ORIGINAL ARTICLE

Evaluation of clinico-etiological aspects of pancytopenia in patients presenting at a tertiary care hospital in Lahore

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ABSTRACT

Background and Objective: Pancytopenia is a clinical condition characterized by the simultaneous presence of anemia, leukopenia, and thrombocytopenia. It reflects various underlying diseases that affect the bone marrow function, with clinical manifestations varying according to the severity of bone marrow suppression. The objective of this study is to evaluate the clinical presentation and underlying etiologies of pancytopenia and to determine their associations with age and gender in pancytopenic patients presenting to a tertiary care hospital in Lahore, Pakistan.

Methods: The study was conducted in the Pathology Department of Al-Aleem Medical College, Gulab Devi Teaching Hospital, Lahore, from January 2020 to December 2023. A total of 71 patients of all ages and both genders who presented with pancytopenia (as per De Gruchy's criteria) during the study period were enrolled through consecutive sampling. Patients receiving myelotoxic therapy or who had undergone recent blood transfusions were excluded. Clinical history, examination, and laboratory investigations, including complete blood count (CBC), peripheral blood smear, bone marrow aspiration, and trephine biopsy, were performed. Data were analyzed using Statistical Package for Social Sciences (SPSS) version 27.0. Descriptive statistics and Fisher's exact test were used to assess associations, with a *p* value of <0.05 considered as statistically significant.

Results: A total of 71 patients with pancytopenia were included in the study. The mean age of enrolled patients was 38.9 ± 19.5 years (range: 7–72 years), with a male-to-female ratio of 1.3:1. Fever was the most common presenting symptom (50.70%), followed by generalized weakness (32.39%), pallor (30.98%), and shortness of breath (28.17%). Aplastic anemia emerged as the most frequent underlying cause (33.80%), followed by megaloblastic anemia (12.68%), acute leukemia (12.68%), and metastatic infiltration (9.86%). There was no statistically significant association between frequency of various causes of pancytopenia across different age groups (p = 0.565) or gender (p = 0.877).

Conclusion: Aplastic anemia was the most common underlying cause of pancytopenia, followed by megaloblastic anemia and acute leukemia. The etiological spectrum showed no significant association with age or gender, highlighting the importance of comprehensive hematological evaluation, including bone marrow examination, for accurate diagnosis and appropriate management.

Keywords: Pancytopenia, etiology, bone marrow examination, megaloblastic anemia, aplastic anemia, acute leukemia.

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Introduction

Pancytopenia is a clinical-hematological condition commonly encountered in medical practice due to bone marrow disorders.[1] Pancytopenia is characterized by a simultaneous reduction in red blood cells, white blood cells, and platelets. It is a manifestation of various underlying diseases affecting the bone marrow function. The clinical presentation varies based on the severity of bone marrow suppression. Patients usually present with the symptoms of generalized weakness and fatigue due to anemia, fever, increased susceptibility to infections resulting from leukopenia, and abnormal bleeding tendencies such as petechiae, purpura, or ecchymosis caused by thrombocytopenia. Additional symptoms may include weight loss, shortness of breath, and splenomegaly. [1,2].

The most common etiological factors of pancytopenia, as reported by various studies, include aplastic anemia (24–36% of cases), megaloblastic anemia (21–22% of cases), acute leukemia (8–14% of cases), myelodysplastic syndrome

(6–17% of cases), and chronic liver disease (6% cases).[2,3] Other notable causes include multiple myeloma, malaria, typhoid fever, dengue fever, systemic lupus erythematosus, and hypersplenism.[2]

A cross-sectional study by Gajbhiye et al. (2022), conducted in Kolkata, found pancytopenia to be most prevalent among individuals aged 25–34 years, with a male predominance.[1] Fatigue and fever were the most frequently reported symptoms, while pallor was observed in all patients.[1]

Diagnostic investigations like CBC play a crucial role in confirming pancytopenia. Treatment plans and prognosis depends on the underlying etiology and severity of the condition.[1]The bone marrow biopsy provides crucial insights into the pathological processes affecting hematopoiesis, enabling the differentiation between malignant and non-malignant causes.[2,4] Studies have shown that bone marrow cellularity can vary significantly, with findings of hypo-cellular marrow in 46% of cases, hyper-cellular marrow in 38% of cases, and normo-cellular marrow in 16% of cases.[3] Bone marrow biopsy not only plays a critical role in diagnosing pancytopenia but also guides about the treatment decisions and prognosis.[1,4]

Multiple cross-sectional studies from Pakistan have consistently identified megaloblastic anemia as the leading etiology of pancytopenia. Reported frequencies include 41.7% in Karachi, 25.8% in Rawalpindi, and 18.1% in Lahore. Other commonly reported causes include leukemia (25.1% in Rawalpindi, 11% in Lahore) and aplastic anemia (14.4% in Rawalpindi and 12.9% in Lahore).[5-7] Across all studies, the predominant clinical manifestations were fever, fatigue, pallor, and organomegaly. [5-7]

Pancytopenia encompasses a diverse spectrum of underlying disorders, with etiological patterns varying across populations and healthcare settings. Limited local data are available regarding its clinicopathological spectrum in Pakistan. This study was therefore undertaken to characterize the common causes and clinical presentation of pancytopenia and their distribution across age and gender in patients presenting to a tertiary care hospital in Lahore.

Methods

This cross-sectional study was conducted at the Department of Pathology, Al-Aleem Medical College, Gulab Devi Teaching Hospital, Lahore, Pakistan. Ethical approval was obtained from the Institutional Review Board (IRB) of Al-Aleem Medical College Lahore, Pakistan. The study included 71 patients who presented with pancytopenia over a period of 4 years, from January 1, 2020, to December 31, 2023. Patients of all ages and both genders were included using consecutive sampling after taking informed consent.

The study included patients with pancytopenia, defined according to De Gruchy's criteria as the presence of anemia (hemoglobin (Hb) <13.5 g/dl in males, <11.5 g/dl in females), leukopenia (total leukocyte count (TLC) <4 × 10^9/L), and thrombocytopenia (platelets <150 × 10^9/l).[5] Patients receiving myelotoxic chemotherapy or radiotherapy, or those with a recent blood transfusion, were excluded from the study. The diagnostic criteria for the underlying causes of pancytopenia including aplastic anemia, megaloblastic anemia, and acute leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, myelodysplastic syndrome, and plasma cell myeloma were defined in accordance with the standard hematological parameters and morphological findings.[8]

A comprehensive clinical history and physical examination were performed for all patients. Following informed consent, 3 ml of venous blood was collected in an ethylene diamine tetra-acetic acid (EDTA) tube for CBC analysis, performed using the Mindray BC-30s automated hematology analyzer. A peripheral blood smear was prepared from EDTA sample. Bone marrow aspiration and trephine biopsy were conducted under local anesthesia (2% xylocaine injection) and aseptic conditions, from the posterior superior iliac spine, using a disposable bone marrow biopsy needle. Peripheral blood and aspirate smears were stained with Giemsa stain for cytological evaluation, while trephine biopsy specimens were fixed, processed, and stained with hematoxylin and eosin (H&E) for histopathological assessment. Immunohistochemical staining was employed where necessary to support diagnostic interpretation.

Demographic data, including age and gender, along with clinical presentations, were recorded for all patients. Laboratory investigations such as CBC, peripheral blood smear, bone marrow aspiration, and trephine biopsy results were systematically documented using a standardized data collection proforma.

Statistical analysis

Data were collected and analyzed by using SPSS version 27.0. Frequencies and percentages were calculated for gender, clinical presentations, and underlying causes of pancytopenia. Mean, standard deviation, and range were calculated for numeric variables including age, hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), total leukocyte count (TLC), and platelet count. The Fisher's exact test was applied to assess associations of age groups and gender with causes of pancytopenia. A p-value of ≤ 0.05 was considered statistically significant.

Results

A total of 192 patients presented to the Department of Pathology, Al-Aleem Medical College, Gulab Devi Teaching

Hospital for bone marrow biopsy during the study period. Of these, 71 patients (36.98%) met the diagnostic criteria for pancytopenia and were included in the study. The male-to-female ratio was 1.3:1, with 40 males (56.33%) and 31 females (43.66%). The mean age of the patients was 38.9 ± 19.5 years, with an age range of 7 to 72 years. Pancytopenia was found in 15 (21.1%) pediatric patients (less than 18 years old) including 8 girls and 7 boys.

The mean hemoglobin level was 7.94 ± 1.97 g/dl (range: 2.3–12 g/dl). The MCV was 87.3 ± 10.9 fl (range: 60.9–117 fl), while the MCH was 28.21 ± 3.77 pg (range: 17.7–37.9 pg). The mean white blood cell count was 2.46 ± 1.04 × 10^9/l (range: 0.4–3.9/l), and the mean platelet count was 63.56 ± 43.25 × 10^9/l (range: 2–148/l). Clinical presentation of patients with pancytopenia is shown in Table 1.

Table 1. *Clinical presentation in patients with pancytopenia (n = 71)*

Clinical feature	No. of cases	Percentage (%)
Fever	36	50.70%
Generalized weakness	23	32.39%
Pallor	22	30.98%
Shortness of breath	20	28.17%
Splenomegaly	14	19.72%
Gastrointestinal symptoms (diarrhea, indigestion)	14	19.72%
Bleeding manifestations	10	14.08%
Weight loss	9	12.68%
Bony tenderness/aches	9	12.68%
Lymphadenopathy	9	12.68%
Hepatomegaly	6	8.45%
Jaundice	2	2.82%

Fever was the most prevalent presenting complaint in patients with pancytopenia, followed by generalized weakness, pallor, and shortness of breath. Patients with primary myelofibrosis, non-Hodgkin's lymphoma, and hypersplenism have been found to have splenomegaly. In those with megaloblastic anemia, gastrointestinal problems were more common. In patients with both non-Hodgkin's and Hodgkin's lymphomas, as well as in one with acute leukemia, lymphadenopathy was more frequently observed.

Aplastic anemia was the most common cause of pancytopenia, found in 24 (33.80%) patients. A significant proportion of these patients, 9 (37.50%), was under 18 years of age. Bone marrow cellularity of most of these patients (n = 22) was hypocellular, with cellularity less than 20%. Trilineage hematopoiesis was reduced in all cases. In 2 cases, 1-2 reactive lymphoid follicles were noted on trephine biopsy.

Of the 71 patients with pancytopenia, 9 (12.68%) were diagnosed with megaloblastic anemia, and 4 (44.44%) of these patients were between 18 and 40 years old. Bone marrow examination in these patients showed erythroid hyperplasia with megaloblastic change. Giant myelocytes and metamyelocytes were found along with large megakaryocytes. Few patients also showed mild degree of erythroid dysplasia.

Acute leukemia was diagnosed in 9 (12.68%) of the 71 patients presenting with pancytopenia. Among these, 6 cases were identified as acute lymphoblastic leukemia, with 5 being B-cell ALL and 1 being T-cell ALL. The remaining three cases were diagnosed as acute myeloid

Table 2. *Distribution and association of causes of pancytopenia across age groups*

Cause of pancytopenia	<18	18–40	41–60	>60	Total
Aplastic anemia	9 (37.50%)	6 (25.00%)	5 (20.83%)	4 (16.67%)	24 (100%)
Megaloblastic anemia	3 (33.33%)	4 (44.44%)	1 (11.11%)	1 (11.11%)	9 (100%)
Acute leukemia	3 (33.33%)	1 (11.11%)	2 (22.22%)	3 (33.33%)	9 (100%)
Metastatic infiltration	0 (0%)	2 (28.57%)	2 (28.57%)	3 (42.86%)	7 (100%)
Non-Hodgkin lymphoma	0 (0%)	2 (40.00%)	3 (60.00%)	0 (0%)	5 (100%)
Myelodysplastic syndrome	0 (0%)	1 (20.00%)	2 (40.00%)	2 (40.00%)	5 (100%)
Trilineage hematopoiesis	0 (0%)	2 (40.00%)	2 (40.00%)	1 (20.00%)	5 (100%)
Hypersplenism	0 (0%)	2 (100%)	0 (0%)	0 (0%)	2 (100%)
Plasma cell myeloma	0 (0%)	0 (0%)	1 (50.00%)	1 (50.00%)	2 (100%)
Primary myelofibrosis	0 (0%)	0 (0%)	1 (100%)	0 (0%)	1 (100%)
Chronic granulomatous inflammation	0 (0%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)
Hodgkin lymphoma	0 (0%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)
Total	15 (21.12%)	22 (30.99%)	19 (26.76%)	15 (21.12%)	71 (100%)
Fisher's exact test (p-value)	p = 0.588				

Table 3. *Association between gender and causes of pancytopenia*

Cause of pancytopenia	Female (F)	Male (M)	Total (*n* = 71)
Aplastic anemia	11 (35.48%)	13 (32.50%)	24 (33.80%)
Megaloblastic anemia	5 (16.13%)	4 (10.00%)	9 (12.68%)
Acute leukemia	4 (12.90%)	5 (12.50%)	9 (12.68%)
Metastatic infiltration	3 (9.68%)	4 (10.00%)	7 (9.86%)
Non-Hodgkin lymphoma	2 (6.45%)	3 (7.50%)	5 (7.04%)
Myelodysplastic Syndrome	2 (6.45%)	3 (7.50%)	5 (7.04%)
Trilineage hematopoiesis	1 (3.23%)	4 (10.00%)	5 (7.04%)
Hypersplenism	1 (3.23%)	1 (2.50%)	2 (2.82%)
Plasma cell myeloma	1 (3.23%)	1 (2.50%)	2 (2.82%)
Primary myelofibrosis	0 (0.00%)	1 (2.50%)	1 (1.41%)
Chronic granulomatous inflammation	0 (0.00%)	1 (2.50%)	1 (1.41%)
Hodgkin lymphoma	1 (3.23%)	0 (0.00%)	1 (1.41%)
Total	31 (43.66%)	40 (56.34%)	71 (100%)
Fisher's exact test (p-value)	$p = 0.890$	—	

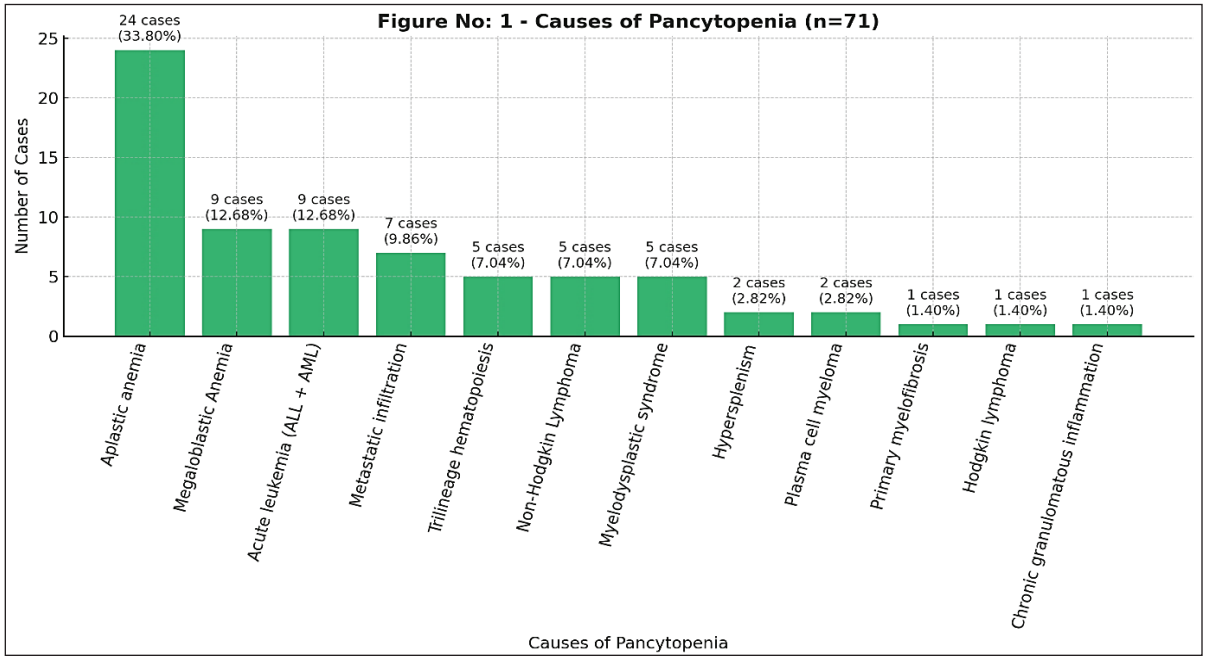


Figure 1. *The distribution of cases according to cause of pancytopenia.*

leukemia (AML), which included two cases of AML without maturation and 1 case of acute myelomonocytic leukemia. Trilineage hematopoiesis was suppressed in all cases of acute leukemia.

Among the pancytopenic patients, 7 (9.86%) had metastatic infiltration, including two cases of breast carcinoma and one case of prostatic carcinoma.

The distribution of different causes of pancytopenia across various age groups and gender are shown in Figure 1 and Tables 2 & 3, respectively.

Discussion

Pancytopenia comprises of anemia, thrombocytopenia, and leukopenia which can result from various underlying conditions. In this study, we evaluated clinical, hematological, and etiological profile of 71 patients who presented with pancytopenia. In the present study, patients' age ranged from 7 to 72 years, with a mean age of 38.9 ± 19.5 years. The most common age group was 18–40 years (30.99%), followed by the 41–60 years age group (26.76%). The male-to-female ratio was 1.3:1, which is comparable to the findings of Patel

et al. (2022), who studied 546 patients with pancytopenia.[9] In their study, patients' age ranged from 18 to 93 years, with a mean age of 40.3 years and a male-to-female ratio of 1.26:1. The most prevalent age group in this study was 21–30 years (24%), followed by 41–50 years (20%) and 31–40 years (18%).[9]

Gayathri et al. (2011) reported on 104 pancytopenia cases from India, where patients' age ranged from 2 to 80 years with a median age of 41 years and a predominance of male patients.[10] Dhooria et al. (2020) reported that the highest prevalence of pancytopenia was in the 51–60 year age group (23%), with a mean age of 45.69 ± 17.05 years and a male-to-female ratio of 1.4:1.[11] These studies consistently demonstrate a male predominance among patients with pancytopenia and highlight a wide age distribution, with a notable concentration in younger to middle-aged adults.[9-11]

The clinical features associated with pancytopenia are diverse and can indicate serious underlying conditions. In our study, the most common presenting complaint was fever (50.70%), which is followed by generalized weakness (32.39%), pallor (30.98%) and shortness of breath (28.17%). According to a study conducted in Rawat by Naval et al. (2024), the most frequent complaints in patients presenting with pancytopenia were pallor (82.6%), weakness and weight loss (63.2%), and petechial hemorrhages on the skin (45.9%).[12] Fever (23.5%) was additionally reported by several patients.[12] Generalized weakness and pallor were noted as the primary complaint with 100% of patients with pancytopenia in a study by Gayathri et al. (2011).[10]

In another study conducted by Sharma et al. (2023) on pediatric patients aged 1 month to 12 years admitted with bicytopenia and pancytopenia, fever and pallor were each observed in 87.5% of the cases.[13] Vargas-Carretero et al. (2019) studied 109 patients aged over 15 years with pancytopenia and reported that more than 80% of patients presented with anemia-related symptoms, including pallor (82.6%) and weakness (81.7%).[14] Hemorrhagic manifestations such as ecchymosis (29.4%) and petechiae (17.4%) were also common in their study.[14] In comparison, bleeding manifestations were observed in 14.08% of patients in our study.

The various etiologies of pancytopenia include decreased blood cells production (such as aplastic anemia and nutritional deficiencies) and increased blood cells destruction (such as autoimmune disorders and hypersplenism).[15] The most common cause of pancytopenia in our study was aplastic anemia (33.80%), which was followed by megaloblastic anemia and acute leukemia (12.68% each. This finding contrasts with earlier studies conducted in Pakistan, which identified megaloblastic anemia as the most common cause.[5-7]

In a study conducted in Eastern India, Dasgupta et al. (2015) found that aplastic anemia was the most prevalent cause of pancytopenia, accounting for 83 cases (33.47%) out of 248 patients. Megaloblastic anemia was the second most common cause, seen in 52 cases (20.97%).[16] The incidence of aplastic anemia was notably higher among children (≤15 years).[16] These findings are consistent with our results, where 9 out of 15 pediatric patients (<18 years) were diagnosed with aplastic anemia. In a study conducted in Pakistan, Makheja et al. (2013) analyzed bone marrow examinations and identified hypoplastic bone marrow (29.05%) and megaloblastic anemia (23.64%) as the leading causes of pancytopenia.[17] The study emphasized the importance of bone marrow examination in determining the underlying etiology and guiding appropriate treatment strategies.[17]

Megaloblastic anemia has been reported as the most common cause of pancytopenia in several regional studies, with its frequency generally ranging from 13% to 47%. [5-7,10,18] A study conducted in Uttarakhand, India, by Gupta et al. (2019) identified megaloblastic anemia as the most common cause of pancytopenia, accounting for 25% of cases.[18] Aleukemic leukemia and aplastic anemia were the next most frequent causes, each representing 19.1% of cases.[18] The study also highlighted visceral leishmaniasis as a notable regional cause, observed in 11.7% of patients.[18] In a study involving 98 adult patients with new-onset pancytopenia, Naval et al. (2024) reported megaloblastic anemia as the predominant cause (43.8%), followed by aplastic anemia (17.3%) and portal hypertension-induced splenomegaly (13.2%).[12] The study also highlighted gender differences in etiology, with megaloblastic anemia being more common among females, whereas aplastic anemia was more prevalent in males.[12]

In another study, Batool et al. (2021) found megaloblastic anemia to be the most common cause of pancytopenia (27.0%), followed by aplastic anemia (15.6%) and acute leukemias (13.1%).[19] Megaloblastic anemia is quite prevalent, maybe resulting from dietary factors, and can be readily corrected with the proper medication.[20] Therefore, while evaluating pancytopenia in Asian countries, megaloblastic anemia should always be taken into account.[20]

In our study, acute leukemia was found in 9 out of 24 patient and was the second most prevalent cause along with megaloblastic anemia. ALL was found to be more common in pediatric population and AML in adult population. Patel et al. (2022) studied 546 adult patients, and the most common cause of pancytopenia was found to be acute leukemia (17.9%).[9] ALL was found in 46.9% of patients, whereas 43.8% of cases were AML, 6.1% of cases were acute promyelocytic leukemia, and 3.1% of cases were mixed phenotypic acute leukemia type.[9] In Indian studies, Mallik et al. (2016) and Gupta et al. (2019) reported acute leukemia as the second

most common cause of pancytopenia, 30.5% and 19%, respectively, following megaloblastic anemia as the most frequent cause.[18, 21] In another study that involved 106 pediatric patients, the most common etiological factor for pancytopenia was ALL, accounting for 58.5% of cases, followed by aplastic anemia at 19.8%.[22]

Myelodysplastic syndrome was noted in 5 (7.04%) patients in our study, and mostly were more than 40 years of age. Myelodysplastic syndrome represents a spectrum of disorders caused by ineffective hematopoiesis and can progress to AML.[14] In a study conducted in Mexico, Vargas-Carretero et al. (2019) found myelodysplastic syndrome to be the most common cause of pancytopenia (20.2%) among 109 adult patients, followed by megaloblastic anemia (18.3%) and AML (12.8%).[14] The study further suggested that malignant neoplasms are more frequently observed in developed and industrialized countries, whereas vitamin deficiencies, infections, and hypersplenism are more prevalent in developing nations.[14]

Limitations of the Study

The findings of the study cannot be generalized due to small sample size. The information was gathered from a single institution, which could limit the results' universality to different contexts or demographics and create institutional biases. Future research should include larger, multi-center studies to validate and broaden the findings of this study.

Conclusion

Aplastic anemia was the most common underlying cause of pancytopenia, followed by megaloblastic anemia and acute leukemia. The etiological spectrum showed no significant association with age or gender, highlighting the importance of comprehensive hematological evaluation, including bone marrow examination, for accurate diagnosis and appropriate management

This approach must include detailed clinical assessments, routine evaluations for nutritional deficiencies, and advanced diagnostic tools such as immunophenotyping. Timely interventions for treatable conditions, along with continuous education for healthcare professionals on the latest research and guidelines, are crucial for improving patient outcomes.

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List of Abbreviations

CBC	Complete blood count
EDTA	Ethylene diamine tetra-acetic acid
Hb	Hemoglobin
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
AML	myeloid leukemia
SPSS	Statistical Package for Social Sciences

Conflict of interest:

None to declare.

Grant support and financial disclosure

None to disclose.

Ethics approval

The study was approved by the Institutional Review Board of Al-Aleem Medical College, Lahore, Pakistan vide Letter No: AAMC/IRB/EA42/2024, dated 27/06/2024.

Informed consent (if applicable)

Informed consent was taken from all the patients.

Authors' contributions

SK: Principal investigator, concept and design of study, critical intellectual input, drafting of the manuscript

SF, AA, RA, FJ, GA: Drafting of the manuscript, acquisition of data, critical intellectual input.

ALL AUTHORS: Approval and responsibility of the final version of the manuscript to be published.

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