular focus on conducting a comprehensive hemogram, with specific attention to leukocyte analysis. Subsequently, lymphocytes were isolated, and the expression levels of CD3, CD4, and tumor necrosis factor-alpha (TNF-alpha) markers were quantified using a four-color flow cytometry approach. The complete hemograms were carried out using an automated hematology analyzer (Sysmex XK-21N) in accordance with the manufacturer's guidelines. To assess extracellular TNF-alpha levels in serum, the ELISA technique was employed, utilizing the Quantikine Human TNF-alpha Immunoassay.

Data Management

A dedicated data sheet was utilized to consolidate and oversee the collected data. Throughout the data collection and the management processes, the lead investigator provided supervision and oversight.

Data Analysis

The data collected was extracted from records and transferred to an Excel spreadsheet containing all the variables relevant to the study. Subsequently, data analysis was conducted using SPSS after the completion of data management. The findings were interpreted through the use of statements, tables, and figures, with a predetermined significance level of $p \leq 0.05$. To identify potential risk factors, the Chi-Square test was employed, and correlation analysis was used to assess the statistical significance of the various factors.

Ethics Approval and Informed Consent

This study adhered to the ethical principles outlined in the Declaration of Helsinki. Approval from the Institutional Review Board (IRB) at the Faculty of Medical Laboratory, University of the Khartoum, was obtained. Before participating in the study, all participants provided informed consent.

RESULTS:

This study imparts the valuable insights into the interplay between clinical presentations, complete blood count components, and flow cytometry measurements in individuals affected by leukemia and leukemia with pancytopenia. The study you mentioned encompassed 150 participants who were categorized into distinct groups. Among them, 50 individuals were diagnosed with leukemia, another 50 had leukemia with pancytopenia, & the remaining 50 constituted the control group. A majority of the participants were the female, accounting for 84 individuals or 56% of the total cohort. The largest portion of participants fell within the age group of 65, making up 43.3% of the participants. However, there were also 50 participants under 18 years old, comprising 33.3% of the total and 14 participants over 60 years old, representing 9.3% of the group. The study established significant associations between age and the presence of AML or ALL, both types of leukemia, in relation to the leukemia and leukemia with pancytopenia. Additionally, the study examined the clinical manifestations of the participants at the time of sample collection, as presented in **Table 1**, and **Fig. 1**.

Table 1: Distribution according to clinical Presentation.

Presentation	Leukemia N (%)	L with Pancytopenia N (%)	Total N (%)	p-value
Fever	30 (30)	34 (34)	64 (64)	0.40
Fatigability	24(24)	37 (37)	47 (47)	0.84
Lymphadenopathy	15(15)	21 (21)	36 (36)	0.21
Organomegaly	17(17)	17 (17)	34 (34)	1.00
Bleeding	9 (9)	9 (9)	18 (18)	1.00
Others	6 (6)	8 (8)	14 (14)	0.56

The most prevalent symptom reported was fever, noted by 64 participants, which constituted 64% of the group. Other symptoms included fatigue (47%), lymphadenopathy (36%), the organomegaly (34%), bleeding disorders (18%), and various other presentations (14%). Statistical analysis underscored a

substantial correlation between the clinical presentation and the presence of leukemia and leukemia with pancytopenia. Furthermore, the study conducted a comparative analysis of various components of the complete blood count (CBC) between the study groups and the control group. The results revealed highly significant disparities in parameters such as total white blood cell count, red blood cell count, platelet count, hemoglobin levels, granulocyte count, lymphocyte count, and immature cell count. However, no significant association was observed for monocyte count, as indicated in the **Table 2**. Moreover, the study utilized flow cytometry to assess CD3, CD4, CD34, & TNF levels. Significant variations were observed for CD3 & CD4, although no significant differences were found for CD34 and TNF levels, as detailed in **Table 3**.

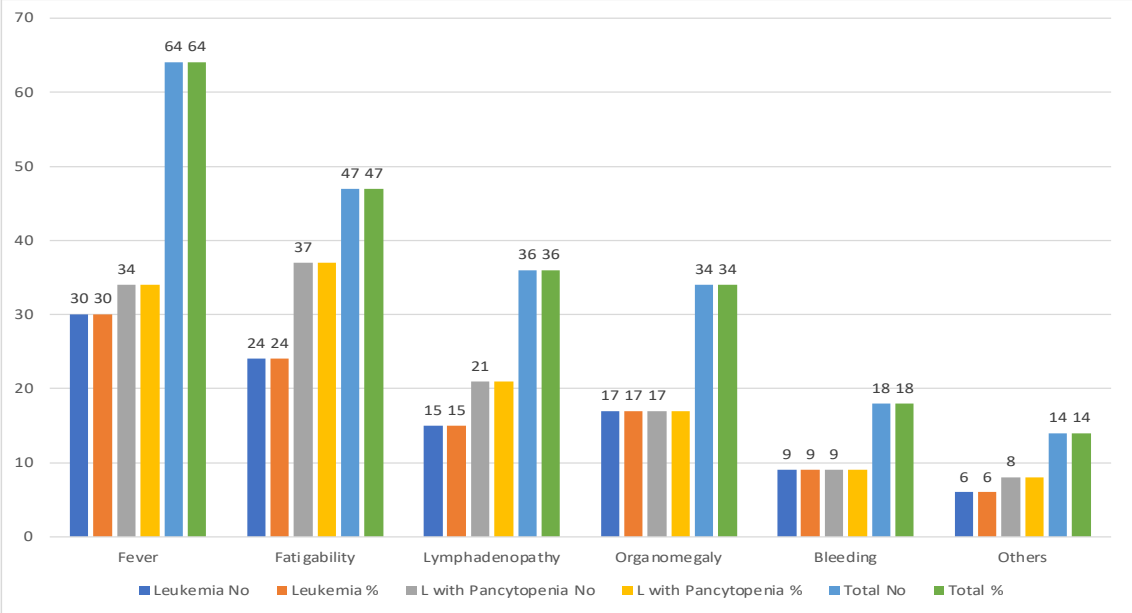

Fig. 1: Distribution according to clinical presentation.

Table 2: CBC among the study and control groups assessed by ELISA.

Presentation		TWBCs	RBCs	PLTs	HB	Granulocytes	Monocytes	Lymphocytes	Immature cell
LC	Mean	41.89	2.76	51.06	8.62	14.64	4.56	27.20	56.22
	N	50.00	49.00	50.00	50.00	50.00	30.00	50.00	49.00
	Std. D	44.52	1.11	50.39	2.30	13.14	4.16	22.36	25.72
	Min	1.70	0.90	2.00	4.30	2.00	1.00	6.00	2.00
	Max	193.70	7.70	238.00	13.40	52.00	21.00	96.00	91.00
NC	Mean	6.12	4.75	266.26	14.29	50.00		10.03	
	N	50.00	50.00	50.00	50.00	46.00		46.00	
	Std. D	1.66	0.41	73.31	1.31	10.85		3.78	
	Min	3.20	3.97	111.00	11.20	33.40		2.70	
	Max	11.00	5.39	406.00	16.80	76.30		23.90	
PAN	Mean	2.03	2.28	49.88	6.14	28.43	7.21	52.32	16.67
	N	50.00	50.00	50.00	50.00	49.00	28.00	50.00	43.00
	Std. D	0.62	0.62	36.83	1.11	18.04	11.06	21.30	15.46
	Min	1.10	1.19	2.00	3.30	2.00	1.00	10.00	2.00
	Max	3.60	3.60	125.00	8.90	71.00	39.00	90.00	80.00
Total	Mean	16.68	3.27	122.40	9.68	30.52	5.84	30.39	37.74
	N	150.00	149.00	150.00	150.00	145.00	58.00	146.00	92.00
	Std. D	31.23	1.32	116.04	3.80	20.35	8.28	25.05	29.20
	Min	1.10	0.90	2.00	3.30	2.00	1.00	2.70	2.00
	Max	193.70	7.70	406.00	16.80	76.30	39.00	96.00	91.00
P-value		0.00	0.00	0.00	0.00	0.00	0.22	0.00	0.00

Table 3: Measurements of CD3, CD4, CD34, and TF levels in three different groups: Leukemia (n=50), Leukemia with pancytopenia (n=50), and Control (n=50).

Presentation		CD3	CD4	CD34	TNF
Leukemia	Mean	4.63	46.17	0.13	3.25
	N	49.00	49.00	49.00	49.00
	Std. D	4.21	15.50	0.82	14.09
	Min	0.19	3.84	0.00	0.00
	Max	20.10	96.80	5.70	91.80
Control	Mean	12.80	54.04	0.00	0.48
	No.	50.00	50.00	50.00	50.00
	Std	3.86	9.50	0.00	2.12
	Min	6.53	24.90	0.00	0.00
	Max	23.30	75.20	0.00	13.70
Leukemia with pancytopenia	Mean	6.95	45.85	0.00	0.19
	No.	50	50	50	50
	Std	4.94	13.59	0.01	0.44
	Min	0.19	14.10	0.00	0.00
	Max	19.90	73.90	0.07	2.79
Total	Mean	8.15	48.71	0.04	1.29
	No.	149.00	149.00	149.00	149.00
	Std	5.54	13.54	0.47	8.23
	Min	0.19	3.84	0.00	0.00
	Max	23.30	96.80	5.70	91.80
P-value		0.00	0.04	0.29	0.12

DISCUSSION:

Flow cytometry is of the utmost importance in the development of a standardized analytical method for assessing the clinical significance of intracellular interleukins and tumor necrosis factor-alpha in the patients with acute leukemia (Wang M *et al.,* 2018). Furthermore, ELISA is the employed to gauge the extracellular TNF-alpha cytokine levels (Sumarawati T & Fatmawati D, 2023). The overarching objective is to the enhance patient care, facilitate research inquiries, & employ this methodology for prognostic prediction and the detection of transitions into other hematological disorders, like Myelodysplastic syndromes. In Sudan, among all the documented cancer cases for which information is available, the top five most frequently occurring cancers in adults include breast cancer, leukemia, prostate cancer, lymphoma, and colorectal cancer (Saeed IE, 2014). This research uncovered notable connections between age and the occurrence of either AML or ALL in relation to leukemia, as well as between leukemia & pancytopenia. ALL, although it can manifest at any age, is most prevalent in individuals under the age of 20 (Brocas I & Carrillo JD., 2021). It represents the predominant form of leukemia diagnosed within this age category (Mjali A, 2019). The research also unveiled highly noteworthy distinctions between the study groups and the control group when evaluating various complete blood count (CBC) parameters, including total white blood cell count (TWBC), red blood cell count (RBC), platelets (PLT), hemoglobin (Hb), the granulocytes, lymphocytes, and immature cells. The study groups, encompassing individuals with leukemia, leukemia with pancytopenia, & the control group, underwent a comprehensive assessment of CBC parameters, with a specific focus on white blood cells and differential cell counts. Except for monocytes, all cellular parameters displayed significant correlations across the study groups. The CBC stands as a pivotal predictive factor for the early detection of the leukemia and its associated complications (Ali *et al.,* 2023). It frequently serves as the initial laboratory test for individuals suspected of having leukemia. Deviations in white blood cell count, red blood cell count, or platelet count can raise suspicions regarding the presence of leukemia, prompting further evaluation, often including a bone marrow biopsy to determine the precise leukemia subtype. In this research, utilization of flow cytometry was pivotal in assessing both intracellular and extracellular TNF-alpha levels. The flow cytometer gauged parameters including CD3, CD4, CD34, & TNF, and the noteworthy findings were observed, particularly with CD3 (p-value 0.00) and CD4 (p-

value 0.04). Earlier studies have similarly confirmed the effectiveness of the flow cytometry in detecting intracellular and extra-cellular TNF-alpha, emphasizing its sensitivity & specificity (Pieragostino *et al.,* 2019). Nevertheless, it is crucial to recognize the constraints of this investigation. The study incurred significant costs, and the procurement of essential reagents was notably difficult, especially given the prevailing conditions in Sudan. Moreover, acquiring untreated samples, specifically cases of leukemia with pancytopenia, presented a formidable obstacle. Additionally, it's worth noting that the utilization of flow cytometry is not widespread in Sudan. The implementation of the valuable tools such as flow cytometry holds significant importance in improving patient care & fore-casting prognosis. We whole heartedly advocate for the regular integration of flow cytometry into public healthcare facilities for the diagnosis of leukemia and leukemia with cytopenia, spanning all phases of the illness.

Limitations

Several constraints affected the scope of this study. Notably, the research incurred substantial expenses, primarily due to the challenging circumstances prevailing in the Sudan, which posed difficulties in the acquiring necessary reagents. Additionally, the procurement of untreated samples of leukemia with pancytopenia presented a significant challenge. Another limitation stemmed from the limited utilization of flow cytometry within Sudan.

CONCLUSION:

The key to effective disease management lies in the introduction of reliable tools that facilitate prognosis prediction and enhance patient care. Therefore, we strongly recommend the integration of flow cytometry into public healthcare settings. Our resolute endorsement is for the routine utilization of flow cytometry for diagnosing leukemia and leukemia with cytopenia across all disease stages.

Abbreviations

CD (Cluster of Differentiation), ELISA (Enzyme-Linked Immunosorbent Assay), TNF-alpha (Tumor Necrosis Factor-Alpha), and CBC (Complete Blood Count).

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