

Prevalence and patterns of high hyperdiploidy in Pakistani Paediatric B-lymphoblastic leukaemia

Kiran Sachwani¹, Bushra Kaleem², Neelum Mansoor³

Abstract

Objective: To determine the prevalence and cytogenetic patterns of high hyperdiploidy in Pakistani children with B-lymphoblastic leukaemia.

Method: The retrospective, descriptive, cross-sectional study was conducted at the Cytogenetics Laboratory, Indus Hospital and Health Network, Karachi, and comprised data from November 2020 to August 2022 of paediatric patients aged 1-16 years of either gender who had been diagnosed with B-lymphoblastic leukaemia. Standard G-banding techniques were used and karyotypes were evaluated using a semi-automated system. Data was analysed using SPSS 25.

Results: Of the 562 paediatric patients included in the study, 342 (60.9%) were males and 220 (39.1%) were females, with an age range of 1-16 years. Cytogenetic aberrations were identified in 289 (51.4%) cases, while 273 (48.6%) had normal karyotypes. Overall, 171 (30.4%) cases displayed high hyperdiploidy. Gains were seen in chromosomes X, 4, 6, 10, 14, 17, 18 and 21. Chromosome 21 gain was the most frequently observed chromosomal gain among cases with high hyperdiploidy. High hyperdiploidy (chromosome 51-65) was revealed to be the most common subtype of hyperdiploidy. Translocation t(1;19) was the most common structural aberration observed in association with hyperdiploidy.

Conclusion: High hyperdiploidy was the most prevalent chromosomal abnormality found in paediatric B-lymphoblastic leukaemia patients. Consistent trisomy of chromosome 21 and frequent structural aberrations were also noted.

Keywords: Prevalence, Patterns, High hyperdiploidy, Pakistani children, B-Lymphoblastic Leukaemia, Paediatric, Cytogenetics, hyperdiploidy. (JPMA 76: 1835; 2026) DOI: <https://doi.org/10.47391/JPMA.30235>

Introduction

Acute lymphoblastic leukaemia (ALL) is the most common childhood malignancy, characterised by the clonal proliferation of immature lymphoid precursors in the bone marrow, blood and extramedullary sites. White blood cell (WBC) dynamics play a critical role in the diagnosis, prognosis and clinical course of ALL. At presentation, WBC count is one of the most important parameters used in risk stratification, with higher counts ($>50 \times 10^9/L$) often associated with inferior outcomes, increased risk of central nervous system (CNS) involvement, and higher relapse rates.¹ Conversely, lower WBC counts at diagnosis are generally linked with a more favourable prognosis. In addition, variation in WBC counts during therapy, particularly early treatment response measured through minimal residual disease (MRD) kinetics, provides further prognostic information that guides treatment intensity. Thus, WBC parameters, in conjunction with cytogenetic and molecular features, form the foundation of modern risk-adapted therapy in paediatric ALL.²

Paediatric B-lymphoblastic leukaemia (B-ALL) has been reported to show regional variations in incidence and prevalence, such as that between Western and Asian populations, and is also characterised by strong sex differences. In Western countries, paediatric B-ALL is a significant disease among childhood cancers, and is estimated to be about 25%.³ Childhood ALL, with or without B-lineage disease, is influenced by socioeconomic factors, and differs across racial and ethnic lines.⁴ In the United States, for instance, the prevalence of ALL is worse in non-Hispanic White groups than in Hispanic groups.⁴

The incidence of B-ALL in Asian cohorts is lower compared to the Western populations, although it is increasing. This trend can be explained by the amplification of risk factors and the improvement of cancer registries.⁵ Similar rising rates have been observed in other low- and middle-income countries (LMICs), whereby malignancies have been on the rise with better control of infectious diseases.⁶

B-ALL frequently exhibits chromosomal aneuploidy, which significantly influences prognosis and treatment approaches. The main types of aneuploidy observed include hypodiploidy (fewer than 46 chromosomes, typically 30-39) associated with poor outcomes; near-haploidy (approximately 24-31 chromosomes) linked to adverse prognosis; high hyperdiploidy, defined by the latest World Health Organisation (WHO) Classification⁷ as

^{1,3}Department of Cytogenetics, Indus Hospital and Health Network, Karachi, Pakistan; ²Indus Hospital Research Centre, Indus Hospital and Health Network, Karachi, Pakistan.

Correspondence: Neelum Mansoor. e-mail: neelum.mansoor@tih.org.pk
ORCID ID: 0000-0003-1650-0694

Submission completed: 27-05-2025 **1st Revision received:** 03-10-2025

Acceptance: 17-06-2026

Last Revision received: 16-06-2026

leukaemic cells harbouring 51-65 chromosomes; near-triploidy (67-80 chromosomes); and tetraploidy (81-103 chromosomes). The last two are less common and have variable clinical significance. Overall, high hyperdiploidy is the most prevalent cytogenetic abnormality in paediatric B-ALL, accounting for 30-35% of cases and is consistently associated with favourable prognosis.^{8,9}

Over several decades, multiple studies have demonstrated a correlation between high hyperdiploidy and favourable outcomes (survival >90%).^{8,10} Notwithstanding this positive association, the substantial number of patients with high hyperdiploid ALL results in this subgroup accounting for up to 25% of all relapses, particularly in LMICs where outcomes for this condition are inferior to those in developed nations.¹¹ Various studies have investigated cytogenetic risk factors within the high hyperdiploid ALL subgroup, examining aspects such as modal chromosome number, specific trisomies and the occurrence of structural abnormalities.^{11,12} Research has demonstrated improved outcomes for patients with higher modal chromosome numbers and certain trisomies (+4, +6, +10, +15, +17, +18) as well as triple trisomies (+4, +10, +17), which are frequently interrelated.¹³ However, these investigations did not examine the pattern of all possible combinations of chromosomal gains.

The latest WHO Classification of Haematolymphoid Tumours (WHO-HEM5) in 2022 renamed this entity as B-ALL with high hyperdiploidy (formerly known as B-ALL with hyperdiploidy) and defined the range of chromosome numbers to be 51-65.⁷ Several studies have been published on its frequency and outcome in the West, but data from Pakistan is sparse.¹⁴

The current study was planned to fill the gap in literature by determining the prevalence and cytogenetic patterns of high hyperdiploidy in Pakistani children with B-ALL.

Patients and Methods

The retrospective, descriptive, cross-sectional study was conducted at the Cytogenetics Laboratory, Indus Hospital and Health Network (IHHN), Karachi and comprised data from November 2020 to August 2022. After approval from the institutional ethics review board, consecutive sampling method was used to raise the sample by including data of all paediatric patients aged 1-16 years regardless of gender who had been diagnosed with B-ALL within the specified period. Patients were excluded in case of insufficient bone marrow aspirate samples for cytogenetic analysis, culture failure, lack of confirmed B-ALL diagnosis, or incomplete clinical documentation.

Metaphase chromosomes were isolated from 24-hour

unstimulated bone marrow aspirate samples collected as part of routine diagnostic workup. The bone marrow aspirates were processed within 24 hours of collection. The samples were dual cultured in RPMI media supplemented with foetal bovine serum (FBS) and L-Glutamine, using both routine and overnight colcemid treatment to arrest cells in metaphase. The cultures were incubated at 37°C in a 5% carbon dioxide (CO₂) atmosphere. Potassium chloride was used for hypotonic treatment, followed by Carnoy's Fixative washing. Slide-making was done using heat fixing and aging techniques. G-banding was performed using trypsin and Giemsa stain. Conventional chromosomal analyses were performed on 20 metaphases per patient, and the results were reported as per the International System for Human Cytogenetic Nomenclature (ISCN, 2024).¹⁵ For the calculation of frequencies and percentages of chromosomal abnormalities, the denominator was defined as the total number of B-ALL patients included in the study. Each patient was counted once based on the primary cytogenetic abnormality identified in the karyotype analysis. Karyotypes were evaluated using a semi-automated system (Cytovision MB8, Leica Biosystems, Germany).

Numerical and structural abnormalities were categorised according to the cytogenetic findings obtained from conventional karyotyping. High hyperdiploidy was operationally defined as the presence of 51-65 chromosomes in leukaemic cells, in accordance with WHO-HEM5.⁷ Patients with high hyperdiploidy were classified based on their primary cytogenetic abnormality; any concomitant structural abnormalities were documented separately to ensure a consistent counting method for reporting the distribution of chromosomal anomalies.

Data was analysed using SPSS 25. Descriptive statistics were utilised to calculate frequencies and percentages of the identified chromosomal abnormalities.

Results

Of the 562 paediatric B-ALL cases included in the study, 342 (60.9%) were males and 220 (39.1%) were females, with an age range of 1–16 years. Of the 562 cases, 289(51.4%) had abnormal karyotypes and 273(48.6%) had normal cytogenetic profiles. Of the abnormal cases, 171(59.2%) had high hyperdiploidy, and, among them, 78(45.6%) patients exhibited hyperdiploidy with additional abnormalities, while 93(54.4%) had isolated hyperdiploidy. The remaining patients had structural abnormalities without hyperdiploidy. The distribution of chromosomal gains in paediatric B-ALL with high hyperdiploidy was noted in detail (Figure 1).

Certain chromosomes showed a high frequency of

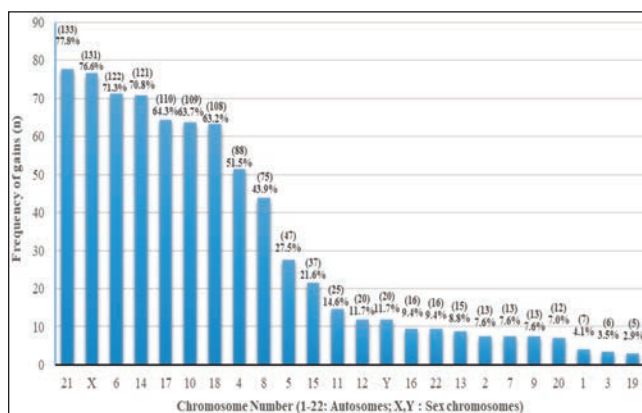


Figure-1: Distribution of chromosomal gains among paediatric B-ALL cases with high hyperdiploidy (n = 171).

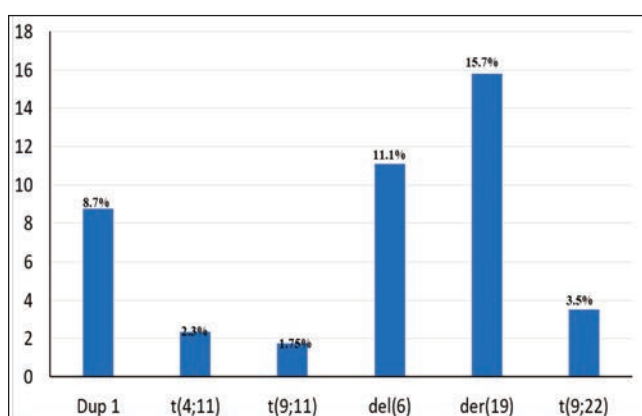


Figure-2: Distribution of selected recurrent structural chromosomal abnormalities among abnormal cases (n=289).

Percentages were calculated based on the total abnormal cohort; therefore, only selected abnormalities are presented.

involvement among abnormal cases. Of the 171 such cases, chromosome X was found in 131 (76.6%) patients, chromosome 4 in 88 (51.5%), chromosome 6 in 122 (71.3%), chromosome 10 in 109 (63.7%), chromosome 14 in 121 (70.8%), chromosome 17 in 110 (64.3%), chromosome 18 in 108 (63.2%) and chromosome 21 in 133 (77.8%). In addition to hyperdiploidy, some structural chromosomal abnormalities were also observed in the studied cohort (Figure 2).

Discussion

Risk stratification and prognosis of ALL patients are critically dependent on cytogenetic abnormalities. However, the incidence of chromosomal abnormalities is age-dependent and can have a major impact on treatment outcomes.¹⁶ It is interesting to note that the frequency of some chromosomal abnormalities varies with age. For example, the incidence of t(9;22) increases in each successive decade; to 24% in the 40-49 group, while t(4;11) and t(1;19) are rare at age >60 years. Younger patients are

more likely to have high hyperdiploidy, with 13% of patients aged <20 years and 5% of patients aged >20.¹⁶

The present study evaluated the cytogenetics of paediatric B-ALL with an emphasis on hyperdiploidy. The findings revealed that >50% of the B-ALL patients had abnormal karyotype. Literature reported that about 30% of paediatric ALL patients have no abnormalities with clinical relevance by traditional cytogenetic analysis.¹⁷⁻¹⁹ Wang et al. reported a prevalence of 56% chromosomal abnormalities with a clinical relevance which were detected via karyotype and/or fluorescence in situ hybridisation (FISH) analyses.²⁰ This was very much in line with the current findings in which 54.3% had abnormal karyotype results. As the sensitivity of conventional karyotyping is comparatively low considering the advanced techniques, like FISH and next generation sequencing (NGS), therefore, the number of cytogenetic/genetic aberrations are not truly reflective until a combination of testing has been performed. However, in resource-constrained settings conventional karyotype is still a crucial tool to detect these aberrations in a significant number of cases at a reasonable cost.

In the studied cohort, 51.4% patients had cytogenetic aberrations, and overall 30.4% had high hyperdiploidy. Forestier and Schmiegelow reported that in ALL, high-hyperdiploid clones (51-61 chromosomes) were common in B-ALL cases, particularly in the patients aged 2-7 years.²¹

High hyperdiploidy represents one of the most common genetic subtypes of paediatric B-ALL, typically defined by a modal chromosome number of 51-65 (occasionally up to 67) with characteristic non-random gains, most frequently involving chromosomes X, 4, 6, 10, 14, 17, 18 and 21. Both WHO-HEM5 and the International Consensus Classification (ICC)22 acknowledge hyperdiploid B-ALL as a distinct entity associated with favourable prognosis, particularly in cases harbouring double (+4, +10) or triple (+4, +10, +17) trisomies. However, subtle differences exist between these frameworks: WHO-HEM5 emphasises cytogenetic and mutational criteria as the essential basis for diagnosis, using the explicit term "high-hyperdiploid B-ALL", while the ICC favours the term "B-ALL, hyperdiploid" and highlights the role of whole-transcriptome profiling for classification, especially in complex or ambiguous cases. Minor discrepancies also remain regarding the precise chromosome-count thresholds used to define the entity. Furthermore, both systems stipulate that the presence of overriding defining abnormalities, such as BCR, ABL1, KMT2A rearrangements, or low-hypodiploidy/near-haploidy, should take precedence over a hyperdiploid designation, although the order of prioritisation may differ. These variations, while seemingly semantic, have practical implications: diagnostic assignment may differ for

borderline or composite cases, the extent of ancillary testing (cytogenetics versus transcriptome analysis) may vary, and, ultimately, risk stratification and therapeutic decisions can be influenced, particularly as many clinical protocols rely on precise identification of low-risk hyperdiploid subgroups for therapy de-intensification. Thus, harmonisation between classification systems and consistent reporting of karyotypic details remain crucial to ensuring optimal diagnosis, prognostication and treatment planning in B-ALL.

Cytogenetic abnormality of high hyperdiploidy (51-67 chromosomes) is the most common cytogenetic abnormality in childhood B-ALL; 25-30% of cases. Non-random gains of chromosomes X, 4, 6, 10, 14, 17, 18 and 21 define this subgroup, which has a favourable prognosis.²² This subtype has a high rate of RAS mutations, especially when maternal age is <30 years.²³ The present study identified recurrent gains involving chromosomes X, 4, 6, 10, 14, 17, 18 and 21 among cases with high hyperdiploidy. Hyperdiploidy implicating chromosome 21 was the most commonly implicated chromosome. In particular, chromosome 21 has been widely associated with leukaemia pathogenesis because of its relationship with gene dosage effects (overexpression of oncogenes such as RUNX1). Interestingly, while high hyperdiploidy is a common feature in paediatric B-ALL, adult B-ALL has rather different patterns of chromosomal abnormalities. The ZNF384 subtype comprises 22.6% of cases in adult B-ALL.²⁴ Furthermore, adult B-ALL subtypes, such as CDX2 high and IDH1/2mut, have been identified with gain of chromosome 1q and specific mutations, respectively.²⁵

Structural aberrations were identified in the hyperdiploid cohort in addition to numerical chromosomal abnormalities, with der(19) being the most frequent abnormality. Unlike the present study, the der(19) chromosome is not explicitly mentioned as the most frequent chromosome abnormality in published literature. The t(1;19) can result in der(19), and was reported in 25% of B-ALL cases in one study.²⁵ Indeed, deletions of chromosome 6q, particularly the del(6)(q21), are recurrent in ALL, and in one study, 11% of children had this abnormality.²⁶ The t(12;21) translocation, resulting in the ETV6::RUNX1 fusion gene is actually considered the most frequent chromosomal rearrangement in childhood B-ALL.²⁶ Secondary mutations, such as deletions of chromosomes 6q and 9p, and duplications of chromosome 4q, often accompany this translocation.²⁶ However, Hayashi et al. reported that del(6q) was found in 11% of paediatric ALL cases, with the 6q21 band being consistently involved, a finding that may implicate the involvement of 6q21 in leukemogenesis.²⁷ Both B- and T-lineage ALL cases have

been found to contain the Philadelphia chromosome, or t(9;22).²⁸ This translocation is one of the recurring abnormalities with clinical relevance in the form of poor prognosis in B-ALL.²⁰ Paediatric B-ALL patients with t(1;19) and t(9;22) translocations have different disease outcomes. The TCF3::PBX1 gene fusion created by t(1;19)(q23;p13.3) is considered one of the most frequent genetic rearrangements in childhood B-ALL.²⁹ Children aged 1-9 years with a t(1;19) translocation tend to experience more favourable treatment results.³⁰ Paediatric ALL cases with 3-4% Philadelphia chromosome show the t(9;22)(q34;q11) translocation which generates the BCR-ABL1 fusion gene.²⁶ Children with Ph+ ALL are known to have a very poor prognosis.^{2,26}

The most important strength of the current study is the addition of the findings to the local data generated via karyotypic analysis from one of the largest paediatric haematology-oncology centres in Pakistan. The study provides one of the largest datasets from Pakistan to date, documenting the prevalence and cytogenetic spectrum of high hyperdiploidy in paediatric B-ALL. The inherent limitations of the study include its retrospective design, selection bias and incomplete treatment outcome data. In addition, molecular characterisation of structural abnormalities has not been incorporated, preventing a full understanding of their biological implications. Recent advances in genomic and immunophenotypic profiling continue to refine the biological understanding and risk stratification of paediatric B-ALL.³¹

The observed chromosomal gain profiles in the current study underscore the clinical utility of cytogenetic analysis for risk stratification and treatment planning, especially in resource-constrained settings. The study highlights the critical importance of integrating cytogenetic evaluation into routine leukaemia diagnostics. To enhance diagnostic accuracy and prognostic precision, the development of cytogenetic expertise and the adoption of complementary molecular tools, such as FISH and NGS, are recommended. Future research should focus on larger, multi-institutional cohorts, detailed cytogenetic subgroup analyses, and the integration of cytogenetic and molecular data along with treatment outcomes to provide a more comprehensive genomic risk assessment in paediatric B-ALL.

Conclusion

High hyperdiploidy was found to be the most common numerical chromosomal abnormality paediatric B-ALL cases, with recurrent gains in chromosomes X, 6, 14, 18, and 21 and the gain of chromosome 21 was the most common. These patterns are consistent with global trends and reinforce the established association between high

hyperdiploidy and favourable clinical outcomes, including improved treatment responsiveness and survival rates.

Acknowledgement: We are grateful to the Cytogenetics Laboratory and the Department of Paediatric Oncology, Indus Hospital and Health Network, Karachi, for providing administrative and logistical support, and to the hospital management and laboratory staff for facilitating the study.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

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Author Contribution:

KS: Concept, data acquisition, analysis, drafting, final approval and agreement to be accountable for all aspects of the work.

BK: Data analysis, drafting, final approval and agreement to be accountable for all aspects of the work.

NM: Concept, revision, final approval and agreement to be accountable for all aspects of the work.