

# Clinical Presentations of Acute Leukemia

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## ABSTRACT

**Objective:** To document the clinical presentation and epidemiology of various types of acute leukemia with their respective referral source at a tertiary level centre in Peshawar.

**Study Design:** An observational study.

**Place and Duration of Study:** Department of Pathology, Hayatabad Medical Complex (HMC), Peshawar, from January 2011 to May 2012.

**Methodology:** A total of 618 bone marrow biopsy reports were reviewed. All biopsy reports labeled as acute leukemia were reviewed for age, gender, address, referring unit, diagnosis on bone marrow examination, presenting complaints, duration of illness and findings of clinical examination.

**Results:** Ninety-two patients were diagnosed as suffering from acute leukemias (15%). ALL was most prevalent (46%), followed by AML (38%) and undifferentiated acute leukemia (16%). Males were affected more compared to females (60% vs. 40%). ALL and AML were predominant in pediatric (64%) and adults (77%) patients respectively. Patients from Afghanistan accounted for 33% of all cases followed by Peshawar (14%). Fever (77%), pallor (33%) and bleeding disorders (23%) were the main presenting complaints. Enlargement of liver, spleen and lymph nodes together was associated with ALL compared with AML ( $p = 0.004$ ).

**Conclusion:** ALL-L1 and AML-M4 were the most common sub-types. Fever, pallor and bleeding disorders were the main presenting complaints. Enlargement of liver, spleen and lymph nodes was more frequently associated with ALL compared to AML.

**Key Words:** Acute leukemia. Acute lymphoblastic leukemia. Acute myelogenous leukemia.

## INTRODUCTION

Acute leukemias (ALs) are one of the most common cancers with about 20,000 cancer diagnoses and over 10,000 annual deaths in the United States.<sup>1</sup> Acute leukemias represent neoplasm of the hematopoietic cell precursors manifested as clonal expansion of myeloid and lymphoid hematopoiesis.<sup>2</sup> Acute leukemia can be broadly classified into Acute Lymphocytic Leukemia and Acute Myelogenous Leukemia depending on the type of cell lineage affected.

Acute Lymphocytic Leukemia (ALL) is the most common malignancy diagnosed in children. It is clinically and morphologically heterogeneous.<sup>1</sup> Morphologically, it is classified according to FAB (French, American and British) criteria into L-1, L-2 and L-3 sub-types, which is clinically reproducible.<sup>3</sup> Acute Myelogenous Leukemia (AML) refers to a group of hematological malignancies that arise within bone marrow precursors of myeloid, monocyte, erythroid and megakaryotic cell lineages. FAB classification system divides Acute Myelogenous Leukemia into M-0 to M-7 sub-types.<sup>3</sup>

Bone marrow aspiration with trephine biopsy is used as a standard for diagnosis of leukemia.<sup>4</sup> This technique is cheap and reliable. Cytogenetic studies, flow cytometry and Immunohistochemical (IHC) studies play a key-role in the determining the exact diagnosis and ultimate prognosis of acute leukemia.<sup>5</sup> These facilities are not commonly available and the high-cost associated with them makes it difficult for every patient to do such studies especially in developing countries.<sup>6</sup> This makes bone marrow aspiration with biopsy as the most favored investigation to confirm the diagnosis of acute leukemia in resource poor or developing countries where the majority of patients cannot afford the high cost of cytogenetic study. It is very important to make an accurate diagnosis of acute leukemia as therapy is based on subtype according to various classifications.<sup>7</sup>

Currently, there is limited data regarding the prevalence of different types of acute leukemias in northern part of Pakistan.<sup>8</sup> At present, there are no cancer registry programs in Pakistan which can keep a track and notify regarding the prevalence and incidence of various types of cancers including leukemias. This is of utmost importance as Pakistan is an Asian country and cancer is becoming a serious health issue, being the leading cause of death in Asia Pacific countries.<sup>9</sup>

The clinical presentation of acute leukemias is very variable and it makes diagnoses difficult for the treating physician.<sup>10</sup> Early diagnosis is very important as early

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treatment can lead to good remission and cure rates. There have been very few studies which have reported the various clinical presentations of such patients, physical examination findings and their association.<sup>10</sup>

The objectives of this study were to document the age and gender distribution of various types of acute leukemias with their respective classifications, to determine the main presenting complaints and clinical findings of acute leukemias and to find association between them (if any).

## METHODOLOGY

A retrospective, chart-based, descriptive, institution-based study was conducted in Department of Pathology, Hayatabad Medical Complex (HMC), Peshawar. The study was approved by the hospitals' Institute Review and Ethics Board (IREB).

A total of 618 bone marrow biopsy reports were reviewed which were performed from January, 2011 to May, 2012. Out of these, 92 patients were diagnosed as suffering from different types of acute leukemias.

The inclusion criterion was all patients which were newly diagnosed as acute leukemia by bone marrow examination irrespective of age, gender, socio-economic status, ethnicity and geographical location. The exclusion criteria was all patients which had been previously diagnosed as acute leukemia, in whom bone marrow examination was performed for remission status; and those with diagnosis other than leukemia (e.g. anemia, myelodysplastic syndrome (MDS), multiply myeloma, etc.).

The data was collected after filling out a proforma regarding age, gender, address, referring unit, diagnosis on bone marrow examination, presenting complaints, duration of illness and findings of clinical examination. Data was recorded and analyzed using Statistical Package for Social Sciences version 20.0 (SPSS, Inc., Chicago, IL, USA). Fisher's exact test was applied to test the association. Results were recorded as frequencies, means  $\pm$  standard deviations (SD) and p-values. For all purposes, a p-value of  $< 0.05$  (95% confidence level) was considered as the criteria of significance.

## RESULTS

Out of a total 618 bone marrow aspirations performed during the study period, 92 (15%) revealed that patients were suffering from different forms of acute leukemias. Forty-two (46%) patients were suffering from ALL, 35 (38%) patients were diagnosed as AML while differentiation could not be clearly made in 15 (16%) patients (UAL). Figure I shows gender-wise distribution of patients suffering from various sub-types of ALL, AML (according to FAB classification) and acute leukemias.

Sixty percent (n=55) patients suffering from acute leukemias were males while 40% (n=37) were females. ALL in males accounted for 62% of cases while in females, it accounted for 38% of cases. Forty-three percent (n=15) of AML cases were females while 57% (n=20) were male patients. The age-wise distribution various types of leukemias are shown in Table I.

Amongst patients suffering from ALL, majority of patients were of paediatric age group (64%) while for AML, majority were adults (77%). The overall mean age was  $24 \pm 21.5$  years. For ALL, the mean age was  $15.6 \pm 16.1$  years (ranging from 1 to 76 years), median was 9.5 years and mode was 4 years. For AML, the mean age was  $31.4 \pm 22.7$  years (ranging from 1 to 80 years), median was 26 years and mode was 35 years.

Thirty-three percent (n=31) patients belonged to Afghanistan and it was higher than any other area from which patients presented. It accounted for 31% of ALL cases and 34% of all AML cases. Fifteen percent (n=14) patients belonged to Peshawar while rest belonged to other districts of KPK like Swabi, Charsadda, Mardan, Bunair, etc.

**Table II:** Presenting complaints of patients.

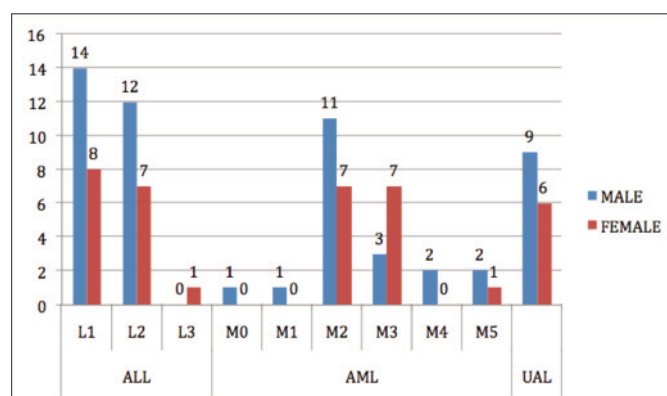
	N	%
Fever	71	77
Pallor	30	33
Bleeding disorders	21	23
Generalized body aches	17	18
Abdominal pain / distention	14	15
Lymph node enlargement	12	13
Weakness	7	8
Weight loss	6	7

**Table I:** Age wise distribution of various types of leukemias.

	Diagnosis										Total	Percentage
	Acute leukemia	ALL-L1	ALL-L2	ALL-L3	AML-0	AML-1	AML-2	AML-3	AML-4	AML-5		
1 - 5 years	2	9	4	0	0	1	0	3	1	1	21	22
6 - 10 years	3	4	6	0	0	0	1	1	0	0	15	16
11 - 15 years	0	1	3	0	0	0	0	0	0	0	4	4
16 - 20 years	2	4	1	0	0	0	5	2	0	0	14	15
21 - 25 years	1	1	1	0	0	0	1	1	0	0	5	5
26 - 30 years	1	1	0	0	0	0	1	1	0	0	4	4
31 - 35 years	1	2	1	0	0	0	5	1	0	1	11	12
> 35 years	5	0	3	1	1	0	5	1	1	1	18	19
Total	15 (16%)	22 (23%)	19 (20%)	1	1	1	18 (19%)	10 (11%)	2	3	92	-

**Table III:** Findings of physical examination.

	ALL			AML						UAL	Total	p-value
	L-1	L-2	L-3	M-0	M-1	M-2	M-3	M-4	M-5			
Hepatomegaly	1	1	0	0	0	1	1	0	0	1	5	1.0
Splenomegaly	4	2	0	0	0	2	0	1	0	2	11	0.5
Lymphadenopathy	2	3	1	0	0	1	0	0	0	3	10	0.1
All 3 enlarged	6	8	0	0	0	1	0	0	1	1	17	0.004
Hepatosplenomegaly	4	1	0	0	0	3	0	1	0	0	9	1.0
Lymphadenopathy + H/S	1	1	0	0	0	0	0	0	1	0	4	1.0
No enlargement	4	2	0	1	1	10	9	0	1	8	36	< 0.001
Total	22	19	1	1	1	18	10	2	3	15	92	

**Figure 1:** Gender-wise distribution of various sub-types of leukemias.

Majority of patients of ALL were referred from Paediatrics unit (43%) and Medical Unit (26%) while 51% of AML patients were referred from Medical Unit. Fourteen percent (n=6) of ALL patients were referred from outpatient department.

Fever was the most common presenting complaint followed by pallor and bleeding disorders. Other presenting complaints which were present in less than 5% of patients included vomiting, cough, shortness of breath, easy fatigability, headache, sore throat, flank pain, fits, amenorrhea, urinary incontinence/retention, anorexia, constipation, lacrimal gland enlargement and loss of consciousness. Table II shows the presenting complaints of patients at the time of admission to hospital.

Table III shows findings on physical examination of patients.

There was a statistically significant difference in physical examination findings between ALL and AML patients. Enlargement of liver, spleen and lymphadenopathy was more often seen in ALL than in AML patients ( $p = 0.004$ ). No organ enlargement was more often seen with patients with AML as compared to ALL ( $p = < 0.001$ ). Presence of lymphadenopathy was seen more in ALL but it was insignificant ( $p = 0.1$ ).

## DISCUSSION

Acute leukemias are not uncommon in Pakistan. Leukemia ranks as the second commonest malignancy

in males and third most commonest in females in northern Pakistan.<sup>11</sup> Therefore, it is very important to determine the number of patients suffering from ALL and AML and their distribution according to age, gender, referring wards and clinical presentations. All these parameters were analyzed in this study. There have been few studies before which have tried to find the prevalence of acute leukemias in this part of country but the latest one was done in 2002.<sup>8</sup>

In this study, 42 patients (46%) were suffering from ALL, 35 patients (38%) were diagnosed as AML while differentiation could not be clearly made in 15 (16%) patients. The ALL to AML ratio was about 6:5, which is different from the 3:1 shown previously by different authors.<sup>8,10,12</sup> A study conducted by Idris *et al.* showed ALL to AML ratio of 2:3.<sup>13</sup> This study was a hospital based study and only those patients were included who presented to us, therefore, this ratio between the two types of acute leukemias should be generalised with caution. The diagnosis of ALL/AML could not be clearly made in 15 patients. Confirmation of such diagnosis requires the use of flow cytometry, immunohistochemical and cytogenetic studies, which are very costly and majority of patients from this region cannot afford such high investigation costs.<sup>5</sup>

FAB classifications for ALL and AML are universally accepted. In this study, L-1 subtype of ALL was found to be more prevalent, followed by L-2 while there was only one patient of L-3 subtype. This classification is important as treatment and prognosis are different. L-1 has been previously reported to be more prevalent than the other two subtypes.<sup>14</sup> M-2 and M-3 were found to be most prevalent amongst AML's FAB subtypes. There were few cases of M-0, M-1, M-4 and M-5 while no case of M-6 and M-7. These findings are different compared with previous studies.<sup>15,16</sup> M-4 was found to be most prevalent by Asif *et al.* and Kakepoto *et al.* found M-1 to be the most prevalent subtype, followed by M-3 in children below 15 years of age.<sup>15,16</sup>

Acute leukemias were found to be more common in males compared to females; {ALL vs. AML [(62% vs. 38%) and (57% vs. 43%)] respectively}. This is consistent with previous studies and literature.<sup>1,17</sup> Some studies have reported female predominance.<sup>16</sup> The

mean age for ALL in this study was 15.6 years with median of 9.5 years. This shows that majority of patients were of pediatric age group. ALL has two peaks, one in infancy and other around 60 years of age. We did not receive many patients from the latter age group compared to the former. Therefore, the median was 9.5 showing that as many as 50% of ALL patients in this study were below age of 10 years. These findings are consistent with the literature.<sup>18</sup> The mean age for AML was 31.4 years (range 1 - 80 years) and median was 26 years which shows that it affects adult population more than pediatric age group, as previously shown by other authors.<sup>15</sup>

The majority of referrals for bone marrow examinations were from Medical Unit, followed by Pediatrics. These two accounted for 69% of total patients. Furthermore, the majority of referrals from Medical unit were of AML and from paediatrics unit of ALL, which are understandable considering the mean age of both types of leukemias. The Outpatient Department accounted for 10% referrals. There were few referrals from Oncology unit. This shows that the presentation of patients is so vague and variable that they are admitted to other units and not to specialized oncology unit. There were few referrals from Gynaecology, ENT and Eye units. These patients had bleeding disorders and one had lacrimal gland enlargement and bone marrow confirmed presence of acute leukemias.

As there are no proper cancer registry programs in Pakistan,<sup>19</sup> demographics of cancer patients in northern Pakistan are unknown. There has been a study by Idris *et al.*, in which they showed patients from several regions diagnosed as having haematological malignancies.<sup>13</sup> These are different from the ones found in this study mainly because it is a tertiary referral centre far away from the place of study. In this study, patients from Afghanistan constituted about 33% of all cases. They had the most number of both cancer types. This shows that our hospital caters for a large number of Afghan patients who come over to Pakistan for medical treatment due to lack of such facilities in their own country.<sup>20</sup>

Clinical presentation of acute leukemias is very vague and variable which makes it difficult to diagnose.<sup>6</sup> In this study, fever (77%), pallor (33%) and bleeding disorders (23%) were found to be the most common presenting complaints of patients. This is consistent finding with several other studies.<sup>14,16</sup> Zaki *et al.* reported fever, bleeding and pallor as main presenting complaints.<sup>21</sup> These findings can be explained by the mechanism of leukemia as a maturation block and/or suppression of erythroid and megakaryocytic cells by increased production of blast cells resulting in decreased/defective production of normal leucocytes/neutrophils (resulting in fever), erythrocytes (resulting in anemia/pallor) and platelets (resulting in bleeding).

There was a statistical significant difference in physical examination findings of patients of ALL and AML. Enlargement of liver, spleen and lymph nodes was more associated with ALL compared with AML. In ALL patients, hepatomegaly was seen in 71% patients, splenomegaly in 66% patients and lymphadenopathy in 71% patients. In 31% of patients all three were enlarged. Yasmeen *et al.* reported similar findings-hepatomegaly (67%), splenomegaly (58%) and lymphadenopathy (75%).<sup>18</sup> These findings are consistent with the notion that patients in our part of world present to hospitals when the disease has reached an advance stage.<sup>18</sup> In AML patients, splenomegaly was found in 29% patients, hepatomegaly in 26% patients and lymphadenopathy in 11% patients. Frascella *et al.* reported slightly different results;<sup>22</sup> hepatomegaly (41% vs. 26%), splenomegaly (37% vs. 29%) and lymphadenopathy (15% vs. 11%).<sup>22</sup> However, Asif *et al.* reported rates of 73%, 69% and 35% for enlargement of liver, spleen and lymph nodes respectively.<sup>15</sup> This increase in number of organ enlargement can be attributed to the fact that the study population was pediatric population and their organs are easily palpable if slight increase in size is compared to that of adults.

There were a number of limitations in this study. It was a retrospective, hospital based study. There was selection bias as all cases were the ones which presented to hospital. Hospital based study also does not account for the number of similar cases within the community, therefore, the estimates of relative prevalence of certain diseases cannot be generalised. The data was taken from history sheets of patients which were filled in by different residents, hence, they were not uniform. There was no confirmation of diagnosis with flow cytometry, immunohistochemical and cytogenetic studies and there was no follow-up of patients to monitor prognosis.

## CONCLUSION

In this study, we found out that acute leukemia are prevalent in northern part of Pakistan. Fifteen percent of all bone marrow examinations done during the study period yielded the diagnosis of acute leukemia. Forty-six percent were ALL, 38% were AML and in 16% differentiation could not be made on microscopic examination alone. Male patients were affected more compared to female patients by ALL and AML (62% vs. 38%) and (57% vs. 43%) respectively. ALL was more prevalent in pediatric age group and there were more referrals from paediatrics unit while AML was more prevalent in adults and hence, more referrals from medical unit. Thirty-three percent of patients in this study were from Afghanistan. Fever, pallor and bleeding disorders were the main presenting complaints. There was a statistical difference in physical examination finding between ALL and AML. Enlargement of all 3, i.e. liver, spleen and lymph nodes was more associated with



ALL compared to AML. No organ enlargement was statistically more associated with AML in comparison to ALL.

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