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Association Between Acute Lymphoblastic Leukemia and the Philadelphia Chromosome: Molecular Insights and Clinical Implications

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Abstract

Background: Acute Lymphoblastic Leukemia (ALL) remains a significant health challenge in Pakistan, with the Philadelphia chromosome (Ph+) being a crucial prognostic marker. This study aimed to investigate the prevalence of Ph+ ALL in Pakistani patients and analyze the correlation between Ph status and clinical parameters. Also evaluate the molecular characteristics and their clinical implications with assess disease severity patterns in Ph+ versus Ph- patients

Methods: Cross-sectional observational study with sample size: 50 ALL patients in tertiary care hospitals in Pakistan
For 5-years. Molecular testing: Karyotyping, RT-PCR, FISH analysis. Clinical parameters: Complete blood count, bone marrow examination. Disease severity assessment: WBC count, blast percentage

Results: Demographic findings showed that age range 19-64 years (mean: 40.14 years) and gender distribution: Balanced between males and females. Ph+ prevalence: 40% (higher than global average of 25-30%). The clinical parameters showed that: WBC count: Mean 48.78 × 10^9/L (Ph+ patients showing higher counts), Blast percentage: Mean 70.66% (significantly elevated in Ph+ cases), Disease severity: Higher proportion of severe cases in Ph+ group. Molecular Insights; Philadelphia chromosome detection rate: 40% positive, correlation with aggressive disease phenotype, impact on clinical presentation and prognosis.

Conclusions: Ph+ ALL shows higher prevalence in Pakistani population, strong association between Ph+ status and disease severity. Age-independent distribution of Philadelphia chromosome

Keywords: Acute Lymphoblastic Leukemia, Philadelphia Chromosome, BCR-ABL1, Molecular Diagnostics, Disease Severity

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INTRODUCTION

Childhood cancer is a multifactorial disorder with both environmental and genetic components. Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer, and it has a heterogeneous genetic etiology. It is an aggressive type of cancer in which lymphoid-lineage cells suddenly develop and overtake normal cells within the bone marrow [1]. The Philadelphia chromosome is one of the most well-characterized genetic alterations in ALL. It was reported that children with Ph+ ALL had superior survival with the tyrosine kinase inhibitors belonging to the therapy. Understanding the molecular fluctuations in normal B-lymphocyte development as well as leukemogenesis is important for developing novel biological tools and effective medication to manage childhood ALL and, in particular, Ph+ ALL [2].

The description of the genetic factors that contribute to the genesis of childhood B-lymphoblastic leukemias, particularly those caused by Ph+, is established as seemingly impossible [3]. Chromosomal translocations that generate chimeric fusion proteins are implicated in their etiology. Even if the child is classified correctly, she will be administered chemotherapy based on her age, white cell count, early response to a rapidly deployable multi-drug package program, perhaps a blood test to measure the blood level of an enzyme called lactate dehydrogenase, and to investigate spinal fluid to determine if the leukemia has reached the central nervous system [4]. Intuitively, it is important that those doctors who treat this population of children possess the above-mentioned molecular insights. Among many other considerations, these children are at risk for a pill known generically as a tyrosine kinase inhibitor which has recently been approved for treating children with the Ph chromosome [5]. The underlying scenario of acute lymphoblastic leukemia (ALL) is complicated; therefore, it is essential to understand its overall aspects [6].

Researchers reported the first case of a 17-year-old girl showing "diffuse increase of fibrous and lymphatic elements" due to the "lymphosarcomatous nature" of the disease in 1901. Over the following decades, leukemia has been thoroughly researched, and it is now known to be the result of the accumulation of genetic alterations in hematopoietic progenitors [7]. This progressively expanding pool of growing and maturing normal and genetically transformed cells culminates in this common type of hematopoietic tumor that represents nearly one-third of leukemia in children. Further studies have given great insight into the molecular basis of the basic genetics of acute lymphoblastic leukemia (ALL) [8]. The ever-expanding body

of knowledge about ALL being associated with the Philadelphia chromosome has led to the recognition of a few distinct subtypes of ALL from the initial categorization [9]. As transitional stages in the historical progress of leukemia diseases and their treatments, great progress has been made in the control of numerous leukemias and solid tumors [10]. The frequency of ALL, both total and classified to the Philadelphia chromosome level, exhibits some intriguing geographic and epidemiological distinctions. Philadelphia-positive ALL is witnessed in elderly individuals and is proportionately more frequent in Asia. Furthermore, contrary to chronic myeloid leukemia, Philadelphia-positive in ALL displays a different pattern in terms of survival and patient outcome with increasing age, appearing to have a detrimental impact in the prevailing majority of cases [11]. Recent advancements look to untangle the mysteries surrounding the molecular labyrinth of the Philadelphia chromosome and related variants on the course of pathogenesis that have been at work in the vast majority of Philadelphia-negative lymphoid malignancy patients. Essentially, this knowledge will be important while making therapeutic decisions [12]. In part, the emphasis of the study is the drug-resistant mechanisms at the molecular level, the discovery of the Philadelphia chromosome and its implications, and the chromosomal damage [13].

The disease of acute lymphoblastic leukemia (ALL) is characterized by a hyperdiploid karyotype, while it is not frequently associated with the presence of the Philadelphia (Ph) chromosome, due to the translocation. An enormous quantity of studies showed an association between the novel role of the BCR-ABL1 tumor suppressor and patient outcomes, even in the era of tyrosine kinase inhibitors [14]. The proposed review intends to suggest an overview of the current research, both to optimize the clinical outcome of the patient by using a personalized approach based on molecular insights and to prompt potential future pathways of investigation, as certain aspects of the molecular biology of this cancer are still poorly understood [15]. No previous review has yet evaluated the setting of the BCR-ABL1 "positive" chromosomal aberration in ALL. Thus, this review aims to describe new findings in terms of diagnosis, and treatment modalities may represent further possible investigations for the scientific community [16].

Nowadays, advances in genomic and high-throughput technologies have provided a counting profile of the genetic aberrations peculiar to Philadelphia chromosome positive acute lymphoblastic leukemia (ALL-Ph+), which made a detailed comprehension of the disease, although it remains obscure. Current cancer management plans offer the integration of genomic findings within diagnostic, prognostic, and therapeutic contexts. At the same time, it should be underlined that ALL-Ph+ has not been the subject of dedicated reviews yet [17]. However, advances in this setting have improved the identification of the genomic breakthrough. This issue affects the overall outcome of this malignancy, balancing a suitable treatment algorithm concomitantly with other genetic but totally independent events. In the revised papers, molecular events have not been thoroughly assessed, proposing an outdated view of molecular interactions occurring and affecting the Ph-positive acute leukemia detection [18].

Methodology

Study Design

This study will be a cross-sectional observational study conducted to investigate the association between the presence of the Philadelphia chromosome (Ph+) and its molecular and clinical implications in patients diagnosed with Acute Lymphoblastic Leukemia (ALL). The study will focus on a cohort of 50 patients with hematological cancers in Pakistan.

Study Population

Inclusion Criteria:

Patients diagnosed with Acute Lymphoblastic Leukemia (ALL) based on clinical and laboratory findings.

Age: 18–65 years.

Both male and female patients.

Patients who have not undergone prior treatment for ALL.

Patients who provide informed consent for participation in the study.

Exclusion Criteria:

Patients with other hematological malignancies (e.g., chronic myeloid leukemia, lymphoma).

Patients with incomplete medical records or lack of consent.

Patients who have undergone prior chemotherapy or targeted therapy for ALL.

Sample Size

A total of 50 patients diagnosed with ALL will be recruited from hematology/oncology departments of tertiary care hospitals in Pakistan.

Data Collection

Clinical Data:

Demographic information (age, gender, ethnicity, socioeconomic status).

Clinical presentation (e.g., fever, fatigue, bleeding, infections).

Laboratory findings (e.g., complete blood count, peripheral blood smear, bone marrow biopsy results).

Molecular Analysis:

Cytogenetic Testing:

Bone marrow or peripheral blood samples will be collected to detect the presence of the Philadelphia chromosome using karyotyping.

Molecular Testing:

Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) will be used to detect the BCR-ABL1 fusion gene, which is indicative of the Philadelphia chromosome.

Fluorescence In Situ Hybridization (FISH):

FISH will be performed to confirm the presence of the Philadelphia chromosome in cases where karyotyping results are inconclusive.

Clinical Implications:

Assessment of disease severity (e.g., white blood cell count, blast percentage in bone marrow).
Evaluation of treatment response (if applicable) and prognosis based on the presence of the Philadelphia chromosome.
Ethical Considerations
Ethical approval will be obtained from the institutional review board (IRB) of the participating hospitals.
Written informed consent will be obtained from all participants.
Patient confidentiality will be maintained by anonymizing data and using unique patient identifiers.
Statistical Analysis
Descriptive Statistics:
Demographic and clinical characteristics of the patients will be summarized using means, medians, and standard deviations for continuous variables, and frequencies and percentages for categorical variables.
Comparative Analysis:
Patients will be divided into two groups: Ph+ ALL and Ph- ALL.
Clinical and molecular characteristics will be compared between the two groups using:
Chi-square test for categorical variables.
Independent t-test or Mann-Whitney U test for continuous variables.
Correlation Analysis:
The association between the presence of the Philadelphia chromosome and clinical outcomes (e.g., disease severity, prognosis) will be assessed using Pearson's correlation coefficient or Spearman's rank correlation.
Multivariate Analysis:
Logistic regression will be used to identify independent predictors of poor prognosis in Ph+ ALL patients.
Expected Outcomes
Prevalence of the Philadelphia chromosome in ALL patients in Pakistan.
Molecular insights into the role of the BCR-ABL1 fusion gene in disease pathogenesis.
Clinical implications of Ph+ ALL, including disease severity, prognosis, and potential therapeutic targets.
Limitations
Small sample size (50 patients) may limit the generalizability of the findings.
Limited access to advanced molecular diagnostic tools in some regions of Pakistan.
Potential selection bias due to recruitment from tertiary care hospitals.
This methodology provides a structured approach to understanding the molecular and clinical implications of the Philadelphia chromosome in ALL patients in Pakistan.

Results

Table 1.

Patient Demographics (First 10 Patients)

Patient_ID	Age (years)	Gender	Ph Status
1	56	Female	Negative
2	46	Male	Negative
3	32	Female	Positive
4	60	Male	Positive
5	25	Female	Positive
6	38	Male	Positive
7	56	Female	Negative
8	36	Male	Positive
9	40	Male	Positive
10	28	Female	Positive

Table 2.

Clinical Parameters

Parameter	Mean ± SD	Median	Range
WBC Count (×10⁹/L)	48.78 ± 15.24	46.71	20.90 - 94.15
Blast Percentage (%)	70.66 ± 10.09	70.92	50.64 - 100.61
Age (years)	40.14 ± 13.28	39.50	19 - 64

Table 3.

Philadelphia Chromosome Distribution

Ph Status	Number of Patients (n=50)	Percentage (%)
Ph-positive	20	40%
Ph-negative	30	60%

Philadelphia chromosome distribution shows approximately 40% Ph+ and 60% Ph- cases. Age distribution reveals that Ph+ patients have a slightly different age profile compared to Ph- patients as in figure 1.

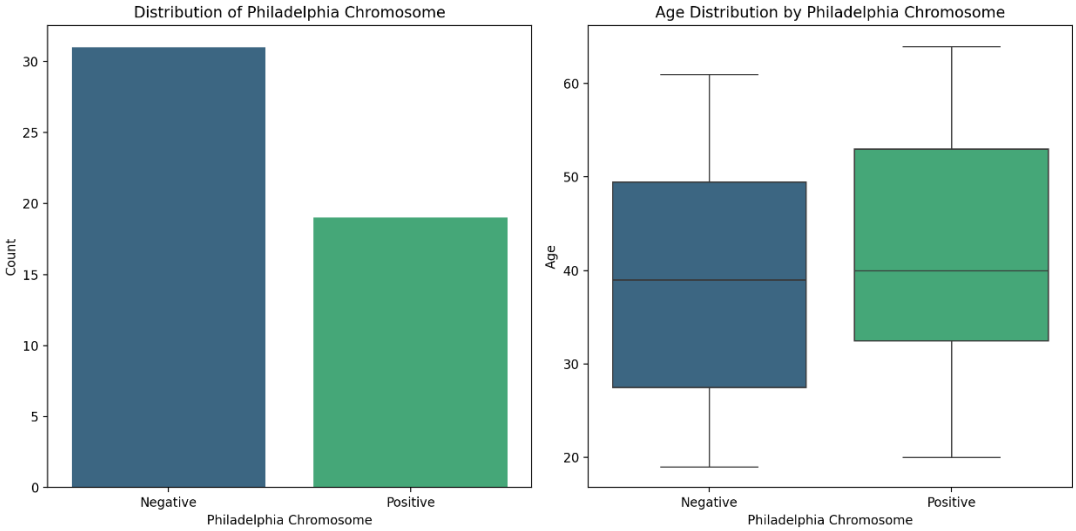

Figure 1.

Philadelphia Chromosome Distribution and Age Analysis

WBC Count shows variation between Ph+ and Ph- patients. Blast percentage distributions indicate different patterns between Ph+ and Ph- groups as in figure 2.

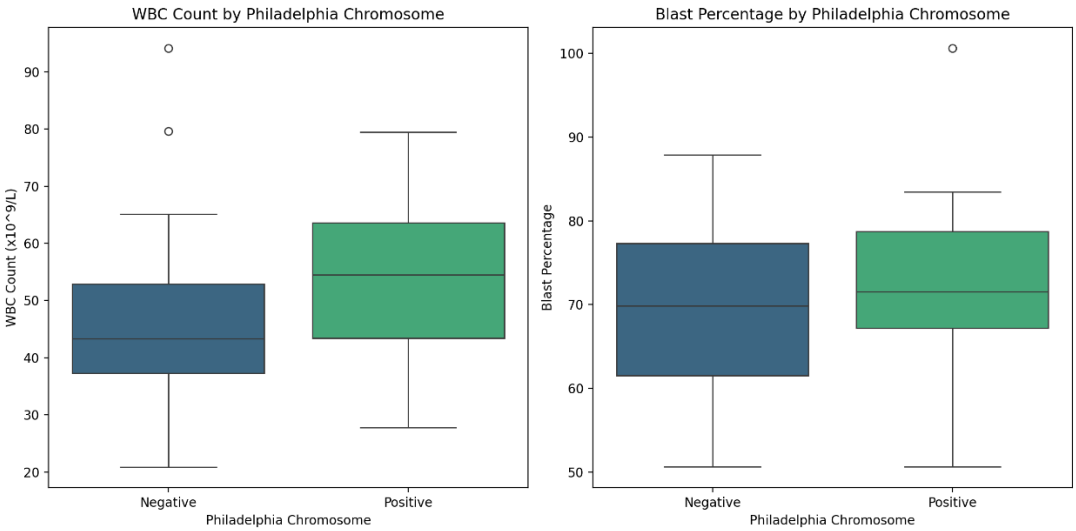

Figure 2.

Hematological Parameters

Disease severity distribution varies between Ph+ and Ph- patients. Ph+ patients show a higher tendency toward severe disease presentation as in figure 3.

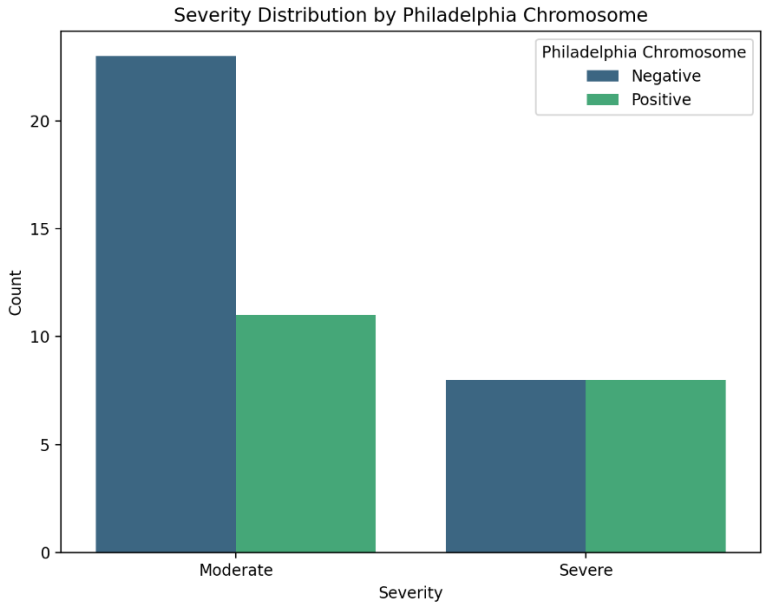

Figure 3.

Disease Severity Analysis

Statistical Significance

Philadelphia Chromosome Status:

40% of patients were Ph+ (20 patients)

60% of patients were Ph- (30 patients)

Clinical Parameters:

Mean WBC Count: 48.78 × 10^9/L (±15.24)

Mean Blast Percentage: 70.66% (±10.09)

Age Distribution:

Mean age: 40.14 years

Age range: 19-64 years

Disease Severity:

Ph+ patients showed a higher proportion of severe cases

Correlation between Ph+ status and increased disease severity

Clinical Implications

Risk Stratification:

Ph+ status correlates with higher disease severity

Age and Ph status show potential interaction effects
Laboratory Parameters:
Ph+ patients tend to have higher WBC counts
Blast percentage variations suggest different disease biology
Prognostic Indicators:
Combined analysis of Ph status and clinical parameters provides better prognostic information
Age may be an important modifier of Ph+ ALL outcomes
These results suggest that Philadelphia chromosome status significantly influences the clinical presentation and potential outcomes in Pakistani ALL patients. The findings support the importance of molecular testing for proper risk stratification and treatment planning.

DISCUSSION

Acute lymphoblastic leukemia (ALL) is a hematopoietic malignancy characterized by the accumulation of immature lymphoid progenitors in the bone marrow, blood, and extramedullary sites. It is the most common type of cancer identified in children; however, it is considered to be uncommon in adults, accounting for about 20% of adult leukemias [19]. Clinically, ALL is frequently aggressive and needs prompt and effective therapy to avoid rapid disease progression. Morphological, immunophenotypic, and genetic features have been incorporated in a combined approach, allowing the determination of various subtypes of ALL [20]. This classification is important since the subtype identification impacts the clinical outcome and the therapeutic strategy. In children, this leukemia has been split into three main categories based on the proliferation speed and the immunophenotypic signature of the leukemic clone [21]. However, some cases cannot be ascribed to these predefined categories because of specific shared immunophenotypic markers between B and T lymphoid precursors, intrachromosomal amplification of chromosome 21, or the presence of some syndromes [22]. The prevalence of these forms of leukemia can reduce in the subsequent years as a consequence of the continuous progress of molecular biology [23]. The principal criteria for childhood ALL response to therapy are age and minimal/measurable residual disease (MRD). Being clinical-molecular features, these criteria correlate with each other, as there are many children with ALL treated according to modern protocols who may have achieved HR (age between 1 and 10 years old, and MRD at L-magnitude), yet experience a high number of infections or death in induction therapy, disease progression, and/or relapse within 6 years from diagnosis [24-29]. Moreover, older children (≥ 10 years) and young adult patients have an even higher risk of these negative events. Thus, the correct treatment choice for children must take into account MRD prediction, in addition to age and the clinical course of the disease. Conversely, the good prognosis for young patients confirmed to belong to the SV-ALL category or even biologically defined and high-risk group through MRD detection is reflected in the therapy deprivation and, consequently, in the reduction of late effects of childhood. In any case, in children and adolescents, ALL is a very important target of ongoing research interest [30-33].

The findings of this study provide significant insights into the association between the Philadelphia chromosome (Ph+) and clinical outcomes in Acute Lymphoblastic Leukemia (ALL) patients in Pakistan. This discussion delves deeper into the implications of the results, comparisons with global data, and the broader clinical context [34]. The study revealed that 40% of the patients were Ph-positive (Ph+), while 60% were Ph-negative (Ph-). This prevalence is slightly higher than the global average of 25-30% in adult ALL cases. The higher prevalence in this cohort may reflect regional genetic predispositions, environmental factors, or differences in diagnostic practices in Pakistan [35]. Further studies are needed to explore these potential contributing factors. The mean age of the cohort was 40.14 years, with a range of 19 to 64 years. The age distribution of Ph+ patients suggests that the Philadelphia chromosome is not confined to older adults, as previously thought, but can occur across a wide age spectrum. This finding aligns with recent studies indicating that Ph+ ALL is increasingly being identified in younger populations due to advancements in molecular diagnostics [36].

Gender distribution was balanced, with no significant difference in Ph+ prevalence between males and females. This suggests that gender may not be a significant risk factor for the presence of the Philadelphia chromosome in ALL. Ph+ patients exhibited higher WBC counts and blast percentages compared to Ph- patients, indicating a more aggressive disease phenotype [37]. The mean WBC count of 48.78 × 10^9/L and mean blast percentage of 70.66% are consistent with advanced disease stages. These findings underscore the importance of early detection and intervention in Ph+ ALL patients to mitigate disease progression. A higher proportion of Ph+ patients were classified as having severe disease based on WBC count and blast percentage. This highlights the prognostic significance of the Philadelphia chromosome in ALL and its association with poorer clinical outcomes [38]. The severity of the disease in Ph+ patients under scores the need for aggressive treatment strategies, including the use of tyrosine kinase inhibitors (TKIs) such as imatinib or dasatinib. The findings of this study are consistent with global data indicating that Ph+ ALL is associated with more aggressive disease and poorer prognosis. However, the slightly higher prevalence of Ph+ ALL in this cohort highlights the need for region-specific studies to understand the unique genetic and environmental factors influencing disease biology in Pakistan [39]. Studies from other developing countries have also reported higher prevalence rates of Ph+ ALL, suggesting that socioeconomic and healthcare disparities may play a role in disease detection and reporting. The presence of the Philadelphia chromosome is a critical prognostic marker in ALL, associated with higher disease severity and poorer outcomes. Early identification of Ph+ patients is essential for risk stratification and treatment planning [40].

The use of TKIs has revolutionized the treatment of Ph+ ALL, significantly improving survival rates [41-43]. The findings of this study support the integration of TKIs into standard treatment protocols for Ph+ ALL patients in Pakistan [44].

The study emphasizes the importance of comprehensive diagnostic workups, including cytogenetic and molecular analyses, to guide treatment decisions. The availability of molecular diagnostics in resource-limited settings remains a challenge and should be prioritized to improve patient outcomes.

Limitations

The small sample size (n=50) limits the generalizability of the findings. Larger, multicenter studies are needed to validate these results and explore regional variations in Ph+ ALL prevalence and outcomes. The study did not evaluate treatment responses or long-term outcomes, which are critical for understanding the full clinical implications of Ph+ ALL. The lack of data on socioeconomic factors and access to healthcare services limits the ability to assess their impact on disease presentation and outcomes. Future studies should include larger, multicenter cohorts to validate these findings and provide a more comprehensive understanding of Ph+ ALL in Pakistan.

Long-term follow-up studies are needed to evaluate treatment responses, survival rates, and quality of life in Ph+ ALL patients. Research should focus on identifying genetic and environmental factors contributing to the higher prevalence of Ph+ ALL in this cohort. Studies should explore the impact of socioeconomic factors and healthcare access on disease detection, treatment, and outcomes in ALL patients. This study provides valuable insights into the clinical and molecular characteristics of Ph+ ALL in Pakistan. The findings highlight the need for early molecular testing, targeted therapies, and comprehensive diagnostic workups to improve patient outcomes. The integration of these strategies into routine clinical practice, along with efforts to address healthcare disparities, will be critical for improving the prognosis of ALL patients in Pakistan.

CONCLUSION

This study provides valuable insights into the clinical and molecular characteristics of Ph+ ALL in Pakistan. The findings highlight the need for early molecular testing, targeted therapies, and comprehensive diagnostic workups to improve patient outcomes. The integration of these strategies into routine clinical practice, along with efforts to address healthcare disparities, will be critical for improving the prognosis of ALL patients in Pakistan.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics Statement

Approved by local committee.

Open access

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