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HEMATOLOGICAL AND DEMOGRAPHIC PROFILE IN PATIENTS WITH BCR-ABL TRANSCRIPTS POSITIVE CHRONIC MYELOID LEUKEMIA IN A TERTIARY CARE HOSPITAL, BANGLADESH.

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ABSTRACT

Background: Chronic Myeloid Leukemia (CML) with BCR-ABL positivity is one of the most common genetic abnormalities among blood neoplasm that usually requires regular blood examination to diagnose. If detected early, it has a high cure rate. This study aims to assess the hematological and demographic profile among BCR-ABL (p210) transcripts positive CML patients in a tertiary care hospital, Dhaka, Bangladesh. **Methods:** Forty-five CML patients who came to Microbiology and Immunology department, Bangabandhu Sheikh Mujib Medical University and detected as BCR-ABL positive cases were enrolled in this study. **Results:** Among forty-five BCR-ABL (p210 kDa) positive CML patients, most common age group affected was between 35-44 years. Hemoglobin value ranged from 12.2 g/dL to 16.9 g/dL with a mean value of 10.44 ± 2.48g/dL. Most of the patients (57.79%) had a hemoglobin level between 7 g/dL to 11 g/dL. Most of the patients (48.89%) had their leukocyte count $>100\times10^9$/L. Platelet count ranged from 16×10^9/L to 2100×10^9/L with a mean value of $409.13 \pm 380.52\times10^9$/L. **Conclusion:** Unlike the western countries, Chronic Myeloid Leukemia more prevalent in young age group in Bangladesh. Chronic myeloid leukemia patients displayed variable hematological presentation.

KEYWORDS: Chronic myeloid leukemia, p210 kDa, Bangladesh.

INTRODUCTION

Chronic myelogenous or myeloid leukemia (CML) is one of the common types of myeloproliferative neoplasm characterized by the increased and uncontrolled growth of myeloid cells in the bone marrow, and eventually their accumulation in the peripheral blood.[1]

Cytogenetic abnormality of Philadelphia (Ph) chromosome is associated with CML.[2] The Philadelphia chromosome arises from a reciprocal translocation t (9; 22) between chromosome 9 and 22.[3,4] Philadelphia chromosome is present in approximately 95% of patients with CML and this is one of the definitive diagnostic marker.[5] Ph chromosome may not be demonstrated in few CML patients and might have normal karyotype. Among one third of these patients might have occult BCR–ABL fusion gene (Ph chromosome negative and BCR–ABL positive).[6]

The ABL protooncogene has a similarity with Abelson murine leukemia found on chromosome 22, and the BCR gene (Breakpoint cluster region) is mapped to chromosome 9. Ph chromosome results from joining of 3' sequences of the tyrosine kinase c-ABL proto-oncogene on chromosome 9 to the 5'sequences of the BCR gene on chromosome 22.[7] Presence of BCR–ABL in these cases can be confirmed by molecular analysis.[8]

Major (M-BCR), minor (m-BCR), and micro (µ-BCR) cluster regions are the three main break point in BCR gene.[4] On chromosome 22, majority of CML patients have breakpoints in M-BCR region.[9] Among majority of CML patients, the classic transcript found is b2a2 or b3a2, formed by fusing exon 13 (b2) or exon 14 (b3) of BCR to exon 2 (a2) of ABL gene, respectively. Both of them code for a 210 kDa (p210) novel protein. Reverse transcriptase PCR (RT-PCR) test is one of the most sensitive molecular techniques for identification of BCR–ABL transcripts associated with CML.[10] Among several RT-PCR techniques Multiplex RT-PCR method is currently one of the most popular methods designed and optimized for detecting the transcript of M-BCR and m-BCR breakpoints of BCR–ABL variants in patients with CML.[11] In this study, multiplex RT-PCR was used

for the detection of all major BCR–ABL transcripts in CML patients.

Fifteen percent of cases were found at adult ages among the total CML patients.[12] Average age varies between sixty and sixty-five years in another study.[13] Ten percent of Children and adolescents were diagnosed as CML.[14] Male predominance was found slightly higher than female.[15] Various prognostic systems have been used to stratify the risk of the CML patients on the basis of age, sex and their hematological parameter.[16,17] These parameters can guide treatment decisions, response to treatment and patient's prognosis follow up after treatment.

Bangladesh is a developing country with densely populated region where food adulteration is one of the major threats. As a result, various genetic and nongenetic diseases affected patients are increasing day by day. In addition to that, exposure to high level of radiation, smoking, exposure to pesticides increasing the susceptibility to various forms of cancers. Which consequences the increasing rate of CML and ALL patients at an appalling rate.[18]

This study was aimed to observe the hematological and demographic profile among CML patients along BCR-ABL p210 transcripts positive patients in a tertiary care hospital, Dhaka.

MATERIAL AND METHODS

This cross-sectional study was carried out from January 2022 to June 2022. A total of 45 patients with established CML irrespective of age and gender, visited the Bangabandhu Sheikh Mujib Medical University (BSMMU), during the study period were recruited for the study. Molecular analysis was carried out in the Microbiology and Immunology Department of BSMMU. Informed consent was taken from each patient. The study was approved by the ethical review committee of the Department.

Ten ml of venous blood were aspirated from patients by clean venipuncture and delivered into sterile EDTA tubes (3ml), then stored at 4◦C to be used within three days for molecular study, second EDTA tubes (2ml) for doing complete blood pictures using Sysmex Automated Hematology (XN-1000^{TM}).

Molecular Diagnosis

The molecular diagnosis of CML included three steps: RNA isolation, cDNA preparation and qPCR.

i. RNA isolation: RNA isolation was performed using QI Amp nucleic acid extraction kit.
ii. cDNA preparation: The cDNA preparation was performed using cDNA reagents of TRU-PCR BCR ABL1 kit (Ref:3B1267, 3B Black Bio Biotech India Ltd.) for detection of BCR-ABL1 gene.
iii. Real time PCR Following the synthesis of cDNA, detection of major (M), minor (m) and micro (μ) transcripts of BCR-ABL1 genes were performed using the TRUPCR BCR-ABL kit. For each sample, four reaction volumes each of 20μl was prepared using 10μl 2X high master mix, 4μl of RNase free water and 5μl of template cDNA. One microliter (1μl) of four different primer probe mix targeting major, minor, micro and ABL1 genes were added separately in one of each four reactions. Six different standards STD1($1.08x10^6$) to STD6($1.08x10^1$) were used in place of template with major-BCR-ABL1 primer probe mix for quantification. The quantitative result done with standard curve method and standard curve should be run for both ABL1 and BCR-ABL1.

Data Analysis

Data were collected, complied and tabulated according to key variables and functional assessment scoring. The analysis of different variable was done according to standard statistical analysis. Qualitative data were expressed as frequency and percentage and quantitative data were expressed as mean and standard deviation. Statistical Package for Social Science (SPSSv23.0) was used to process data.

Conflict of interest: There was no conflict of interest.

RESULTS

A total of 45 patients with documented CML were enrolled in this study. Overall, most common age group affected was between 35-44 years (Figure 1).

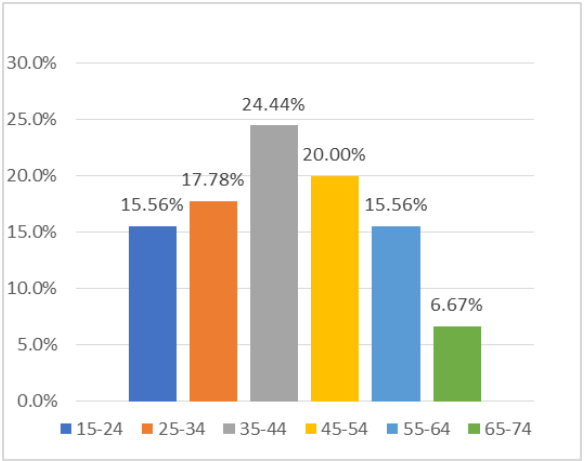

Figure 1: Age distribution of patients with CML.

Table: I Clinical and laboratory details of CML patients in study population.

Number of patients (n)	45
Mean age (years)	38.73± 16.90
Range of age (years)	15–74
Male/female (n)	28/17
Male-to-female ratio	1.64:1.0
Mean leukocytes count ($\times10^9$/L)	149.88 ± 147.28
Mean hemoglobin levels (g/dL)	10.44 ± 2.48
Mean platelets count ($\times10^9$/L)	409.13 ± 380.52

Demographic details of these patients are presented in Table 1. Patients' age range and mean age (±SD) were 15 to 71 years and 38.73±16.9 years, respectively. Twenty-eight (62%) patients were male and 17 (38%) patients were females with a M: F is 1.64:1.0. Mean leukocytes count ($\times 10^9$/L) was 149.88 ± 147.28, Mean hemoglobin levels (g/dL) was 10.44 ± 2.48 and Mean platelets count ($\times 10^9$/L) was 409.13 ± 380.52.

Hematological data:

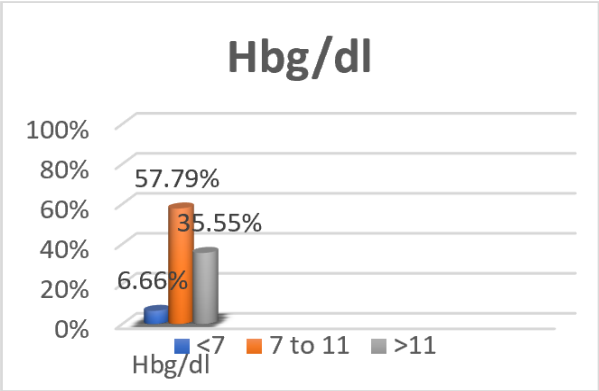

Figure 2(a): Represents the frequency of all study patients with different ranges of hemoglobin concentration.

About (64.45%) of patients were anemic. Hemoglobin value ranged from 12.2 to 16.9 with a mean value of 10.44 ± 2.48g/dL. Most of the patients (57.79%) had a hemoglobin level between 7 to 11 g/dL. The anemia was moderate for 57.79% and severe for 6.66% of the study group. (Figure 2a).

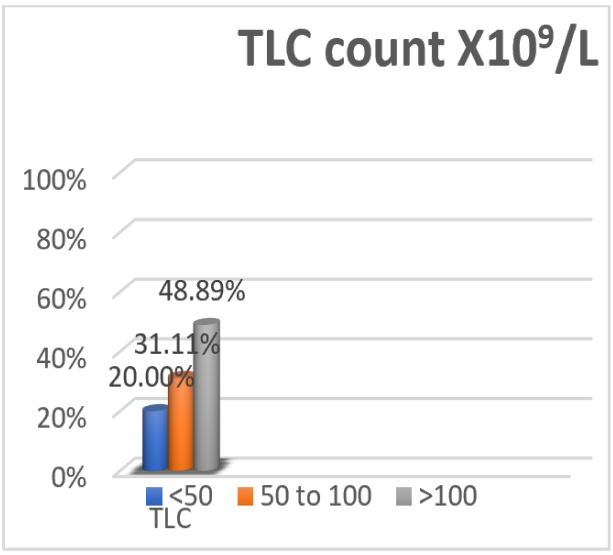

Figure 2(b): Represents the frequency of all study patients with different ranges of leucocyte count.

All patients presented the marked leukocytosis involving the granulocytic lineage, associated with early myeloid cells. Leukocytosis ranged from 5.37 to 500.13×10^9/L with a mean value of 149.88 ± 147.28 ×10^9/L. Most of the patients (48.89%) had their leukocyte count >100×10^9/L. Twenty percent patients had leukocyte values <50×10^9/L. (Figure 2b).

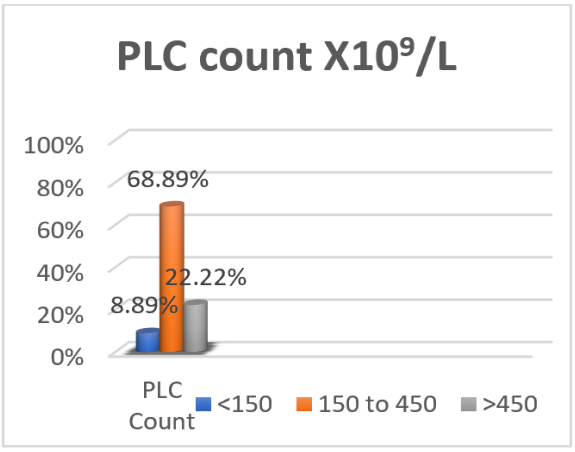

Figure 2(c): Represents the frequency of all study patients with different ranges of platelet count.

Platelet count ranged from 16 to 2100×10^9/L with a mean value of 409.13 ± 380.52×10^9/L. Most of patients (68.89%) had platelets count between 150 to 450×10^9/L, while 8.89% had thrombocytopenia and 22.22% patients had thrombocytosis (Figure 2c).

Table II: Salient Hematological Profile of patients in CML at the time of diagnosis.

Parameters	(n=45)	
	n	%
Age (years)		
<45	32	71.11
45 and above	13	28.89
Gender		
Male	28	62
Female	17	38
Hemoglobin levels (g/dL)		
<7 g/dL	3	6.66
7–11 g/dL	26	57.79
>11 g/dL	16	35.55
Total leukocyte count 10^9/L		
<50	9	20
50–100	14	31.11
>100	22	48.89
Platelet count ×10^9/L		
<150	4	8.89
150–450	31	68.89
>450	10	22.22
Blast (in numbers)		
1-9	34	75.7
10-19	3	6.6
≥20	8	17.7

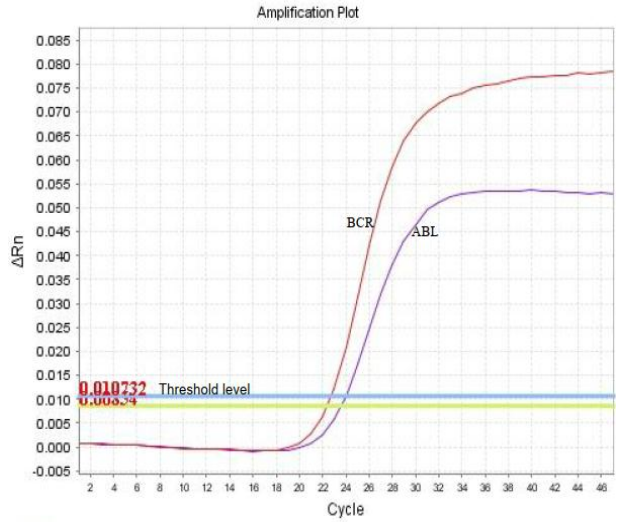

Figure 3: Real-time RT-PCR amplification plots of the BCR/ABL fusion transcripts.

The BCR/ABL amplification plot in CML sample is shown in Figure 3. Straight line parallel to X axis denotes the threshold level above which indicates BCR-ABL positive. All studied patients 45/45 (100%) were positive for typical BCR–ABL (p210 kDa).

DISCUSSION

A total of forty-five patients with documented CML were enrolled in this study. The aim of this study was to detect and analyze the demographic and hematological characteristics in BCR–ABL p210 kDa positive CML patients in a tertiary care hospital of Dhaka city. Among 45 patients twenty-eight (62.22%) were male and 17 (37.78%) were female with a ratio of 1.64:1.0.

Previously done another study in Bangladesh, it was found that males (67%) were affected more frequently than females (33%); the male to female ratio was 2.1:1.0.[19] This ratio was imperceptibly higher in India where male: female ratio was 1.9:1.0 and in Pakistan where male: female ratio was 1.7:1.0.[20,21] But another study conducted in India and UK reported similar result.[20] Chang *et al* and Kumar *et al* also demonstrated male's predominance among the enrolled CML patients with M:F ratio were (1.4:1, 1.6:1).[22,23] All these findings of male predominance's may be due to their greater exposure to environmental or occupational hazards. In this study, the mean age of study patients was found to be 38.73 ± 16.9 years (range, 15–74 years). A study conducted in Iraq reported a higher mean age of 50.4 years.[24] Kumar *et al* in Uttar Pradesh, India showed mean age 38.6 years that is consistent with our result.[23] Our findings were also similar with studies done by Chetcha *et al.* in Cameroon, Segbena *et al.* in Togo, Oyekunle *et al.* in Nigeria, Silué *et al*.in Ivory Coast and Mupepe *et al.* in Democratic Republic of Congo that were 39 years,40 years,38 years, 39 years and 40 years respectively.[25][26,27,28,29] The mean age of CML patients in France and USA was 55 years and 66 years respectively was not similar with the current study.[30,31]

All these epidemiological data give a thought that diagnosis of CML at the lower age is found more to low- and middle-income countries in contrary to high-income countries.[32,33,34]

In densely populated country like Bangladesh exposure to carcinogenic chemicals, food adulteration, overuse of pesticides, smoking, exposure to radiation consumption etc are increasing day by day and may be the main reason for the increasing susceptibility to develop CML among younger generation. In Europe and North America these preceding contributing factors are lower or absent. Majority of CML patients in this study were in the 4th and 5th decade of life that corresponds to study obtained by Gupta *et al*. who found that (45.94%) of their Indian patients were in the 5th decade.[35]

Full blood count (FBC), blood film and bone marrow aspiration were performed in 100%, 58.8% and 2.6% of our patients respectively. Total mean WBCs count, Hb and platelets count were found 149.8x10^9/L, 10.44 g/dl, 409.1 X10^9/L respectively in the study patients. Chang *et al.* found the mean WBCs, Hb and platelets were 121 x10^9/L, 9.5 g/dl, 285 x10^9/L respectively, that disagree with our results.[22] A study in India showed mean WBCs, Hb and platelets were 153.3 x10^9/L, 9.7 g/dl, 448 x10^9/L, which showed similar findings with our study.[35]

Among our study population, hemoglobin levels ranged from 4.7 to 16.9 g/dL with a mean of 12.2 and 64.45% had anaemia. Most of the patients Hb level were between 7 to 11 g/dL. The anaemia was moderate for 57.7% and severe for 6.6% of the study group. Our data found similar result to that of Kueviakoe *et al* who found an anaemia among 68.9% of patients Their patients were also mostly in moderate anaemia.[36]

Concerning platelet count, it ranged from 42 ×10^9/L to 500×10^9/L, with a mean of 409×10^9/L in our study. Most of our patients (68.89%) had platelet count between 150-450×10^9/L and while 22.2% had thrombocytosis. Our findings were similar to that of Mupepe *et al.* and Mukiibi *et al.* and who found most of their patients with a normal platelet count.[29,37]

Among the study group 75.7% of CML patients had <10% blast in their peripheral blood. Three patients (6.6%) had blasts between 10%–19% in peripheral blood. Eight patients had ≥20% blasts in their peripheral blood. Myelocytes and metamyelocytes were found the most common type of immature WBCs. A Study done in Pakistan showed the myelocytes as the prominent immature WBCs in the peripheral blood.[22]

CONCLUSION

Very few studies have reported demographic and hematological profile of patients with CML in Bangladesh who have been confirmed with BCR-ABL(p210) transcript by PCR. Our study described the demographic and hematological profile with CML in a

tertiary care hospital in Bangladesh. Most common age groups diagnosed as BCR-abl transcripts positive CML cases were middle aged (35-54 years). Males were more commonly affected than females. Their hematological parameters were similar, as reported in the literature. Study patients presented mainly with moderately anaemic. Further prospective studies with more laboratory technical platform are needed to improve diagnosis.

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