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Original Research Article.

Frequency of BCR-ABL Positive Acute Lymphoblastic Leukaemia in a Single Centre Study in Dhaka

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ABSTRACT

Background: BCR-ABL positivity is the most common genetic abnormality associated with adult ALL. BCR-ABL positive ALL has an aggressive clinical course with a variable leukocyte count at presentation and is associated with a poor prognosis.

Aim: The aim of the study was to assess the frequency of BCR-ABL positive acute lymphoblastic leukaemia in our context.

Methodology: This cross-sectional observational study enrolled total 38 ALL patients from August 2018 to July 2019 who came to the Department of Haematology in Bangabandhu Sheikh Mujib Medical University. BCR-ABL was detected by RT-PCR. Clinical and laboratory information was recorded with a semi structured questionnaire.

Results: Among 38 Acute Lymphoblastic Leukemia patients, the median age at diagnosis was 27.5 years with male (76.3%) predominance. Among the positive group most common immunophenotype was B lineage 13(86.8%) and one was T-Acute Lymphoblastic Leukemia. BCR-ABL rearrangements was found in 14(36.9%) patients with the distribution of p190 (85.7%) and p210 (14.3%). Aberrant myeloid marker was found in 9(64.3%) patients who were BCR-ABL positive. CD13 and TdT were statistically significant ($p<0.05$) when compared between BCR-ABL positive and negative cases. Age, sex, clinical features, haematological profile, immunophenotyping diagnosis were not statistically significant when compared between BCR-ABL positive and negative group.

Conclusion: These results confirms the high frequency of BCR-ABL rearrangements in ALL patients in our country. We recommend to identify the BCR-ABL transcript type in every patient with ALL at diagnosis, using a RT-PCR verified method for p190/p210.

Key words: Acute Lymphoblastic Leukaemia (ALL), BCR-ABL.

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INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is a haematological malignancy characterized by abnormal proliferation and accumulation of immature lymphoid cells in the bone marrow and lymphoid tissues[1,2] (Azevedo et al. 2014; Terwilliger and Abdul-Hay, 2017).

Evidence suggested that, it is the most common malignant disease in childhood, peaking in incidence between ages 2 to 5 years[3] (Pui et al. 2008).

In contrast, ALL only accounts for approximately 20% of acute leukemias in adults with another peak of incidence were observed

above the age of 50 years[2] (Terwilliger and Abdul-Hay, 2017). Within scarcity of large population based study, one report from multicenter document suggested that, in Bangladesh 14.1% of all hematological malignancies were ALL with median age 27 years[4] (Hossain et al. 2014).

While in the United States, the incidence of ALL was estimated 1.6 per 100000 populations[2] (Terwilliger and Abdul-Hay, 2017). This malignant disorder of blood progenitor cells originates from the uncontrolled clonal expansion of immature lymphoid progenitors that have faced with a series of disastrous genetic alternations. Common genetic lesions include structural chromosome rearrangements, aneuploidy, and cooperative mutations in genes that encode for transcription factors regulating lymphoid development, tumor suppressors, proteins that regulate cell cycle progression, and epigenetic modifiers[5] (Li et al. 2015; Iacobucci and Mullighan, 2017).

BCR-ABL positive ALL is the most common genetic abnormality associated with adult ALL which arises from a reciprocal translocation involving the ABL1 oncogene on the long arm of chromosome 9 and a breakpoint cluster region (BCR) on the long arm of chromosome 22, t(9;22)(q34;q112)[6,7] (Ravandi and Kebriaei, 2009; Leoni and Biondi, 2015). The resulting fusion gene, BCR-ABL1, encodes for a chimerical oncoprotein (BCR-ABL) with constitutive tyrosine kinase activity, which leads to uncontrolled cell proliferation, reduced apoptosis, and impaired cell adhesion[8] (Piccaluga et al. 2007).

In their study[6,7] Ravandi and Kebriaei, (2009); Leoni and Biondi, (2015), stated that the frequency of BCR-ABL positive ALL increases with age and approximately 25 – 40% of adult ALL was BCR-ABL positive, while among children it was less prevalent (3 - 5%).

BCR-ABL positive ALL had an aggressive clinical course with a variable leukocyte count at presentation and increased risk for central nervous system (CNS) involvement during the course of treatment[9,10] (Enrico and Milone, 2013; Bleckmann and Schrappe, 2016). It was associated with poorer prognosis compared with BCR-ABL negative ALL. The presence of the BCR-ABL transcript was done by real time polymerase chain reaction (RT PCR). Beside this, quantification of BCR-ABL transcript by real time PCR (RT PCR) had prognostic relevance also[10,11] (Bleckmann and Schrappe, 2016; Thomas and Heiblig, 2016).

Treatment of BCR-ABL positive ALL patients with conventional chemotherapy showed no substantial improvement in long-term outcomes, rather high relapse rates were reported[7,8] (Piccaluga et al. 2007; Leoni and Biondi, 2015). Again, allogeneic haemopoietic stem cell transplantation (allo HSCT) which was the standard strategy in adult BCR-ABL positive ALL patients also demonstrated poor survival. But after the introduction of effective tyrosine kinase inhibitors (TKIs), such as imatinib and dasatinib, the treatment of BCR-ABL positive ALL patients were undergone a revolutionary transformation with improved outcomes not only for patients who were eligible for and were able to receive allo HSCT but also for those who were not candidates for or were unable to undergo such treatment[6,10] (Ravandi and Kebriaei, 2009; Bleckmann and Schrappe, 2016).

Till date there were no sufficient statistics related to the BCR-ABL positive ALL in our country. Therefore, the purpose of the study was to observe the frequency of BCR-ABL positive ALL with an aim for betterment of the patients with ALL.

OBJECTIVES

General Objective

- To determine the frequency of BCR-ABL positive acute lymphoblastic leukaemia.

Secondary Objectives

- To assess the clinic-laboratory characteristics of the BCR-ABL positive ALL patients.

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MATERIALS AND METHODS

Study Design: This was a cross sectional observational study.

Place of Study: This study was done at the Department of Haematology Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka, Bangladesh.

Study Period: August 2018 to July 2019.

Study Population: Indoor & outdoor patients with acute lymphoblastic leukaemia (confirmed by bone marrow study and immunophenotyping), in department of Haematology in BSMMU, Dhaka.

Sampling Method: Purposive sampling.

Methods:

The study group comprised 38 diagnosed ALL patients of any age group of both gender came to haematology dept. of Bangabandhu Sheikh Mujib Medical University (BSMMU) for outdoor and indoor service from August 2018 to July 2019. The diagnosis was established by clinical, cytomorphological and immunophenotypic criteria. This study was approved by the Research Ethics Committee of the institution and the study was conducted in accordance with the Declaration of Helsinki 2008. Clinical and laboratory data were obtained from a semi structured questionnaire. Samples of peripheral blood and bone marrow were collected after informed consent had been given. The identification of the p190 and p210 BCR-ABL gene rearrangements was performed by reverse transcription polymerase chain reaction (RT-PCR) according to the international BIOMED-1 protocol.

Data Analysis

The data collected was edited by the principle investigator on the same day of collection. Data obtained was recorded, then entered into the computer using Microsoft excel and analyzed with SPSS version 23.0 software package with the help of a statistician. Qualitative variables (sex) of these studies were expressed as percentage. Quantitative variable (age) was expressed as mean ± standard deviation. Categorical comparisons were performed using chi-square test. Continuous variables were expressed as mean values ± standard deviation and compared using Student's t-test/unpaired t-test. Validity test was done to detect sensitivity, specificity, accuracy, positive predictive value and negative predictive value of the myeloid aberrant antigens. For all statistical tests, P –value less than 0.05 was considered as statistically significant.

SELECTION CRITERIA

Inclusion Criteria

- All newly diagnosed ALL cases.
- ALL cases attended to haematology department (indoor and outdoor).

Exclusion Criteria

- Partial or complete treatment cases of ALL
- Secondary acute lymphoblastic leukaemia.

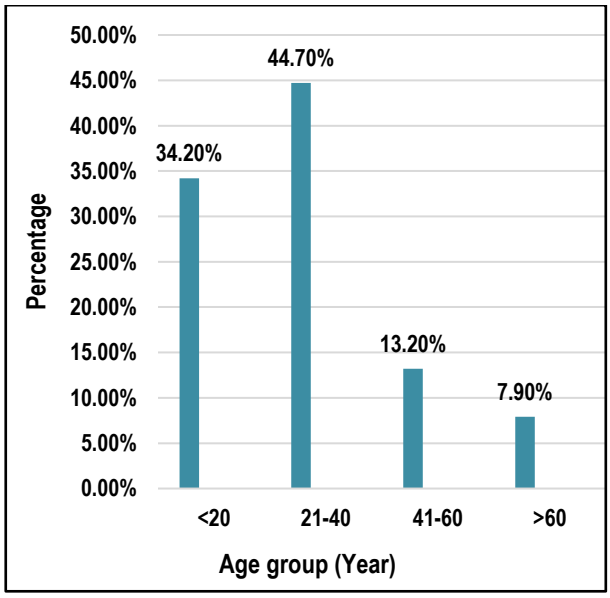

Figure I: Bar diagram showing age distribution of the study patients (n=38)

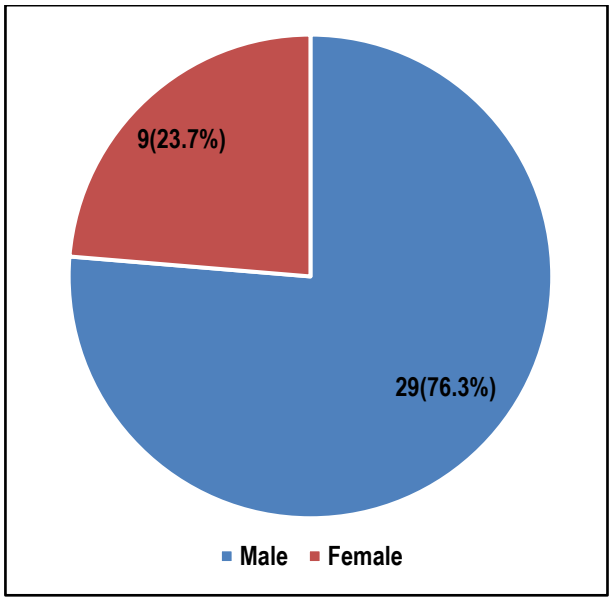

Figure II: Pie chart showing sex distribution of the study patients (n=38)

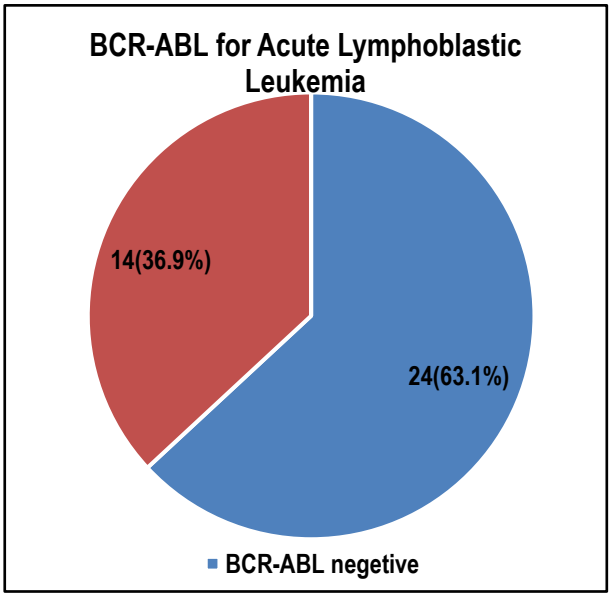

Figure III: Pie chart showing BCR-ABL positivity for ALL patients (n=38)

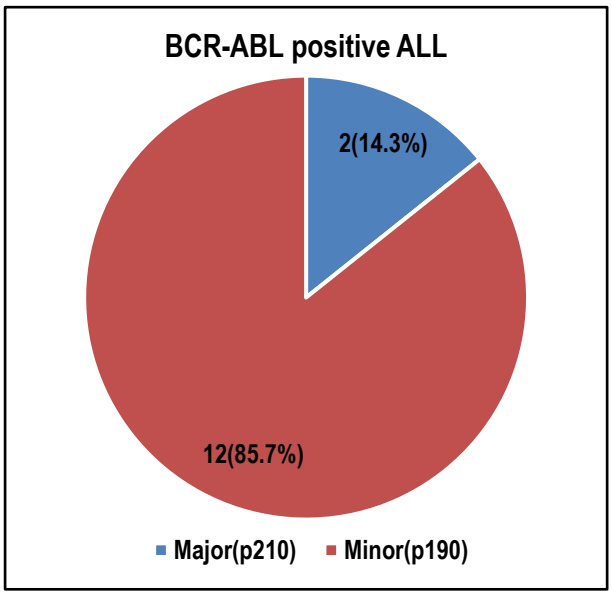

Figure IV: Pie chart showing BCR-ABL transcript frequencies of the study patients.

Table I: Showing laboratory parameters of study patients.

Clinical features	N%
Hb (gm./dl) median (range)	9.7 (4.9 – 12.6)
WBC count (/cumm of blood) median/range	10250 (1000 – 233000)
Blast% median/range	50% (0% - 90%)
Platelet (/cumm) median/range	38500 (5000 – 216000)
Bone Marrow morphology	N%
ALL	35 (92.1%)
AML	1 (2.6%)
Acute Mixed Cell Leukemia	1 (2.6%)
Lymphoid disorder	1 (2.6%)
Immunophenotyping	N%
Precursor B ALL	13 (34.2%)
B ALL	20 (52.6%)
T ALL	5 (13.2%)

Table II: Showing clinical and laboratory features of BCR-ABL negative and BCR-ABL positive ALL of study patients.

Variables	BCR-ABL negative N 24	BCR-ABL positive N 14	P - value
Age (years) Median N	27	28.5	0.532^{ns}
Sex N (%) Male/Female	17/7 (70.8%/ 29.2%)	12/2 (85.7%/ 14.3%)	0.264^{ns}
Hb (gm./dl) Median (range)	10 (4.9 – 11.5)	9.6 (5.9 – 12.6)	0.966^{ns}
Leukocytes (/cumm of blood) Median (range)	7350 (1000 – 233000)	11250 (1780 – 162000)	0.767^{ns}
Platelets (/cumm of blood) Median (range)	37500 (5000 – 216000)	41000 (6000 – 120000)	0.559^{ns}
Lymphoblast's % (range%)	50% (0 – 90%)	45% (3 – 90%)	0.967^{ns}
Immunophenotype – N (%)			0.701^{ns}
Precursor B – ALL	8 (33.3%)	5 (35.7%)	
B –ALL	12 (50%)	8 (57.1%)	
T - ALL	4 (16.7%)	1 (7.1%)	

RESULTS

This cross-sectional observational study was carried out with the aim to assess the frequency of BCR-ABL positive acute lymphoblastic leukaemia. Patients' age, sex, WBC count, platelet count, blast counts have also been analyzed in association with BCR-ABL positivity.

Figure I show that majority (44.7%) patients belonged to age 21-40 years. The mean age was found 30.0±14.6 years and median age 27.5 years with range from 7 to 65 years.

Figure II shows that more than three fourth (76.3%) patients were male and (23.7%) patients were female. Male female ratio was 3.2:1.

Table I shows median hemoglobin was found 9.7 g/dl, total count WBC 10250.0 /cumm of blood, blast 50.0%, platelet count 38500.0 /cumm of blood, bone marrow majority 35 (92.1%) patients diagnosed as ALL, 1 (2.6%) AML, 1 (2.6%) acute mixed cell leukaemia and 1 (2.6%) lymphoid disorder, immunophenotyping findings, B-ALL was found in 20 (52.6%) patients, precursor B-ALL in 13 (34.2%) and T-ALL in 5 (13.2%) cases.

Figure V shows that positive for BCR-ABL in 14 (36.9%) and negative for BCR-ABL in 24 (63.1%) cases.

Figure VI shows that BCR-ABL was found positive in 14 cases, among them minor (p190) fusion protein was present in 12 (85.7%) and major (p210) fusion protein was present in 2 (14.3%) cases.

Table II shows median age was found 28.5 years in positive BCR-ABL group and 27.0 years in negative BCR-ABL group. The difference was not statistically significant (p value 0.532^{ns}) between two groups.

BCR-ABL positivity was found in 12 (85.7%) male and 2 (14.3%) female. BCR-ABL negativity was found in 17 (70.8%) male and 7 (29.2%) female. The difference was not statistically significant (p value 0.264^{ns}) between two groups.

Median hemoglobin (p value 0.966^{ns}), total count of WBC (p value 0.767^{ns}), platelet count (p value 0.559^{ns}) and blast (p value 0.967^{ns}) were not statistically significant (p>0.05) when compared between BCR-ABL positive and negative group. Immunophenotypically in BCR-ABL positive group majority patients were B- ALL 8 (57.1%) and in BCR-ABL negative group it was 12 (50%). The difference was not statistically significant (p value 0.701^{ns}) between two groups.

DISCUSSION

This was a cross sectional, observational study carried out with an aim to assess the frequency, clinical and laboratory characteristics of the BCR-ABL positive ALL patients. A single centre study from August 2018 to July 2019 in indoor and outdoor Haematology Dept. of BSMMU, Dhaka. The present study findings were discussed and compared with previously published relevant studies.

In this study, it was observed that majority (44.7%) patients belonged to age 21-40 years. The mean age was found 30.0±14.6 years and median age 27.5 years with range from 7 to 65 years. Similarly, a study in Mexico[12] by Olarte-Carrillo et al. (2015) reported that mean age was 29 years. Another study in Brazil [1] conducted by Azevedo et al. (2014) where they found majority 23(56.0%) patients belonged to age 18-34 years and median age was 33 years. Study in India[13] by Bhatia et al. (2013) found median age 40 years. Another study[14] by Corrente et al. (2018) found median age of 49 years. The reason for the difference of age at presentation in various regions of the world may be due to geographic/ ethnic influence.

We found more than three fourth 29 (76.3%) patients were male and 9 (23.7%) patients were female. Male female ratio was 3.2:1. Study[1] conducted by Azevedo et al. 1 (2014) which showed male was found 61.0% and female was 39.0%. Another study[15] by Pfeifer et al. (2012) reported that male was 52.3% and female was 47.7%. Another study[13] documented by Bhatia et al. (2013) where they found M/F ratio was 2.3:1.

Regarding the haematological profile we found that median hemoglobin was 9.7 g/dl, while median WBC count was 10,250 /cu mm, median platelet count was 38,500 /cu mm and median blast was 50.0%. In a study[1] conducted by Azevedo et al. (2014) where they documented that median hemoglobin was 8.5 g/dl, median WBC count was 47 ×10^9/L, median platelet was 47 ×10^9/L, median blast was 78%. Our findings of haemoglobin and platelet were consistent with other study but there were dissimilarities between WBC and blast counts. This may be due to smaller sample size in our study.

Regarding bone marrow diagnosis in this study it was observed that majority 35 (92.1%) patients was diagnosed as ALL, 1 (2.6%) as AML, 1(2.6%) as acute mixed cell leukaemia and 1 (2.6%) as lymphoid disorder. In 35 (92.1%) cases there was a similarity and in 3 (7.9%) cases there was a difference between morphological

diagnosis and immunophenotyping findings. In a study[16] Gupta et al. (2015) showed during morphological diagnosis of ALL patients it was found that morphologically 60 (89%) marrow were of ALL, 3 (4%) of AML and 4 (6%) were of acute undifferentiated leukemia and stated that in 73% cases morphological and immunophenotyping diagnosis was similar. In 27% cases there was a difference between morphological diagnosis and immunophenotyping findings.

Considering immunophenotypic findings in our study it was found that 86.8% cases were from B-lineage which consisted of 20 (52.6%) B-ALL and 13 (34.2%) precursor B-ALL. Remaining 13.2% cases were from T-ALL. These findings were consistent with previous several studies. In a study[5] Li et al. (2015) showed that in their study there was an increased incidence of B-cell ALL (77.78%). Another one[1] by Azevedo et al. (2014) stated that B-ALL was found in 21 (76.0%) and T-ALL was in 9 (22.0%) cases in their study. Further one more study[17] by Arana-Trejo et al. (2016) found that B-ALL was about 80%.

In this study we observed that 14 (36.9%) cases were positive for BCR-ABL and 24 (63.1%) were negative for BCR-ABL. Among the BCR-ABL positive 14 cases, 12 (85.7%) had minor (p190) and 2 (14.3%) had major (p210) fusion protein**.** Among BCR-ABL positive cases B cell lineage were 13 (92.8%) and T-ALL were 1 (7.1%) cases. Out of five T-ALL cases 1 (7.1%) was found positive for BCR-ABL**.** These findings of this study mostly correlated with the findings of several other studies. Like one study[1] by Azevedo et al. (2014) found that 14 (34%) cases were BCR-ABL positive with transcriptions p190 (28%), p210 (50%) and both positive (22%). Another one[18] by Gleiβer et al. (2002) found among 478 adult ALL patients 37% were positive for the *BCR-ABL* fusion gene including the p190 (77%) and p210 (20%) rearrangements and both (3%). A study[19] by Dombret et al. (2002) showed among 154 adult ALL patients: p190 (68%), p210 (28%) and both (4%) and other study[20] by Hamid, M. and Bokharaei, H., (2017) described among their 12.5% BCR-ABL positive cases 66.7% were p190 and 33.3% were p210. Another study[14] observed by Corrente et al. (2018) documented BCR-ABL positivity 40.9% and among them 72.2% displayed p190 and 27.8% p210 fusion protein and also another[17] by Arana-Trejo et al. (2016) found that in their study among BCR-ABL positive cases B-ALL was 80%, bilineal 5%, other had no data. A older study[21] by Quentmeier et al. (2005) stated majority of BCR-ABL positive ALL cases belonged to the category of B-cell precursor ALL, whereas BCR-ABL positive T-ALL cases are rather rare and reported T-ALL cell line expressing the e6-a2 *BCR-ABL1* fusion transcript.

In our study BCR-ABL positive group displayed male was 12(85.7%) and female was 2(14.3%). Among them 10(83.3%) male and 2(16.7%) female had p190 and 2(100.0%) male had p210 fusion protein. The difference was not statistically significant (p>0.05) between two groups. A study[5] by Li et al. (2015) stated that the BCR-ABL positive rates in males and females were 58% and 32%, respectively (P=0.931). Another[12] by Olarte-Carrillo et al. (2015) found male were 53.0% and female were 47% among BCR-ABL positive group. The present study considered that this difference may be associated with small sample size of this study, exposure to environmental pollution including pesticides, geographical and ethnic variation.

In this study it was observed that haematological parameters of BCR-ABL positive cases such as median hemoglobin (9.6 g/dl), WBC count (11,250 /cu mm), platelet count (41,000/cu mm) and blast (45%) were not statistically significant (p>0.05) when compared between BCR-ABL positive and negative group. These findings were consistent with other studies[12,1,13] conducted by Olarte-Carrillo et al. (2015), and Azevedo et al. (2014). Bhatia et al. (2013) found all positive cases had high WBC count (>20×109/L) and low platelet count (<100×109/L). Some investigators[22, 23] Westbrook et al. 1992; Schrappe et al. 1998), found no significant difference in WBC count, percentage of blasts while others[18] (Gleissner et al. 2002) found that BCR-ABL positive children and adults had higher WBC counts.

CONCLUSION

Frequency of BCR-ABL expression by RT-PCR has not previously been reported in Bangladesh. Our study confirms the high frequency of BCR-ABL rearrangements in ALL patients in our country. It is also found that a significant number of BCR-ABL positive ALL patient expressed aberrant myeloid antigen in immunophenotype. Identification of BCR–ABL transcript is important, especially in B-ALL cases as a significant proportion of them are positive. We recommend to identify the BCR-ABL transcript type in every patient with ALL at diagnosis, using a RT-PCR verified method for p190/p210.

STRENGTHS OF THE STUDY

The study was conducted under the guidance of designated guide. Thesis protocol was reviewed by Institutional Review Board (IRB) of BSMMU.

LIMITATIONS

- The study population was selected from one selected hospital –BSMMU, Dhaka. So, the results of the study may not reflect the exact picture of the country.
- The present study was conducted at a very short period of time.
- Small sample size was also a limitation of the present study.
- Patients were not sorted as children and adults, which may exert certain influences on the conclusions.

However, the present study continues to be valuable, as it enriches the knowledge of the clinical characteristics of ALL in Bangladesh.

RECOMMENDATIONS

- Study period may be extended.
- Further multi-centered prospective analytical study with larger sample size is recommended.

ABBREVIATIONS:

ABL = Abelson; Allo HSCT = Allogeneic hemopoietic stem cell transplantation; ALL = Acute lymphoblastic leukemia; AML = Acute myeloid leukemia; BCR = Breakpoint cluster region; BCR- ABL = Breakpoint cluster region- Abelson; BMI = Body mass index; BSMMU = Bangabandhu Sheikh Mujib Medical University; CBC = Complete blood count; CML = Chronic myeloid leukemia; CNS = Central nervous system; IRB = Institutional Review Board; PCR = Polymerase chain reaction; Ph = Philadelphia; RT = Real time; RT PCR = Real time polymerase chain reaction; SD = Standard deviation; SPSS =

Statistical Package of Social Sciences; TKIs = Tyrosine kinase inhibitors; WBC = White cell count; WHO = World Health Organization.

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