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Study Of Clinico-Hematological Profile Of Patients With Acute Leukemia And Its Outcome In A Tertiary Centre In Manipur

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Abstract:
Background*: Acute leukemia is a malignant neoplasm of hematopoietic stem cells characterized by proliferation and growth of neoplastic cells in the bone marrow and blood. It consists of Acute Myeloid Leukemia and Acute Lymphoid Leukemia. They have symptoms due to anemia, thrombocytopenia and neutropenia. Early detection and treatment has tremendously improved the survival of these patients. Therefore, the study will give us an idea about acute leukemia patient profile in Manipur.*
Materials and Methods*: A longitudinal study was conducted at JNIMS who were admitted at Medicine and Pediatric wards from November 2020 to November 2022. All new diagnosed cases of acute leukemia were included. However, those who had relapse or initially treated outside were excluded from the study. Clinical and laboratory parameters were taken. Treatment outcome were studied to look into clinical remission at the end of induction and mortality during and after induction.*
Results*: Out of the 43 patients, majority of the patients were in the age group of 11 to 20 years (44.2%) with female preponderance (53.5%). M: F=1:1.5 and Hindus (Meitei) comprising the majority (62.8%). Most of the patients belong to BPL (93%) out of which 58.1% and 34.9% were CMHT and Ayushman Bharat beneficiaries respectively. In our study the majority are Acute Myeloid Leukemia (51%), followed by Acute Lymphoid Leukemia (49%). Fever and generalized weakness were the most common presenting symptoms. Pallor was present in 69.8% of the patients. Febrile neutropenia was a common complication (58.1%). In the study, 28 patients (65.1%) went into Clinical Remission of which 23.3% were AML while 41.9% were ALL. There was no mortality during induction however 12 patients died after induction mainly due to infection and other complications, while relapse occurred in 11 patients.*
Conclusion: *Acute Myeloid Leukemia is the most common type of leukemia followed by Acute Lymphoid Leukemia. ALL is predominant in children while the frequency of AML is higher in elderly population. Among subtypes of ALL, B-ALL is more common than T-ALL. Infections are associated with increased mortality rate and causing decreased Clinical Remission.*
Key Word*: Acute Leukemia, Acute Myeloid Leukemia, Acute Lymphoid Leukemia, Induction Outcome.*

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I. Introduction

Leukemia is a malignant neoplasm of the hematopoietic stem cells characterized by proliferation and growth of neoplastic cells in the bone marrow and blood.[1] Based on average survival, leukemias were earlier divided into acute and chronic leukemias. On the basis of cellular morphology with the help of cyto-chemical staining and expression of lineage of progenitor cells, they are classified into myeloid and lymphoid leukemias. The defect in maturation and differentiation of lymphoid progenitor stem cell produces acute lymphoblastic leukemia (ALL). Morphologically, ALL is subdivided into L1, L2 and L3 subtypes according to French-American-British (FAB) classification. Also, ALL is subdivided based on the immunologic (T-cell and B-cell) and cytogenetic abnormalities

The defect in maturation and differentiation of myeloid progenitor stem cell causes acute myeloid leukemia (AML). The different sub-types of AML are categorized on the basis of stage of maturation of WBC precursors and their malignant transformation characteristics, along with the cytochemical, molecular and genetic criteria. According to FAB classification AML is divided into 8 sub-types according to morphology of myeloblast and cytochemistry. According to WHO, the presence of >20% blasts in the bone marrow is definitive of acute myeloid leukemia. It takes into account the morphology, immunophenotype and cytogenetics to classify AML. They have symptoms due to anemia, thrombocytopenia and neutropenia. Early detection and treatment has tremendously improved the survival of these patients. The study will throw light on the nature of illness and it outcomes among patients. Therefore, the study will give us an idea about acute leukemia patient profile in Manipur. This study will help to analyse the difficulties faced by the patient and the study also will help and give a platform to analyse their long term outcome in future.

II. Material And Methods

A longitudinal study was conducted to describe the clinico-hematological profile along with outcome after induction in patients with acute leukemia. It was conducted in the medicine and pediatric wards of Jawaharlal Nehru Institute of Medical Sciences, Imphal from November 2020 to November 2022. Ethical approval for the study was obtained from the Institutional Ethics Committee of JNIMS (No. Ac/03/IEC/JNIMS/2018) and written consent and assent taken from patients.

Study Design: Longitudinal study

Study Location: The study was conducted at Medicine ward (hematology) and Pediatric (child extension) ward of JNIMS.

Study Duration: November 2020 to November 2022

Sample size: The previous study at RIMS[2] has 103 cases over a period of 5 years. So, we are taking a minimum of 30 patients in our study.

Subjects & selection method

Patients admitted to Medicine ward (hematology) and Pediatric (child extension) ward of JNIMS, satisfying inclusion criteria were taken up for study population. Patients with acute leukemia admitted consecutively at JNIMS during the time period of November 2020 to November 2022 were taken.

Inclusion criteria:

All patients newly diagnosed with acute leukemia admitted in Medicine ward (hematology) and Pediatric (child extension) ward, JNIMS.

Exclusion criteria:

1. Patients who have presented with relapse.
2. Patients with acute leukemia who have started treatment outside JNIMS.
3. Patients who are not willing to participate in the study.

Procedure methodology

Ethical approval was taken from the Institute's ethics committee, JNIMS before the start of the study. Informed consent taken from all patients >18 years willing to participate in the study, below 12 years from the parents/guardian whereas assent was taken from age group 12-18 years. After which a well-designed performa was made to collect the details of patient's age, duration of illness, history of initial symptoms, initial hospital visit and diagnosis of acute leukemia. This was followed by detailed general physical and systemic examination. Laboratory parameters that included bone marrow aspirate and biopsy for routine exam and molecular analysis by RTPCR with conventional cytogenetics were taken. The diagnosis was based from the above report findings as per the WHO criteria for acute leukemia which was followed by appropriate induction therapy. AML patients were treated with 3+7 Induction while ALL patients up to 30 years of age were treated with augmented BFM protocol. At the end of 4 weeks induction , clinical remission (CR) was assessed by bone marrow examination. If bone marrow blast < 5%, ANC > 1000, Platelet count > 1 lakh with no extra-medullary manifestations, then the patient is in remission. Treatment outcome were studied to look into clinical remission and mortality during and after induction.

Statistical analysis

All statistical tests were performed using SPSS version 22 software. The data obtained were subjected to statistical analysis using statistical methods such as frequency, percentage, Chi square test, Fisher exact test, etc. P-value of less than 0.05 was significant.

III. Result

Forty eight patients diagnosed with acute leukemia were admitted at JNIMS medicine and pediatric wards during the study period. Out of these 48 patients, 43 met the inclusion criteria. 2 patients died before induction, 2 were not fit for induction and 1 patient was still undergoing induction while the study was compiled.

Table 1 provides the baseline characteristics of the patients. The majority of patients were in the age group 11-20 years (44.2%). Female patients were 23 (53.5%) and males were 20 (46.5%). Male to female ratio was 1:1.15. Most of the patients belong to BPL (93%) out of which 58.1% and 34.9% were CMHT and Ayushman Bharat beneficiaries respectively as shown in figure 1.

Table no 1: Baseline Characteristics of Patients.

Characteristics	n = 43(%)
Age (years)	
1-10	10 (23.3%)
11-20	19 (44.2%)
21-30	1 (2.3%)
31-40	4 (9.3%)
41-50	7 (16.3%)
>50	2 (4.7%)
Male	20 (46.5%)
Female	23 (53.5%)
Religion	
Hindu/Meitei	27 (62.8%)
Christian	15 (34.9%)
Muslim	1 (2.3%)
Socioeconomic Status	
BPL	40 (93.0%)
Middle class	3 (7.0%)
Upper class	0
Beneficiary group	
CMHT	25 (58.1%)
AYUSHMAN	15 (34.9%)
Self payment	3 (7.0%)

Figure 1: Distribution of government health beneficiary scheme

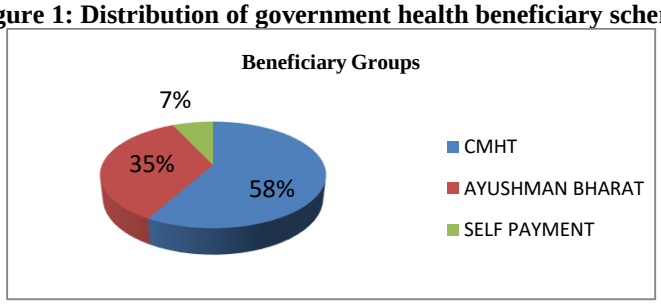

Table 2 shows the clinical presentation of the study population. Among the 43 patients studied, fever (58.1%) and generalized weakness (67.4%) were the most common presenting symptoms while 69.8% had pallor.

Table no 2: Clinical features.

Symptoms:	**n =43 (%)**
Fever	25 (58.1%)
Joint pain	14 (32.6%)
Bleeding:	
- Gum bleeding	6 (14.0%)
- Epistaxis	9 (20.9%)
- Hematuria	2 (4.7%)
- GI bleeding	1 (2.3%)
- Hemoptysis	2 (4.7%)
Pain abdomen	11 (25.6%)
Nausea/Vomitting	9 (20.9%)
Generalized weakness	29 (67.4%)
Signs:	**n =43 (%)**
Pallor	30 (69.8%)
Icterus	3 (7.0%)
Petechiae	10 (23.3%)
Gum hypertrophy	4 (9.3%)
Sternal tenderness	3 (7.0%)
Lymphadenopathy	9 (20.9%)
Hepatomegaly	14 (32.6%)
Splenomegaly	12 (27.9%)

In our study, we found that 22 patients (51%) had AML and 21 patients (49%) had ALL. Among the ALL cases, 16 patients (76.19%) were B-ALL while 5 patients (23.8%) were T-ALL as listed in Table 3. All patients with ALL were below the age of 30 years in the study. Our study found the presence of molecular abnormalities - 14 among AML and 2 in ALL patients respectively. AML1-ETO gene associated with t(8;21)(q21;q22) was present in 11.6% of the study population. We also found that PML-RARA gene was detected in all 4 of the APML patients diagnosed.

Table no 3 : Diagnosis of acute leukemia.

Diagnosis	**n = 43 (%)**
AML	22 (51%)
ALL	21 (49%)
- B-ALL	16 (37.2%)
- T-ALL	5 (11.6%)
Molecular Analysis	
- FLT3	3 (7.0%)
- t(8:21)	5 (11.6%)
- c-kit mutation	1 (2.3%)
- t(17:19)	1 (2.3%)
- PML – RARA	4 (9.3%)
- BCR-ABL 1(major)	1 (2.3%)
- Inv(16)	1 (2.3%)
- NPM1	1(2.3%)
Karyotyping:	
- Growth	19 (44.2%)
- No growth	31 (72.09%)
Karyotyping (prognosis)	
- Good	9 (20.9%)
- Intermediate	6 (14%)
- Bad	4 (9.3%)

Table no 4 shows complications during induction therapy. Out of the 43 patients studied, 25 patients (58.1%) had febrile neutropenia (58.1%), followed by sepsis and fungal pneumonia respectively (20.9%). One patient developed appendicular abscess while another developed sweet syndrome. Steroid induced hyperglycemia was observed in 9 of the ALL patients (20.9%) and was treated with insulin and oral hypoglycemic agents.

Table no 4 : Complications during induction therapy

Complications:	**n=43 (%)**
Febrile Neutropenia	25 (58.1%)
Sepsis	9 (20.9%)
Fungal Pneumonia	9 (20.9%)
Neutrophillic enterocolitis	5 (11.6%)
Pulmonary Koch's	2 (4.7%)
Steroid induced hyperglycemia	9 (20.9%)
Cellulitis	1 (2.3%)
Peripheral neuropathy	1 (2.3%)
Mucositis and bleeding	3 (7%)
Pancreatitis	1 (2.3%)
Treatment mortality	0

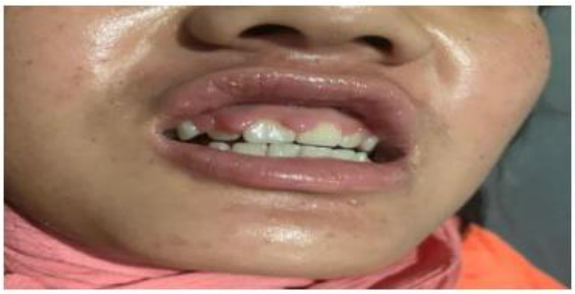

Figure 2: Gum Hypertrophy in a patient with AML

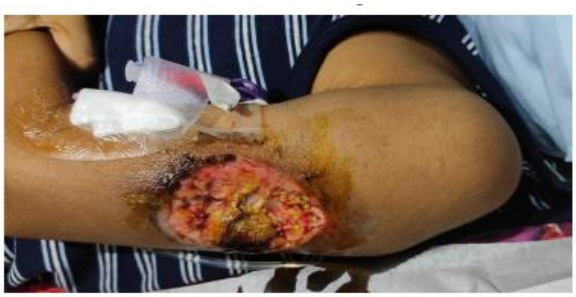

Figure 3: Cellulitis of the forearm in a patient with AML

Table no 5 showing the Outcome of Induction therapy in the study. Of the 43 patients, 28 patients (65.1%) achieved clinical remission at the end of 4 weeks of induction. Of these, 18 (41.9%) were ALL while only 10 (23.3%) were AML patients. 8 (18.6%) were not in remission of which 6 were AML and 1 ALL. Also, 7 (16.3%) patients had clinical remission incomplete count recovery. Relapse was detected in 11 patients. There was no mortality during induction however 12 patients died after induction mainly due to infections.

Table no 5: Outcome of induction treatment.

Outcome	**n= 43 (%)**
Clinical remission (total) - AML - ALL	28 (65.1%) - 10 (23.3%) - 18 (41.9%)
Not in remission (total) - AML - ALL	8 (18.6%) - 6 (14.0%) - 2 (4.7%)
Clinical remission incomplete count recovery - AML - ALL	7 (16.3%) - 6 (14.0%) - 1 (2.3%)
Mortality:-During induction -After induction	0 12 (27.9%)
Relapse: <1year > 1 year	10 (23.3%) 1 (2.3%)

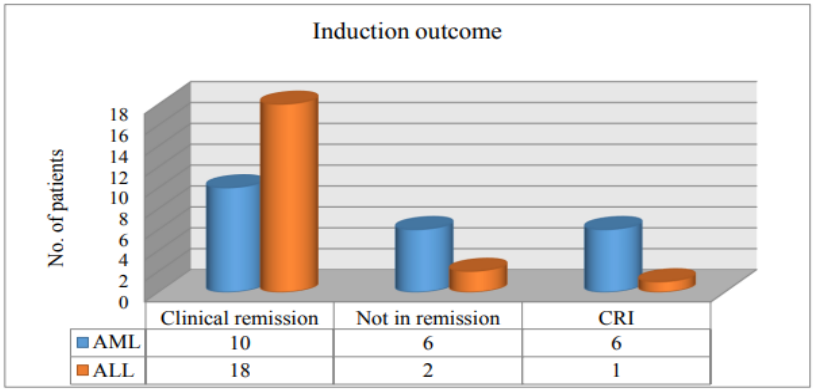

Figure 4: Induction outcome of patients with acute leukemia.

Table 6 provides the relationship of outcome with death. In the study, we found that clinical remission was significantly associated with improved survival because in our study, of the 28 patients in remission only 2 patients died (p=0.003). Out of these 28 patients, 2 patients had relapsed while the remaining were in remission (Table 6). Also, among the 28 patients in remission only 2 patients died (p=0.003). Likewise, it was found that the number of patients with infection was 24, out of which 11 patients died. However, despite infection of which AML constituted 18 and ALL with 6 patients, we found that all 11 patients who died were AML patients. (p-value = 0.012)

Table no 6 : Relationship of outcome with death.

	Mortality		p-value
	No	Yes	
Clinical Remission	26	2	0.003
Infection	13	11	0.012

IV. Discussion

In our study, majority of acute leukemia patients were in age group of 11- 20 years, of which ALL was predominantly seen in 12 out of the 19 patients of this age group. All patients with ALL were below the age of 30 years in the study. Our study population is small but our findings are similar with previous studies such as Saurabh K[3], et al. and Jagannath J[4], et al. who found that 43.35% of all the ALL patients (which comprised the highest number of cases) belonged to 11-20 years of age group. In contrast, AML was higher in adult population which is similar to other previous data[9].

In the present study, there was female preponderance and male to female ratio was 1:1.15. Findings of our study were not similar to other studies such as Shuchismita[5], *et al* (2022) who found that acute leukemia was more common in males, with a male (62.5%) to female (37.5%) ratio of 1.6:1. Other studies[6,7,8] also showed similar male preponderance. Our study findings may be a result of low sample size whose result might have been different with a larger sample size.

Among the 21 patients with ALL, sub-type B-ALL was present in 16 patients (76.19%) while 5 patients (23.8%) had T-ALL. This is consistent with a similar study conducted by Samina N[10], et al. who also reported 72% of ALL patients as B-ALL type, while 28% were T-ALL patients with a significant preponderance of T-ALL in the ages 15-25 years. Another study by Debmalya B[11], et al. also showed 68.3% of all adult ALL cases as B-ALL and 31.7% as T-ALL.

Rajesh S L[2], *et al.* (2013) found that acute leukemia was the most common leukemia in all age groups (85.4%). Out of all leukemia cases reported, maximum cases were of AML while ALL is the most common type of leukemia in children. In our study, we found that out of all the 43 patients studied, 22 (51%) patients had AML and 21 (49%) patients had ALL. Various other studies[8,5] also showed AML to be more common**.**

Among the 43 patients studied, fever (58.1%) and generalized weakness/fatigue (67.4%) was the most common presenting symptom while pallor (69.8%), hepatomegaly (32.6%) and splenomegaly (27.9%) were the most common signs. Gupta R[6], et al. reported pallor (89%) was the most common clinical presentation followed by generalized weakness (81%) and fever (78%). Harpani PT[12], et al. also reported pallor (87.9%), fever (82.7%) and fatigue (86.2%) to be the most common presenting symptoms while signs of pallor (86.2%), splenomegaly (89.6%) and hepatomegaly (84.5%) were most common.

Out of the 22 patients with AML, 4 patients (18.18%) were of subtype APML and comprising approximately 9.3% of cases in the study population. All 4 patients achieved CR. One of them developed ATRA syndrome (25%), febrile neutropenia (50%), and bleeding (50%). A similar study conducted by Bajpai J[13], et al. showed that APML is a highly curable malignancy. Twenty seven patients (82%) achieved CR. Complications during induction therapy were febrile neutropenia (33%), ATRA syndrome (30%), bleeding (58%), and diarrhea in (6%) patients.

In our study, 3 patients (7%) with AML were found to have FLT3 gene mutation and were all associated with relapse and mortality. Santhi S[14], et al. showed that FLT3 gene mutation was a negative prognostic marker for acute myeloid leukemia patients. Ikhwan Rinaldi[34] concluded the same that FLT3-ITD mutation is associated with worse prognosis in adult, non-transplant patients with AML, both for overall survival and event free survival.

In the study, clinical remission was significantly associated with improved survival because out of the 28 patients in remission only 2 patients died (p=0.003). Of these 28 patients, 2 patients had relapsed while the rest were in remission. Out of the 18 AML patients with infection, 11 patients died. There was no infection related mortality among the ALL patients (p- value = 0.012). Similar study by Inaba H[16], et al. showed that incidence of infection-related death was low in childhood ALL with no fungal infection-related deaths.

Overall induction mortality was mainly accounted for by infections. Out of these 28 patients, 2 patients had relapsed while the remaining were in remission. Jain H[17], et al. showed an induction mortality rate of 7.4%, CR in 69% of patients and concluded infections and infection-related mortality are major challenges during AML induction.

A study by Lakshmaiah[18], et al. showed that febrile neutropenia was more common in acute leukemia during induction with overall mortality of 13.5%. Also, Kundan M[19], et al. showed that the mean duration to develop febrile neutropenia was 11.24 days. The number of days required to develop febrile neutropenia was inversely associated with overall survival. In our study, 25 (58.1%) developed febrile neutropenia of which, 18 patients were AML and 7 patients were ALL.

Limitations of the study: The study has a small sample size. The follow up duration of some patients was less than a year while some patients lost to follow up.

V. Conclusion

In our study, Acute Myeloid Leukemia is the most common type of leukemia followed by Acute Lymphoid Leukemia. ALL is predominant in children while the frequency of AML is higher in elderly population. Among subtypes of ALL, B-ALL is more common than T-ALL. All patients with ALL were below the age of 30 years in the study. The Meitei community comprised of the majority of the study group, of which BPL group availing health schemes CMHT and Ayushman Bharat made up for as many as 93%. Fever, generalized weakness and pallor were the most common presenting clinical features. Febrile neutropenia was a common complication (58.1%). A total of 28 (65.1%) patients were in clinical remission, of which 23.3% were AML while 41.9% were ALL. Infections are associated with increased mortality rate and causing decreased Clinical Remission. There was no mortality during induction however 12 patients died after induction mainly due to infection and other complications, while relapse occurred in 11 patients.

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