ORIGINAL ARTICLE

CYTOGENETIC PROFILING IN PAEDIATRIC ACUTE LEUKAEMIA; A REPORT ON 746 NEWLY DIAGNOSED PAEDIATRIC CASES ANALYZING THE SPECTRUM OF RECURRING CHROMOSOMAL REARRANGEMENTS IN B CELL LYMPHOBLASTIC AND ACUTE MYELOID LEUKAEMIA

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Background: Cytogenetics is evolving and different molecular mechanisms we know now have proved to be of diagnostic and prognostic significance in both acute lymphoid (ALL) and myeloid leukaemia (AML). This study aims to find out and compare the occurrence of different cytogenetics in paediatric acute leukaemia. **Methods:** This is a cross-sectional study of diagnosed B-ALL and AML patients presenting at The Indus Hospital. We studied FISH and karyotype in B-ALL and FISH in AML patients. FISH analysis shows a total of 69 (12.8%) of B ALL patients had cytogenetic abnormalities. BCR-ABL1 was positive in 5.1%, ETV6/RUNX1T1 in 8.6% and KMT2A in 2.3% individuals. Karyotype reveals hyper diploidy in 24.3%, Monosomy in 1.94%, and t (1:19) and t (17:19) were observed in 5.8% and 0.24% cases respectively. FISH analysis in AML cases reveal positivity of t (8:21) in 26.4%, INV (16) in 6.1% while PML-RARA t(15:17) was done on morphological suspicion in 17 cases; all of which showed positivity; making 7.9% of the total AMLs. The study demonstrated a wide spectrum of heterogeneity in paediatric acute leukaemia. **Conclusion:** Hyperdiploidy was the most common cytogenetic abnormality. We report a lower incidence of t (12:21), compared to the world. We showed a higher prevalence of RUNX1/RUNX1T1 in young children. The prevalence of core binding factor AML was 32.5%.

Keywords: Acute Lymphoblastic Leukaemia; Acute Myeloid Leukaemia; Cytogenetics

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INTRODUCTION

Acute leukaemia (AL) is among the commonest childhood cancers with an annual prevalence of 30–40 per million children under 18 years of age.[1,2] The lack of population level statistics precludes the exact burden in Pakistan. However, based on institutional data, the estimated incidence is close to 3000 cases per year.[3] Cytogenetics in acute leukaemia have evolved over the past three decades and have provided insights into the molecular mechanisms which have proved to be of diagnostic as well as prognostic significance in both paediatric and adult acute lymphoid (ALL) and myeloid leukaemia (AML). This significance is well known for both chromosome number (ploidy) and structural alterations including deletions, copy number changes and translocations.[4] Several recurrent cytogenetic abnormalities are now a part of WHO Classification 2017. Among them, hyperdiploidy (51–65 chromosomes) and t (12;21) ETV6/RUNX1 carries favourable prognosis whereas hypodiploidy (≤45 chromosomes), t(9;22) BCR/ABL1, KMT2A gene rearrangements and intrachromosomal amplification of 21 (iAMP21) are associated with poor prognosis. Another addition to recurrent cytogenetic lesions is t (1;19) TCF-PBX1 which is considered a risk factor for CNS disease at presentation [5–7]. Similarly AML patients harbouring t(8;21) RUNX1/RUNX1T1, t (15:17) PML/RARA and INV(16) CBFB/MYH11 have favourable prognosis.[4]

Variable prevalence of different cytogenetics has been reported in literature all over the world in different continents and ethnicities. However, due to a lack of well-equipped and validated cytogenetic laboratories and trained human resources in all centers, data on cytogenetic prevalence in childhood leukaemia is limited in Pakistan. The paediatric oncology department of our institute is one of the largest referral facilities in Pakistan seeing more than 350 de novo cases of acute leukaemia annually. In our institute, along with initial diagnostic, morphologic and immunophenotypic workup, cytogenetic status is determined for B lymphoblastic leukaemia (B ALL) and AML only and not in T-ALL. In the current study, we reviewed this data in a large cohort with the rationale of finding out the prevalence of different cytogenetic abnormalities in Pakistan as well as its difference from the rest of the world. Moreover, this information is very important in terms of optimal risk grouping, treatment protocol assignment and prognosis of childhood acute leukaemia.

MATERIAL AND METHODS

The study was conducted in the haematology section of the clinical laboratories of The Indus Hospital and Health Network and Dr. Ziauddin University Hospital along with the paediatric oncology department of The Indus Hospital. The present study includes 746 patients from January 2015 to October 2018. Paediatric patients below 18 years; diagnosed with acute leukaemia by flow cytometry on peripheral blood or bone marrow aspirate samples or immunohistochemistry on bone marrow trephine samples were included as per the inclusion criteria after getting approval from the hospital ethic committee. Out of a total of 746 patients in the study, 531 were B-ALL and 215 were AML. At the time of diagnosis, blood or bone marrow aspirate samples were drawn in sodium heparin tubes and saved for interphase Fluorescent in-situ hybridization (FISH) and bone marrow chromosome analysis (karyotype). For cost effectiveness, the cytogenetic analysis was performed after a confirmed immunophenotypic diagnosis. In B-ALL, the FISH panel included probes for BCR/ABL1, KMT2A rearrangement and ETV6/RUNX1. Similarly, RUNX1/RUNX1T1 and CBFB/MYH11 were tested in AML cases other than acute promyelocytic leukaemia (APL). The testing for PML/RARA was reserved for those cases where there were either morphological or flowcytometric suspicion of acute promyelocytic leukaemia (APL) as shown in Figure-2. Karyotype was ordered in B-ALL patients only due to its role in risk grouping and prognosis. Neither FISH nor karyotype was performed in T-lymphoblastic leukaemia (T-ALL). Among 531 cases of B-ALL, results of conventional karyotype were available in 411. In the remaining, data was not available either due to lack of sampling or absence of metaphases.

The Interphase FISH analysis was performed in the cytogenetic lab of The Indus Hospital and Dr. Ziauddin University Hospital; a panel of Vysis probes with dual colour dual fusion and break apart were used for B-ALL and AML as discussed. A minimum of 200 interphase cells were counted with cutoffs of typical positivity being BCR-ABL1 (0.5%), ETV6-RUNX1 (0.5%), KMT2A rearrangement (2.4%), CBFB (4.5%), RUNX1/RUNX1T1 (0.5%) and PML-RARA (0.5%). The results were analyzed by two separate individuals; a senior cytogeneticist and a haematologist. All the samples for conventional karyotyping were sent to a reference laboratory.

Data was analyzed using SPSS version 21.0. Descriptive statistics were applied to calculate the Mean, standard deviation, median and range for age. Frequency and percentage were computed for qualitative variables like gender, phenotype and cytogenetic status. Chi-square test was used to assess the association between karyotypic findings with age and gender. *p*-value of ≤ 0.05 was considered to be significant.

RESULTS

A total of 746 patients were included in this study and among them 531 were B-ALL and 215 were AML. Patients diagnosed with B-ALL were 321 males (60.5%) and 210 females (39.5%). Male to female ratio was 1.5:1. Patients with B-ALL were mostly younger than 10 years of age 396 (74.5%) with 135 (25.5%) of them older than 10 years. Total 69 (12.8%) of B ALL patients had cytogenetic abnormalities. Among these 24/472(5.1%) were positive for BCR ABL, 34/396(8.6%) for ETV6-RUNX1 and 11/470(2.3%) for KMT2A gene rearrangement as shown in Figure-1.

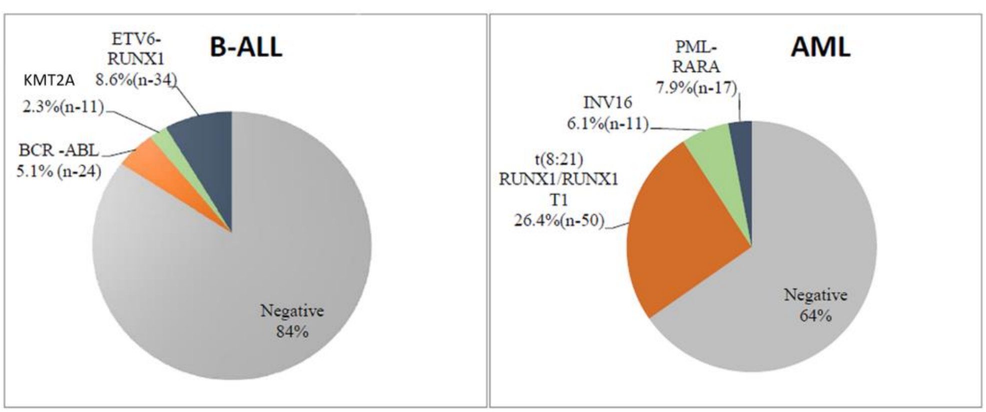

Figure-1: Interphase FISH analysis in B-ALL and AML

Similarly, the cohort with AML showed 78 (36.1%) patients with recurrent cytogenetic abnormalities. Out of which, 50/189(26.4%) were positive for t (8;21) RUNX1/RUNX1T1, 11/179(6.1%) for INV16 CBFB-MYH11. PML-RARA or t (15:17) was processed on morphological suspicion in 17 cases; all of which showed positivity; making 7.9% of the total AMLs in the study period.

Among 531 B-ALL patients included in the study, 69 (32%) of the tested patients had detectable recurrent genetic abnormality identified on interphase FISH. A total of 472 patients were tested for *BCR ABL* out of which 24 (5.0%) were positive, similarly, 396 cases were tested for ETV*6-RUNX1* and 470 cases for *KMT2A* gene rearrangement from which 34 (8.6%) and 11 (2.3%) were positive respectively. The difference in the analyzed sample and total number of enrolled patients in the study is due to the failure to achieve reportable results either due to unavailability of the patient sample, very low count and/or other variables where the required probe could not be processed. Further distribution of positive cases with respect to age and gender were shown in Table 1.

We have compared the prevalence of *BCR-ABL1*, *KMT2A rearrangement*, *ETV6-RUNX1*, t (1:19) with other regional studies (Table 2).[3,5–14]

Karyotyping was performed on 411 cases, and results of 381 cases were reported. The ploidy analysis was classified into various subgroups as depicted in Table 1. A normal karyotype (p=0.005) and Hyperdiploidy (*p*=<0.001) has a significant association with age (Table-1).

Translocations were also observed in our data; t (1:19), t (9;22), t (4;11) and t (17:19) were found in 14 (4.1%), 4(0.9%), 2 (0.4%) and 1 (0.24%) case respectively (Table-1). Sex has significant association with t (1:19) mentioned in Table 1.

Among 215 AML patients, 78 (36%) have cytogenetics abnormalities. A total of 189 tests were analyzed for *RUNX1/*RUNX1T1 in which 50(26.4%) were positive and also have a significant association with age (p=0.027). Similarly, INV16 *CBFB-MYH11* were analyzed in 179 cases in which 11(6.1%) were positive while 17 cases were analyzed for *PML-RARA* or t(15:17) and all were positive (Table-1).

We have also compared our study results with other studies from other Asian countries and the Western population (Table-3).[1,3,15–24]

Table-1: Distribution of Cytogenetic Abnormalities detected in B-ALL and AML patients

Cytogenetics	Age Group			Gender		*p*-value
	<10 years	>10 years	*p*-value	Male	Female	
ALL (FISH)						
BCR-ABL (n=472)	17 (3.6%)	7 (1.5%)	0.583[a]	14 (2.9%)	10 (2.1%)	0.892[a]
KMT2A (n=470)	10 (2.1%)	1 (0.2%)	0.248[b]	5 (1.1%)	6 (1.3%)	0.28[b]
ETV6-RUNX1 (n=396)	30 (7.6%)	4 (1.0%)	0.93[a]	19 (4.8%)	15 (3.8%)	0.535[a]
ALL (Karyotype) n=411						
Normal karyotype	186 (45%)	69 (17%)	0.005[a*]	158 (38%)	97 (24%)	0.053[a]
Hypodiploidy	0	1 (0.24%)	0.228[b]	1 (0.24)	0	1.000[b]
Hyperdiploidy	91 (22.1%)	9 (2.2%)	<0.0001[a*]	53 (13%)	47 (11.3%)	0.191[a]
t(1:19)	14 (3.4%)	3 (0.72%)	0.772[b]	6 (1.4%)	11(2.6%)	0.047[a*]
t(9;22)	3 (0.72%)	1 (0.24%)	1.000[b]	3 (0.72%)	1 (0.24%)	0.645[b]
t(4;11)	0	2 (0.48%)	0.052[b]	0	2 (0.48%)	0.171[b]
t(17:19)	0	1 (0.24%)	0.228[b]	1 (0.24%)	0	1.000[b]
AML (FISH)						
RUNX1/RUNX1T1 (n=189)	39 (20.6%)	11 (5.8%)	0.022[a]*	31 (16.4%)	19 (10.1%)	0.195[a]
CBFB/MYH11 (n=179)	8 (2.2%)	3(3.9%)	0.750[b]	7 (4.0%)	4 (2.2%)	0.511[a]
PML-RARA(n=17)	10 (59%)	7 (41.2%)	0.613[a]	9 (53.0%)	8 (47.1%)	0.925[a]

FISH= Fluorescence in situ hybridization, a= Pearson Chi-square, b = Fisher's Exact test *=Significant value

Table-2: Comparison of reported prevalence of prognostically important cytogenetics with other studies of Paediatric ALL conducted in Pakistan (%).[3–14]

Cytogenetic abnormality	Present Study	Fadoo *et al.* 2015[3]	Shaikh *et al.* 2014[8]	Awan *et al.* 2012[9]	Iqbal *et al.* 2006[10]	Siddiqui *et al.* 2010[11]	Faiz *et al.* 2011[12]	Amjad *et al.* 2019[13]	Nizzamani *et al.* 2016[14]
BCR-ABL	5.0	7.3	7.1	44.5	49.0	3.5	24.0	1.30	6.0
KMT2A	2.3	4.6		16.8	15.5	5.0	14.0	3.0	
ETV6-RUNX1	8.6	13.2		17.8	12.6	3.5	9.7	45	
t (1:19)	5.8		1.6	1.9	2.0	0	2.0		2.0

Table-3: Incidence of recurrent cytogenetic aberrations in Paediatric Acute Leukaemia and Comparison with other Asian & Western populations.[1,3,15–24]

Paediatric ALL & AML									
		Present Study	**India[1]**	**Pakistan[3]**	**Egypt[15] & Saudi Arabia[16]**	**Iran [17]**	**China[18,19]**	**Japan[20,21]**	**Western[22,24]**
B-ALL	**Diploidy**	62				37.5			
	Hypodiploidy	0.24	8	5.1		4.2	3		2-5
	Hyperdiploidy	24.3	44	10.7	16	34.1	12		25–30
	Trisomy 4,10,17	11.6	41						40–60
	Deletions	3.8							
	t(1:19)	5.8	7		2		3	6	5–6
	t(17:19)	0.24	0.6						
	BCR-ABL	5.0	6	7.3	10	7.9	6	3	2–5
	KMT2A	2.3	3	4.6	5	1.5	1.5	1.6	5–8
	ETV6-RUNX1	8.6	12.2	13.2	10		13-19	13	20–25
AML	***RUNX1/RUNX1T1***	26.4	26		12–18.9			25	12–15
	CBFB/MYH11	6.1	5		7				
	PML-RARA	7.9	7.2		6		16-18		4.4–21.9

DISCUSSION

The comprehensive cytogenetic analysis of paediatric leukemic patients in our cohort studied the association of various factors that involves age, incidence, gender and genetic factors. Different other studies from around the world have shown geographic heterogeneity in acute leukaemia. The prevalence of different cytogenetics in childhood acute leukaemia in the Pakistani population however is not clear due to a lack of large scale studies and leukaemia registries. Hence, the rationale of the present study was to observe a large cohort and demonstrate the spectrum of cytogenetic abnormalities and their association with different etiological factors, thereby improving our understanding of the biology of the disease which may help in better care and management of the disease thus improving survival.

Our study demonstrated that in B-ALL, the distribution of the disease within age and gender was similar to reports from other local and international studies. The mean age of the study population was 6.8 years which is similar to that reported in other studies of Pakistan. ALL is more common in males than in females. Our study shows twice as many males which is reflective of the regional data of the disease.[3] B-ALL has diverse cytogenetic subtypes which have a significant impact on risk stratification and hence remain strong independent predictors of disease outcome.[1] Interphase FISH analysis for the mentioned FISH probes remains a mainstay for risk grouping of the B-ALL patients. Table-2 summarizes the reported prevalence of prognostically significant ALL specific cytogenetic abnormalities in different studies from Pakistan.

Prevalence of BCR-ABL1 fusion t (9:22) (q34; q11.2) ranges from 3–5% in paediatric ALL across the world. In our study, the t(9;22) incidence in childhood ALL was 5.1% while another study from Pakistan by Fadoo *et al.*[3] reported 7.3% in their respective cohort. The prevalence in our study is comparable to the Indian population (6%) whereas it showed variable frequencies of 2–6% in Western and other Asian populations.[1] Studies from Saudi Arabia and Egypt show a relatively higher prevalence (10%) of t (9:22) in their population.[15,16]

Translocations involving the KMT2A (11q23) gene occur in up to 5% of childhood and adult B-ALL.[1] We reported a lower incidence of KMT2A rearrangement 2.3% in comparison to other studies from Pakistan as shown in Table-2. Results comparable to our study are reported by an Iranian study that reported a much lower incidence of 1.1% in their cohort.[17] Table-3 shows a comparison of the present study and some similar studies from other Asian countries[1,16,18–21] and Western population[22–24] Incidence of KMT2A rearrangement varies in different populations and different studies from Asia reports less prevalence than that of the Western cohorts. However, KMT2A rearrangement is more prevalent in the infantile group; our study had only 7 patients in this age group; only 1 of whom was positive for MLL. The rest of the KMT2A rearrangement-positive patients were > 1 year of age. Pattern of age distribution in KMT2A rearrangement and t (1;19) positive groups as observed in other studies, suggested that these translocations tend to occur in lower age groups.[1]

ETV6-RUNX1 was the most common translocation in our B-ALL group. This translocation is seen in 17–27% of childhood ALL and has been correlated with favourable outcomes. It shows variable frequency ranging from 12–25% in international literature and 3–17% in local studies as shown in Table-2, but showed a lower incidence of 8.6% in our study. Literature shows that the prevalence of ETV6-RUNX1 fusion gene is maximum in the childhood age group. A recent study from Pakistan reported 3.5% ETV6-RUNX1 in their cohort which is lower than ours; all of their patients were less than 10 years of age.[11] Some other studies from Pakistan, India and China have demonstrated 12–13% previously.[1,3,18,19] Alkhayat *et al*. showed the prevalence of 10% in Arabic population which is slightly higher than our reported prevalence.[15]

Data from various Asian studies also indicated a low prevalence (13–19%) of ETV6/RUNX1 as compared to the Western population.[1,16,18–24] The peak incidence of ETV6/RUNX1 was in the age group of 1–10 years as reported in other studies from Pakistan as well as in studies from other Asian countries with only 3 of our patients elder than 10 years of age. The observed variation in the reported prevalence as seen in Table 2 and noticeable differences in the prevalence of BCR-ABL, ETV6-RUNX1, and KMT2A rearrangement may be due the different ethnicity and practice of selective testing available across Pakistan.

Table-3 summarizes the comparison of our study with the regional and international reported data. Karyotype analysis in the B-ALL cohort revealed a variety of other chromosome number alterations. The incidence of hyperdiploidy in our leukemic cohort was (24.3%) which is higher than that reported in previous studies. Another study from Pakistan karyotyped 316 patients and reported a much lower prevalence of hyperdiploidy to be 10.7% in leukemic children.[3] A much higher prevalence of hyper diploidy was seen in the Indian population (44%) and the paediatric population in Iran (34.1%).[17] However, our reported prevalence is slightly higher than the Chinese (12%) and Arabic population (16%) and is slightly lower than the Western population (25-30%) [16, 18, 19, 22-24]. Hyperdiploidy was associated with lower age group 1–10 years of age with the majority of our patients (91%) younger than 10 years of age which is comparable to the international literature (*p*-value <0.05). As reported in the literature, hyperdiploidy in childhood ALL is strongly associated with the gain of chromosomes 4, 10, 17 and 21.[2,13] We observed 11.6% of patients harbouring Trisomy 4, 10 or 17 alone or in combination.

Hypodiploidy is characterized by fewer than 45 chromosomes and is seen in 5–8% of total B-ALL cases.[1,25] We only had 1 patient with hypodiploidy and haploidy, the incidence of hypodiploidy is lower than that observed in other studies from Pakistan (5.1%), India (8%), Iran (4.2%)[21] & Western (2-5%) cohorts[1,3] Xin Li *et al*.[7] found that 4.9% of paediatric ALL showed hypodiploidy, a similar prevalence (4.2%) was demonstrated in an Iranian study conducted by Safaei A *et al*.[17] Near haploidy with chromosome numbers, 23–29 is a rare hypodiploid group in B-ALL occurring in 0.3–0.5% in ALL group with similar frequency (0.24%) in our cohort falling within the universal frequency of <1% [25]. Shaikh *et al*. karyotyped 153 leukemic children and reported 13.4% hyperdiploidy in their cohort. The prevalence of near haploidy and hypodiploidy in their study was similar to our study, i.e., <1%.[8] It is interesting to note that variable prevalence of certain cytogenetics have been reported across Pakistan. Amjad *et al*. represent a cohort of 150 patients and showed a much lower prevalence of BCR-ABL (1.30%), similar KMT2A rearrangement (3.0%) and a much higher prevalence of ETV6-RUNX1 (45%) in their respective study group.[16] The prevalence of hyperdiploidy was 32% while hypodiploidy was observed in 15% of patients.[16] Trisomy 21 and ETV6 allelic loss were the most frequent additional abnormalities in ETV6/RUNX1 positive group, however, these abnormalities were common in the overall B ALL patients.

The translocation (1; 19) is another cytogenetic subgroup of BALL that occurs more frequently in children than adults. Translocation (1;19) (q23; p13.3)/TCF3(E2A)-PBX1 occurs in 1–3% of adults and 16% of paediatric ALL [26], and can be in either balanced or unbalanced form. However, t (1;19)/TCF3-PBX1 was found to be an independent risk factor for isolated CNS relapse in children. The incidence in our paediatric population is found to be 5.8%. This is comparable to Western data and a few Asian studies.[1] However, lower frequency is reported in some other studies from Pakistan (Table 2), the Chinese population [18,19] and in Arabic population.[16] Our study had a total of 24 patients (5.8%) with t(1:19) out of which two patients (8.3%) had concomitant deletion.

Table-3 summarizes the prevalence of recurrent chromosomal abnormalities in paediatrics AML in the present study and compares the incidence with different populations from India, China, Japan and Western countries.[1,18–24] In the present study, the median age of Paediatric AML is 8 years which is comparable to the Western population and other Asian populations. In paediatric AML, the prevalence of RUNX1/RUNX1T1 t (8;21) was higher (26.4%) than that of the Western population[22–24] and comparable to that in the Indian[1] and Japanese[20,21] population (25–26%). A study in Saudi Arabia reported the prevalence of t (8:21) to be 18.9% in their cohort.[23] The incidence of INV16 CBFB-MYH11 in our study was 6.1% which is comparable to other regional and international studies having a significantly large cohort (Table-3).[1]

The cumulative prevalence of core binding factor acute leukaemia in our cohort is 32.5%, which is higher than the Western population; however

Japanese studies show an even higher prevalence in their cohort [20,21]. This is much higher than that reported in the adult population.

However, the prevalence of t (15;17) (7.9%) was similar to that of the Indian and Western population[1,22–24] and was less than that in the Chinese population (16–18%). The higher incidence of t (15;17) in the Chinese population could be due to the high prevalence of APL in their population.[1] Some studies from Europe show variable prevalence across the continent with the lowest prevalence of acute promyelocytic leukaemia (APL) among acute myeloid leukaemia (AML) in Germany (4.0%)[27] and the highest in Italy (21.9%)[28]. A frequency of t (15:17) similar to our study was found in the United Kingdom (7.6%).[29] There was not much local data available on the prevalence and outcomes of acute promyelocytic leukaemia (APL) in the paediatric population.

CONCLUSION

The present study demonstrated a wide spectrum of heterogeneity in paediatric acute leukaemia that involved various factors, such as age, gender and prevalence of distinct cytogenetic subgroups. Our cytogenetics data, when compared with local, other regional and international studies, revealed geographic heterogeneity which may be due to different genetic makeup, ethnicity, and environmental exposure; all of which can influence the underlying genetic susceptibility. However larger trials are needed in developing countries, next generation sequencing and microarray can add to the valuable data and is the need of time to have a better understanding of the disease biology, prognosis and better outcomes.

Limitations of the study: Comparable results of FISH and karyotype were not available in all cases. Karyotype was not performed in cases of acute myeloid leukaemia and T-ALLs.

AUTHORS' CONTRIBUTION

FM, OJ, NM: Conceptualization. OJ, NM, NJ: Data collection and analysis. OJ, FM: Writing-original draft. SJ, NJ, OJ, MF: Writing- review and edit. OJ, SM: Tables and Analysis.

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