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Clinical Profile, Molecular Characterization and Outcomes in Patients of Acute Lymphoblastic Leukemia

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HIGHLIGHTS

1. Clinical profile includes age, symptoms, risk factors.
2. Molecular characterization identifies genetic mutations, biomarkers.
3. Genetic testing guides treatment decisions, prognosis.
4. Outcomes depend on remission, relapse rates.
5. Early detection improves survival, therapeutic success.

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ABSTRACT

Introduction: Acute Lymphoblastic Leukemia (ALL) comprising 25% of hematological cancer diagnoses. ALL is an aggressive malignancy affecting the bone marrow, blood, and other sites, with an annual adult incidence of approximately 1 in 100,000 globally. Treatment consists of remission induction, consolidation, maintenance and prophylaxis. Emerging therapies such as targeted treatments, immunotherapy and stem cell transplantation offer promise. This study aims to analyze the clinical presentation, cytogenetic profiles via karyotyping and PCR, and outcomes, including disease-free and overall survival, of adult ALL patients. **Methods:** This retrospective and prospective observational study was conducted at Army Hospital (Research & Referral) from January 2013 to May 2019. It included 200 patients aged >15 years diagnosed with ALL. Data were analyzed to correlate hematologic and molecular parameters with clinical outcomes. **Results:** Among 200 patients (mean age 26.34 years; SD 6.36), a male predominance (67%) was observed. Normal cytogenetics was noted in 52.55%, abnormal cytogenetics in 25.51%, and unknown in 18.87%. Complete bone marrow remission at 4 weeks was achieved in 88.32%, while 7.1% did not. Seventeen patients underwent bone marrow transplantation. CD10 and CD19 antigens were expressed in 63% and 68% of patients, respectively. Survival at 1, 2, 3 and 4 years was 95%, 77%, 58% and 52%, respectively. Patients with abnormal cytogenetics, CNS involvement, or treated with adult protocols showed lower survival rates. **Conclusion:** ALL predominantly affected males (67%) aged 15-39 years, with poorer survival in those aged 30-60. Abnormal cytogenetics reduced survival (56% vs. 60%). Hyper-CVAD treatment improved 3-year OS (0.72) over paediatric (0.61) and adult (0.29) protocols. CNS involvement significantly lowered survival.

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INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is a hematologic malignancy that results from the malignant transformation and proliferation of lymphoid precursor cells. It is the second most common form of acute leukemia in adults and is classified into two main types based on the cell lineage of origin: B-cell precursor ALL (B-ALL) and T-cell precursor ALL (T-ALL) [1]. The B-ALL subtype is more prevalent, particularly in adults, where it accounts for approximately 75% of cases, while T-ALL represents the remaining 25%. This classification has significant implications for the clinical management and prognosis of the disease.

ALL demonstrates a bimodal age distribution, with two distinct peaks. The first and most pronounced peak occurs in children around 5 years of age, accounting for approximately 80% of ALL cases. The second, smaller peak is observed in adults around the age of 50, comprising the remaining 20% of cases. Despite its lower prevalence in adults, the disease tends to have a more aggressive course and poorer prognosis compared to pediatric cases. Advances in molecular diagnostics and therapeutic strategies have helped improve survival rates, but challenges persist, particularly in older patients and those with high-risk genetic profiles [2].

Acute Lymphoblastic Leukemia (ALL) is a hematologic malignancy is driven by chromosomal abnormalities and genetic alterations that disrupt normal cellular processes, such as cell cycle regulation, apoptosis, and immune function. These genetic abnormalities often involve translocations, deletions, or mutations that activate oncogenes or inactivate tumor suppressor genes, leading to uncontrolled growth and accumulation of malignant lymphoid cells. The disease typically originates in the bone marrow, where these aberrant cells interfere with the production of healthy blood cells [3].

As the disease progresses, ALL frequently spreads beyond the bone marrow and infiltrates peripheral blood, a hallmark feature of the condition [4]. The unchecked proliferation of lymphoid blasts in the bloodstream can lead to a range of systemic manifestations, including fatigue, pallor, fever, infections, and bleeding tendencies due to anemia, immunosuppression, and thrombocytopenia [5]. The ability of these malignant cells to invade other tissues further contributes to the heterogeneity and severity of the disease [6]. In many cases, ALL involves the lymph nodes, causing lymphadenopathy, and may extend to other extramedullary sites, such as the liver and spleen, resulting in organomegaly [7].

A particularly concerning aspect of ALL is its propensity to invade the central nervous system (CNS), a common site for extramedullary involvement. CNS infiltration can lead to neurological symptoms such as headaches, seizures, cranial nerve palsies, or altered mental status, significantly complicating the clinical course. The involvement of extramedullary sites, including the CNS, is associated with a more aggressive disease phenotype and poorer prognosis, necessitating targeted therapeutic strategies. Advances in treatment, such as CNS-directed therapies and tailored regimens based on cytogenetic and molecular profiles, have improved outcomes, but significant challenges remain in managing high-risk cases and preventing relapses [8].

The aim of this study is to investigate the clinical and cytogenetic profiles of adult patients diagnosed with Acute Lymphoblastic Leukemia. We will utilize conventional karyotyping and PCR to study the cytogenetic characteristics of the patients. Additionally, we will analyze disease-free survival and overall survival to understand the overall outcome in patients with Acute Lymphoblastic Leukemia. By focusing on these key aspects, we aim to gain valuable insights into the nature of the disease and its impact on patient outcomes. The study was carried out at a tertiary care unit, and its primary hypothesis is to describe the Clinical profile, Molecular characterization, and Outcomes in patients with Acute Lymphoblastic Leukemia.

The aim of this study was to analyze the clinical profile of patients with Acute Lymphoblastic Leukemia (ALL), assess their cytogenetic profiles using conventional karyotyping and PCR, and evaluate the overall outcomes, including disease-free survival and overall survival.

MATERIAL AND METHODS

The study was conducted at Army Hospital (Research & Referral) from January 2013 to May 2019 as a combined retrospective and prospective observational study, with ethical approval obtained from the Institutional Ethics Committee. The retrospective phase spanned from January 1, 2013, to May 31, 2018, while the prospective phase covered June 1, 2018, to May 31, 2019.

Study population:

The study included 200 adult patients diagnosed with Acute Lymphoblastic Leukemia (ALL) who met the inclusion criteria.Inclusion criteria were age >15 years, confirmed diagnosis of ALL, and willingness to undergo treatment per institutional protocol. Exclusion criteria included age <15 years, other leukemia types, prior or ongoing non-protocol

leukemia treatments, pregnancy or lactation, and refusal to participate in the study.

Stastical Data Analysis:

The data was meticulously tabulated in Microsoft Excel 2007, and subsequently, descriptive statistics were applied to provide a comprehensive summary of the study population's characteristics. Additionally, measures like mean, median, standard deviation, and percentages to describe demographic data, clinical profiles, and outcomes of patients with Acute Lymphoblastic Leukemia. The log-rank test and Kaplan-Meier method, both nonparametric tests of estimating time-related events, were used to assess the overall survival.

RESULTS

A total of 200 patients diagnosed with Acute Lymphoblastic Leukemia (ALL) were included in this study. Data was recorded and entered into an Excel sheet, yielding the following key findings.The present study comprised 67% (133) male patients and 33% (67) female patients, resulting in a Male to Female ratio of 2:1. Thus, the present study demonstrated a male preponderance, with male patients being twice as numerous as female patients.

The age range of patients presenting with leukemia at the hospital varied from 15 to 39 years. The minimum age of presentation was 15 years, while the maximum age observed was 39 years. The mean age at presentation was calculated to be 26.34 years, with a standard deviation of 6.36.

Cytogenetic studies were conducted for the majority of patients, revealing that 52.55% (103) had normal cytogenetics, while 25.51% (50) displayed abnormal cytogenetics. However, cytogenetic information was unavailable for 3% (6) of patients, and in 18.87% (37) of cases, the cytogenetic status remained unknown.

In the present study, different treatment protocols were employed for the patients with Acute Lymphoblastic Leukemia (ALL). Specifically, 24.5% (49) of the patients received the Pediatrics type treatment protocol, while 52% (104) of the study participants were treated with the Hyper CVAD-like protocol. The remaining 23.5% (47) of patients underwent an adult-like treatment protocol.

Post-therapy, bone marrow evaluations were conducted at 4 weeks. The results indicated that 88.32% (174) of patients achieved complete morphological remission, while 7.1% (14) did not achieve complete remission. In 4.56% (9) of patients, bone marrow evaluation was not feasible.

Furthermore, during the treatment course, 17 patients received bone marrow transplantation, while the majority of patients (91.41%) did not undergo this procedure.

Regarding antigen expression, a significant proportion of patients with ALL exhibited CD10 antigen (63%) and CD19 antigen (68%).

Various chromosomal abnormalities were observed, including PCR (1; 19), PCR (4; 11), PCR (bcr-abl), abnormal karyotype, Philadelphia chromosome, and hyperdiploidy.

Table 1: (Overall Survival)

Variable: Cytogenetics	Overall Survival	Confidence Interval	Log Rank
Normal	0.6060	0.4515 - 0.7293	0.482
Abnormal	0.5698	0.3472 - 0.7415	
Unknown	0.6843	0.4083 - 0.8519	

In the present study, we report the overall survival rates of patients over different time intervals. At the end of 1 year, the overall survival rate was 95%, which decreased to 77% at 2 years, 58% at 3 years, and 52% at 4 years.

Furthermore, the analysis of survival rates based on age groups revealed that patients within the age range of 30-60 years exhibited lower overall survival rates compared to other age groups.

In contrast, the survival rates between male and female patients were found to be relatively similar, showing comparable overall survival outcomes in both groups

Table 2: (Overall Survival and Age Group)

Variable-age group /OS	3 yr Overall Survival (CI)	4 yr Overall Survival (CI)	Log Rank
0-30yrs	0.6213 (0.4891-0.7285)	0.5436 (0.3847-0.6778)	0.545
30-60yrs	0.4940 (0.3027-0.6596)	0.4940 (0.3027-0.6596)	

In the present study, we observed considerably lower survival rates among patients belonging to the 3 risk groups. Specifically, patients with abnormal cytogenetics exhibited lower survival rates (56%) compared to those with normal cytogenetics (60%), though the difference was not statistically significant (log rank p = 0.482).

Furthermore, patients receiving the adult type treatment protocol showed lower survival rates compared to other treatment protocols.

Overall, these findings highlight the impact of risk group stratification and cytogenetic abnormalities on patient survival outcomes in our study cohort.

Table 3: (Overall Survival and Treatment Protocol)

Variable-Treatment protocol/ OS	3 yr Overall Survival (CI)	4 yr Overall Survival (CI)	Log Rank
Adult type	0.2931 (0.1244-0.4854)	0.1954 (0.0464-0.4196)	0.555
Pediatric type	0.6117 (0.3909-0.7732)	0.4587 (0.1665-0.7127)	
Hyper CVAD	0.7237 (0.5706-0.8300)	0.7237 (0.5706-0.8300)	

In the present study, we observed that patients who did not receive Continuous Renal Replacement Therapy (CRRT) exhibited lower survival rates.

Furthermore, patients who did not receive High-Dose Methotrexate (HDMTx) therapy also demonstrated lower survival rates. In the present study, we found that patients with CNS stage 3 had a significantly poor outcome. CNS involvement was identified as a crucial factor reducing the overall survival of patients with Acute Lymphoblastic Leukemia (ALL). These findings emphasize the importance of considering CRRT, HDMTx therapy, and CNS involvement in determining the prognosis and treatment outcomes for ALL patients.

DISCUSSION

. The present study enrolled a total of 200 patients with Acute Lymphoblastic Leukemia, all aged above 15 years. Among them, 67% (133) were male patients, and 33% (67) were female patients, resulting in a male-to-female ratio of 2:1. This finding indicates a male preponderance, with male patients being twice as numerous as female patients, a trend consistent with findings from other studies. For instance, Kulkarni KP et al (2013) [10] conducted a systematic review and reported a male predominance with a Male: Female ratio of 3.1:1. Moreover, Kulkarni et al [10] noted male preponderance in large cities in India consistently since 1984, according to data from the National Cancer Registry Program. Regarding the age distribution, the mean age of the study participants in the present study was 26.34 years, with a standard deviation of 6.36.

Ours is an exclusive Armed forces hospital in which the majority of patients who are referred for treatment are of younger age profile. The data was rechecked and the results are same as depicted. The mean age of the present study was slightly lower than the thirty. The age in the present study represents the age at the time of diagnosis or reporting to our tertiary care centre. The advances in science have helped to diagnose the cases at earlier stages. Access to healthcare also plays important role in timing of diagnosis.

The data about literacy level and urban/rural residence was not collected otherwise it might have been useful to interpret the diagnosis at early age. ALL is a more common in pediatric patients. The possibility of late diagnosis cannot be ruled out as our study population mainly comprised of above 15 year patients. So to have accurate idea of age at diagnosis it would have been better to include patients of all age groups.

However Punit jain et al [11] has done a single-center retrospective study over 10 years and reported median age of 26 years (range, 15 to 67 years), which mainly included 334 patients (65.8%) ≤ 35 years old. The study was conducted in 507 patients belonging to the age group of 15 years and above. The reported age by Punit jain et al [10 - 11] is similar to our findings i.e. 26. 34 years. (Mean). Our study and study of Punit jain et al [11] had similar patient population of above 15 yr and were retrospective in nature.

Gupta eta al [12] 33 (2019) observed Cytogenetic data of 12 cases of ALL, of which 25% (n=3) had normal karyotype and 3% (n=4) had t (9; 22) (q34; q11).Cytogenetic studies were carried out in most of the patients in our study. It was observed that 52.55 % (103) patients have normal cytogenetics while 25.51 % (50) patients have abnormal cytogenetics. Cytogenetics was not available in 3% (6) patients while in 18. 87% (37) patients it was unknown [12].

Karyotyping is helpful to assess the genetic mapping and also aids in the treatment outcome. In a study by Punit jain et al 345/442 patients (78%) had Standard Risk cytogenetics means normal karyotype and other non-High Risk chromosomal abnormalities while patients (21.9%) had High Risk cytogenetics [11].

In the present study, it was observed that 52.55 % (103) patients have normal cytogenetics. Use of FISH technique, may result in higher detection of chromosomal abnormalities. We observed that 3 patients (1.5%) had Hyperdiploid karyotype which is because the present study included data retrospectively, few values and findings might have been missed and the pediatric population was not included. So this inference cannot be confirmed but it may be a possible reason for less number of cases in the present study.

Philadelphia chromosome positive ALL is a specific subset of ALL that has overall poor prognosis and high risk of relapse. It is characterized by t (9; 22) resulting in the distinctly short chromosome 22.54 Philadelphia chromosome was observed to be positive in, 9/204 (4.4%) by Pawan reddy et al [13], 7/63(11.11%) by Siddaiahgari SR et al [14]. It was reported by Punit jain et al [4] that 61/97 with HR cytogenetics (62.8%) were having Philadelphia chromosome positive [t (9; 22)] and 36 (37.1%) were Philadelphia chromosome negative. We have found that 34 (23.12%) patients had Philadelphia Chromosome positive and 113 patients were negative.

t (1; 19) abnormality was observed in 1/89 (1.12%) patient by Siddaiahgari SR et al [14], 8/204 (3.9 %) by Pawan reddy et al [13] whereas in our study it was 3 patients (1.8%).

In the present study, it has been observed that 88.32% (174) patients achieved complete morphological remission while 7.1% (14) patients did not achieve complete remission. Bone marrow of 4.56 % (9) patients was not evaluable. Siddaiahgari SR et al [14] have observed post induction remission in 99 %(99/100). But these studies were done in pediatric age group patients.

Pediatrics type treatment protocols were used in 24.5% (49) of patients while Hyper CVAD like protocol was used in 52 % (104) of the study participants. Remaining 23.5 % (47). patients were used adult like treatment protocol. The choice of therapy was governed by age of the patient and disease status along with institutional protocols. Hyper-CVAD is one of the most frequently used regimens for routine treatment of adult ALL in many countries as it was in our practice during the study period [21–23]. Sixty-eight patients of 166 (41%) who were given intensive chemotherapy had been treated with this regimen.

Hyper-CVAD is one of the most frequently used treatment regimens for management of adult ALL in many countries. In one such previous study, Sixty-eight patients of 166 (41%) were given HyperCVAD regimen. Remaining patients were administered 77 with local adaptations of pediatric protocol. In our centre also, Hyper CVAD is the most commonly used treatment protocol. Hyper CVAD treatment was used for 55/507 patients in a study reported by Punit jain et al [4]. In the present study it was administered to 52 % (104) of the study participants. The choice of treatment is governed by number of things related to the patient, institution, physician preferences and most importantly availability along with affordability of drugs. Our study had limitations as a result of its retrospective nature, and probably selection bias for different treatment regimens.

Buyukasik Y et al [15] observed that Twenty eight (22.9%) patients underwent allogeneic stem cell transplantation (allo SCT) at first CR. In our study 17 patients (8.58%) required bone marrow transplantation.

Common antibodies used in flowcytometric immunophenotyping of acuteleukemia are as follows: stem cell/hematopoietic precursors (CD34, HLA-DR, terminal deoxynucleotidyl transferase/TdT), myeloid markers (cMPO, CD13, CD33, CD117, CD15 , monocyticmarkers (CD64, CD14, CD11b,CD11c, lysozyme) , erythroid (CD71, CD235a), megakaryocytic (CD41, CD61, CD36), B lymphoid markers (CD19, CD10, CD20, CD22, cCD79a), T lymphoid markers (CD3, CD5, CD7, CD1a,CD2, CD4, CD8) and naturalkiller (NK) cells (CD56).

Over the past few years, the treatment of patients with acute lymphoblastic leukemia (ALL) has seen tremendous changes with significant improvement in the outcome. It has been observed that many factors influence the outcome of the treatment and subsequently it will reflect as improved survival of patients with ALL. Age, Gender, Race, WBC count at the time of diagnosis, ALL subtypes and Philadelphia chromosome are some of the factors that have been associated with survival. Younger patients have a better survival than older patients. The girls have showed a better survival than boys, partly due to increased risk of testicular cancer. African-American and Hispanic Individuals have lower survival rates as compared to Caucasian and Asian individual. The Initial white blood cell (WBC) count of less than 50,000/ul has better prognosis than people with higher WBC counts. T-cell ALL have a better prognosis and survival than those with mature B-cell ALL. ALL Patients with Philadelphia chromosome-positive tend to have a poorer prognosis [16 -17].

In the present study, Overall survival at the end of 1 yr, 2 yr, 3 yr and 4 yr was 95%, 77%, 58% and 52% respectively. Five year survival rate has been improved over the years in developed countries. In India it is in the range of 50%-70% [10].

We compared overall survival with several variables. In the present study we found that the patients having abnormal cytogenetics has lower survival (56 % Vs 60 %) as compared to that of normal cytogenetics.

Overall survival rates were lower in patients of age group 30-60 years. Pawan reddy et al [13] had reported that age is significantly associated with overall survival.

Survival rate among male and female patients was almost similar in the present study. The finding is similar to the results observed by Khalid S et al [18]. Patients with abnormal cytogenetics were having lower survival rates in our study.

Patients receiving adult type treatment protocol were having lower survival rates. The 5-year OS was 60% with hyper-CVAD [19] in pediatric age group. We have observed that the 3 and 4year OS was 72% in patients receiving Hyper CVAD regimen.

CNS involvement at the time of ALL diagnosis is reported in about 6% of patients. If prophylactic CNS treatment is not given then almost 50-75% patients may develop CNS disease [20]. Intracranial radiation and HDMTx therapy is used prophylacticall y to prevent CNS disease. We have also observed that Patients who have not given CRRT were having lower survival. Patients who do not receive HDMTx therapy had lower survival rates. CNS involvement and staging of CNS disease reduces overall survival of the ALL patients. Relapse rate was significantly higher in 15-30 age group (P=0.034) and those with High risk cases (p=0.000). LS Arya [21] has reported significantly higher relapse rate in boys. The present study has also the same finding but results were not statistically significant (0.359).

LIMITATIONS

The present study has several limitations. Being retrospective in nature, it relies on previously recorded data, which may result in incomplete or unavailable patient information. Additionally, as an observational and hospital-based study, the findings may not be strictly representative of the broader population, potentially limiting the generalizability of the results.

CONCLUSION

Acute Lymphoblastic Leukemia (ALL), a hematological malignancy of progenitor cells, studied in patients aged 15-39 years, with lower 3-year overall survival (OS) observed in ages 30-60 (0.49 vs 0.62). A male predominance (67%) was noted, Most patients expressed CD10 (63%) and CD19 (68%) antigens. Cytogenetic analysis revealed 52.55% with normal profiles, while 25.51% had abnormalities, correlating with reduced OS (56% vs 60%). Only 9% received bone marrow transplantation. Bone marrow remission was achieved in 88.32% at 4 weeks, with 7% failing. Treatments included Hyper-CVAD (52%) and other protocols, showing 3-year OS rates of 0.72, 0.61, and 0.29, respectively.

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