Original Article

Early Molecular Response to Imatinib Mesylate Predicts Long-Term Outcomes in CML Patients in A Postgraduate Research Institute — A single center Study

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Amin Lutful Kabir[1*], Kazi Mohammad Kamrul Islam[2], Mujahida Rahman[1], Md Salahuddin Shah[3], Munim Ahmed[1], Mahbuba Sharmin[4], Chandan Kumar Roy[5], Farzana Rahman[1]

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*Corresponding Author

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ABSTRACT

Introduction: *Targeted therapies are revolutionizing cancer treatment, and Imatinib mesylate stands as a prime example. This potent medication tackles specific genetic vulnerabilities in certain cancers, embodying the philosophy of precision medicine.* ***Objectives:*** *This study evaluated the early molecular response to Imatinib Mesylate treatment in CML patients diagnosed within the past year, specifically focusing on the achievement of MMR and CMR within the first 12 months.* ***Methods & Materials:*** *We conducted a longitudinal observational study from January to December 2018 in the Hematology department of BSMMU, Bangladesh. Our cohort included 28 newly diagnosed CML patients, aged 15-67 years, encompassing both genders. All participants provided written informed consent, and their clinical histories and physical examinations were meticulously documented. Following established diagnostic protocols, CML was confirmed at BSMMU's Department of Microbiology and Immunology through peripheral blood film (PBF), bone marrow morphology, and BCR-ABL detection*

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1. *Associate Professor, Department of Haematology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh*
2. *Research Assistant, General Emergency, BSMMU, Dhaka, Bangladesh*
3. *Chairman, Department of Haematology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh*
4. *Medical Officer, Department of Haematology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh*
5. *Associate Professor, Department of Microbiology and Immunology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh*

via RT-PCR. Patients received Imatinib based on the standard treatment schedule, and their molecular response was evaluated at 6 and 12 months using BCR-ABL1 RT-PCR. Through rigorous data analysis, we aimed to gain valuable insights into the efficacy of Imatinib Mesylate in this patient population. ***Result****: In this study, at diagnosis, the BCR-ABL1 (%) was 77.82 (±22.49) while at 06 and 12 months the mean RT- PCR BCR-ABL1 was 15.14 (±20.88) and 7.59 (±16.43) respectively. There is significant change of BCR-ABL1 at 06 and 12 months of Imatinib therapy from mean at diagnosis. Out of 28 patients, 4, 3, and 1 patients went to Log 3 (BCR-ABL1 ≤ 0.1), Log 4 (BCR-ABL1 ≤0.01%), and Log 4.5 (BCR-ABL1 ≤ 0.0032) reduction respectively.* ***Conclusion:*** *While our study demonstrated a significant overall drop in BCR-ABL1 levels across patients at 6 and 12 months compared to baseline (p < 0.01%), only 28.57% (8/28) achieved MMR. This suggests that achieving deeper molecular responses in CML may require individualized treatment durations or potentially exploring combination therapies for some patients. Further research with larger cohorts is needed to optimize therapeutic strategies for improved MMR rates in CML.*

Key Words: *Chronic Myeloid Leukemia (CML), Imatinib Mesylate, BCR-ABL1, RT-PCR, Splenomegaly.*

INTRODUCTION

Over the past two decades, groundbreaking advances in CML therapy, led by tyrosine kinase inhibitors like Imatinib, have profoundly impacted patient outcomes. Many individuals diagnosed with chronic phase CML and treated with Imatinib can now achieve life expectancies approaching those of the general population, representing a significant improvement compared to historical benchmarks. This remarkable development not only extends life expectancy but also enhances quality of life and offers long-term hope for CML patients. [1]

At its core, Chronic Myeloid Leukemia (CML) is a hematologic malignancy defined by a single, mutated hematopoietic stem cell that can generate diverse blood cell lines. This deviant cell harbors a unique genetic signature - the BCR-ABL chimeric oncogene - forged by a specific chromosomal rearrangement called the Philadelphia chromosome. This abnormal fusion gene encodes a hyperactive tyrosine kinase protein, acting as a turbocharger for myeloid cell growth, leading to the uncontrolled proliferation characteristic of CML. Notably, the BCR-ABL gene serves as the defining hallmark of CML, playing a central role in its pathogenesis and offering a crucial target for therapy. The increased tyrosine kinase activity disrupts normal cell signaling pathways, promoting malignant cell survival and proliferation, ultimately driving the progression of CML [2-4]. The gold standard for quantifying BCR-ABL transcripts in CML patients remains reverse transcriptase-polymerase chain reaction (qRT-PCR), a highly sensitive technique capable of detecting even a single CML cell amongst a vast majority of normal cells (100,000 to 1 million). This exceptional sensitivity plays a critical role in CML management, as BCR-ABL levels serve as a crucial marker for disease activity and response to treatment. By detecting minimal residual disease (MRD) even when undetectable by conventional methods, qRT-PCR allows for early

intervention and prevents disease relapse. However, research continues to explore even more sensitive BCR-ABL testing methods, aiming to further refine MRD detection and optimize CML patient care [5]. Monitoring BCR-ABL transcript levels over time in CML patients serves as a valuable tool for predicting long-term outcomes. This dynamic assessment provides crucial insights into a patient's response to therapy, allowing for early identification of treatment failure and prompt intervention with optimized therapy adjustments. By detecting non-responsiveness early, BCR-ABL monitoring enables proactive steps to prevent disease progression and improve overall prognosis. Ultimately, this personalized approach to treatment, guided by dynamic BCR-ABL information, empowers clinicians to tailor therapy strategies for each individual CML patient, maximizing their chances of success [6]. Effective monitoring of molecular response in CML patients relies on regular qRT-PCR BCR-ABL quantification, typically performed every 3 to 6 months. The current gold standard for optimal response after 12 months of Imatinib therapy is achieving BCR-ABL levels below 0.1%, representing a 3-log reduction compared to baseline. To guide treatment duration based on these response benchmarks, the European Leukemia Net (ELN) has established a comprehensive framework [7].

A landmark in CML treatment came with Imatinib, the first clinically successful signal transduction inhibitor (STI). Imatinib targets the BCR-ABL protein, a key driver of CML, directly hindering its function in promoting cancer cell growth. This targeted action disrupts crucial signaling pathways involved in cell proliferation, ultimately triggering programmed cell death, or apoptosis, in the malignant CML cells [8].

In 2001, Imatinib mesylate (Imatinib), an oral tyrosine kinase inhibitor (TKI), transformed the landscape of CML treatment with its FDA approval. Before the advent of TKIs, allogeneic bone marrow transplantation (BMT) remained the primary option after first-line therapy, despite its inherent risks and limited availability. [9,10]

Despite offering potentially curative outcomes for some CML patients, bone marrow transplantation (BMT) faces significant real-world challenges. Firstly, access to BMT remains limited in many regions due to its high cost and complex infrastructure requirements, even within developed nations. Secondly, the substantial transplant-related mortality rate associated with BMT, particularly in older patients or those with comorbidities, necessitates careful consideration of patient suitability and alternative treatment options. Furthermore, finding a suitable donor with compatible bone marrow adds another layer of complexity to BMT accessibility, posing ethical and logistical hurdles [11]. The introduction of Imatinib, the first targeted tyrosine kinase inhibitor (TKI), marked a turning point in CML treatment. This groundbreaking innovation revolutionized the prognosis for many patients, shifting from high-risk procedures and limited options to a new era of long-term disease control through convenient oral medications. Compared to the drawbacks of earlier therapies, Imatinib offered a safer, more manageable approach, significantly improving life expectancy and survival rates for CML patients. This success spurred the

development of even more potent TKIs, continuously refining targeted therapy and offering the hope of potential cure for some individuals. Imatinib, and the subsequent generation of TKIs, have undeniably transformed the outlook for CML patients, offering a future of hope and extended life [12].

A Turkish study conducted between 2006 and 2009 investigated Imatinib therapy for CML in 31 patients. They found promising results, with 71% of patients achieving complete cytogenetic response after one year of treatment. This response rate continued to improve over time, reaching 40%, 72%, and 85% for complete or significant molecular response at 12, 18, and 24 months respectively. These findings compare favorably to other studies on Imatinib efficacy, highlighting its potential to achieve optimal long-term outcomes for CML patients. However, additional research with larger datasets is needed to further validate these results and explore factors influencing individual response variability [13].

A 2003 study by Hughes et al. assessed BCR-ABL transcript levels in CML patients treated with Imatinib for 12 months. Their findings showed that at least a 3-log reduction, a strong indicator of successful treatment, occurred in 57% of patients. Notably, these individuals also exhibited a remarkable 100% rate of disease progression-free survival by 24 months. While promising, it's important to consider that this study had a limited sample size and focused on a specific treatment duration. Further research with larger datasets and longer follow-up periods is needed to confirm these results and generalize them to broader CML treatment strategies [14].

METHOD & MATERIALS

Our study, conducted between January and December 2018 at the Hematology department of Bangabandhu Sheikh Mujib Medical University (BSMMU), Bangladesh, focused on 28 newly diagnosed CML patients. Selection criteria based on complete blood count (CBC) with peripheral blood film (PBF) and bone marrow morphology identified individuals receiving care in either the inpatient or outpatient departments. Following informed consent, detailed clinical histories and physical examinations were recorded. BCR-ABL1 testing confirmed diagnoses. Participants received standard-schedule Imatinib, with BCR-ABL1 levels monitored via RT-PCR at 6 and 12 months to assess molecular response. Quantification of BCR-ABL with e13a2 (b2a2) and/or e14a2 (b3a2) and e19a2 translocations used a commercially available kit (ipsogen®BCR-ABL1Mbcr & BCR-ABL1mbcr kit, Version-1, QIAGEN GmbH, Germany) on the ABI 7500 Real Time PCR System (Applied Biosystems, USA). Cycle threshold (Ct) values, indicating cycles needed to detect a signal above threshold, inversely correlate with target molecule concentration. A standard curve generated with control and fusion gene dilutions allowed accurate quantification of the target molecule in blood samples. The normalized copy number, calculated from the ratio of BCR-ABL to ABL copy number, provided the final data point.

Data Analysis

Our data underwent meticulous analysis using the Statistical Package for Social Sciences (SPSS) version 23.0 for Windows. Continuous variables were analyzed using descriptive statistics like mean and standard

deviation (SD), while categorical variables were summarized as frequencies and percentages. To analyze the molecular response patterns in CML patients receiving Imatinib therapy, we employed two-sample z-tests. This test compared BCR-ABL1 expression levels, quantified by quantitative real-time polymerase chain reaction (RT-PCR), between different groups. Statistical significance was assessed using a p-value threshold of 0.05, with values less than 0.05 considered statistically significant.

RESULTS

The study had 28 patients who satisfied the selection criteria. Out of the patients, 17 individuals (60.7%) were male, and 11 individuals (39.3%) were female. The average age was 38.36 years, with a measure of how much the ages varied from the average being 13.25 years. The age range encompassed individuals aged 15 to 67 years. The average age for males was found to be 38.76 (±14.80), while for females it was 37.73 (±11.06).

Table I: Age and Sex Distribution of the Study Subjects (n=28)

Age group (Years)	Sex		Number of Patients (n=28)	Percentage (%)
	Male	Female		
0 – 20	3	1	4	14.3
21 – 30	2	2	4	14.3
31 – 40	4	4	8	28.6
41 – 50	3	3	6	21.4
> 50	5	1	6	21.4
Total	17(60.7%)	11(39.3%)		100
Mean (±SD)	38.76 (±14.80)	37.73(±11.06)	38.36(±13.25)	
Minimum, Maximum	15, 67	20, 55	15, 67	

Splenomegaly was observed in 27 patients 96.4% of the total, while hepatomegaly was present in 16 patients, representing 57.1% of the sample. Eleven patients (39.3%) exhibited fever, seventeen patients (60.7%) experienced anorexia, and sixteen patients (57.1%) reported fatigue. Out of the total number of patients, 6 individuals (21.4%) experienced weight loss, while 23 (82.1%) had an abdominal lump. A smaller percentage, 4 cases (14.3%), reported experiencing headaches. Additionally, 3 patients (10.7%) displayed a bleeding tendency, and 2 patients (7.1%) were found to be asymptomatic. Interestingly, only 1 patient (3.6%) presented with priapism **(Table I)**.

Table II: Sign / Symptoms of Study Subjects (n=28)

Symptoms	Frequency	Percentage
Fever	11	39.3

Anorexia,	17	60.7
Fatigue / Generalized Weakness	16	57.1
Weight Loss	06	21.4
Abdominal lump/ Fullness	23	82.1
Bleeding	03	10.7
Headache	04	14.3
Priapism	01	3.6
Erectile Dysfunction	01	3.6
Asymptotic	2	7.1
Other Symptoms	9	32.1
Signs		
Splenomegaly	27	96.4
Hepatomegaly	16	57.1

Upon diagnosis, it was found that 46.4% of the 28 patients exhibited moderate splenomegaly, while 32.1% had mild splenomegaly, and 17.9% had massive splenomegaly. One patient (3.6%) did not exhibit splenomegaly **(Table II)**.

Table III: Grading of Splenomegaly (Below the level of Left Costal margin) (n=28)

Splenomegaly (cm)	Frequency	Percentage (%)
Mild (1-3)	9	32.1
Moderate (4-8)	13	46.4
Severe/Massive (> 8)	5	17.9
No Splenomegaly	1	3.6
Total	28	100

The average haemoglobin concentration was 10.22 gm/dl, with a standard variation of 1.67. The average white blood cell count was 168.39 x 10^9/L, with a standard deviation of 94.90. The average platelet count was 612.96 x 10^9/L, compromising a standard deviation of 382.54. The average count of basophils was 2.78, with a standard deviation of 1.72. In contrast, the average percentage of blast cells was 3.58, with a standard deviation of 2.46 **(Table III)**.

Table IV: Haematological Parameters at Diagnosis of the Study Subjects (n=28)

Parameters at Diagnosis	Mean ±SD	Range (Min - Max)
Hemoglobin (g/dL)	10.22 (±1.67)	7.2-14.3
WBC x 10^9/L	168.39 (±94.90)	20 - 392
Platelets x 10^9/L	612.96 (±382.54)	150-1428
Neutrophil (%)	55.85 (±10.34)	35-79

Lymphocyte (%)	10.57 (±4.74)	2-25
Eosinophil (%)	2.78 (±1.68)	1-8
Monocyte (%)	2.64 (±3.40)	0 – 6
Basophil (%)	2.78 (±1.72)	1 – 7
Myelocyte (%)	21.76 (±8.10)	1 - 36
Blast (%)	3.58 (±2.46)	0 - 12

Among the 28 patients, 13 (46.4%) were classified as high risk based on their SOKAL Score of 1.63(±.45). Additionally, 09 (32.2%) patients were categorized as low risk, while 06 (21.4%) fell into the intermediate risk category with SOKAL Scores of .71(±.05) and 1.02(±.07) respectively **(Table IV)**.

Table V: Distribution of SOKAL Score of the study Subject (n=28)

SOKAL Score	Frequency	Percentage (%)	Mean (±SD)	Range (Min-Max)
Low Risk (0-0.8)	**9**	**32.2**	**0.71 (±.05)**	**0.63 -0.77**
Intermediate Risk (> 0.8 – 1.2)	**6**	**21.4**	**1.02 (±.07)**	**0.92 – 1.13**
High Risk (> 1.2)	**13**	**46.4**	**1.63 (±.45)**	**1.21 – 2.79**
Total	**28**	**100**	**1.20 (±0.52)**	**0.63 – 2.79**

Upon diagnosis, the BCR-ABL1 level was measured at 77.82 (±22.49). Subsequently, at 06 and 12 months, the average BCR-ABL1 levels were recorded as 15.14 (±20.88) and 7.59 (±16.43) respectively. There is a notable alteration in BCR-ABL1 levels at 06 and 12 months of Imatinib therapy compared to the average at diagnosis **(Table V)**.

Table VI: Distribution of BCR-ABL1 by RQ PCR (n=28)

BCR-ABL1	At diagnosis Mean ±SD	After 6 months Mean ±SD	After 12 months Mean ±SD
Quantitative assay of BCR-ABL1 by RQ PCR (%)	77.82 (±22.49)	15.14 (±20.88)	7.59 (±16.43)
Range (Min-Max) (%)	6.7 - 98.4	0.007 - 76.37	0 - 83.59
p value		< 0.01	< 0.01

Following 6 months of Imatinib treatment, the number of patients achieving different levels of BCR-ABL1 reduction were as follows: 11 patients reached Log 0 (BCR-ABL1 >10%), 16 patients reached Log 1 (BCR-ABL1 ≤ 10%), 7 patients reached

Log 2 (BCR-ABL1 ≤ 1%), 1 patient reached Log 3 (BCR-ABL1 ≤ 0.1), and 1 patient reached Log 4 (BCR-ABL1 ≤0.01%). Within the low-risk group, there are 4 patients in Log 0, 2 patients in Log 1, 2 patients in Log 2, and only 1 patient experienced a reduction to Log 3. Among the High-risk group, there were 4 patients who experienced reductions in Log 0, 1, and 2, while only 1 patient achieved a Log 3 reduction **(Table VI)**.

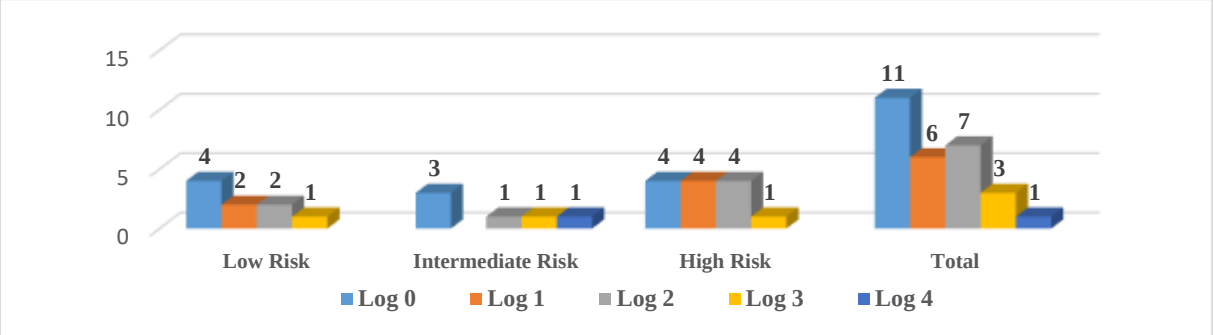

Figure 1: Distribution of BCR-ABL1 at 6 Months of Imatinib Therapy (n=28)

After 12 months of Imatinib therapy, the number of patients who achieved different levels of BCR-ABL1 reduction were as follows: 7 patients reached Log 0 (BCR-ABL1 >10%), 8 patients reached Log 1 (BCR-ABL1 ≤ 10%), 5 patients reached Log 2 (BCR-ABL1 ≤ 1%), 4 patients reached Log 3 (BCR-ABL1 ≤ 0.1), 3 patients reached Log 4 (BCR-ABL1 ≤0.01%), and 1 patient reached Log 4.5 (BCR-ABL1 ≤ 0.0032). In the Low risk group, there are 2 patients in Log 0, 3 patients in Log 1, 2 patients in Log 2, 1 patient in Log 3, and 1 patient who experienced a reduction of Log 4.5. Three patients from the Intermediate risk group were transferred to Log 4. Among the high-risk group, three patients maintained a Log 0 status, while three patients experienced a reduction to Log 3 **(Figure 1)**.

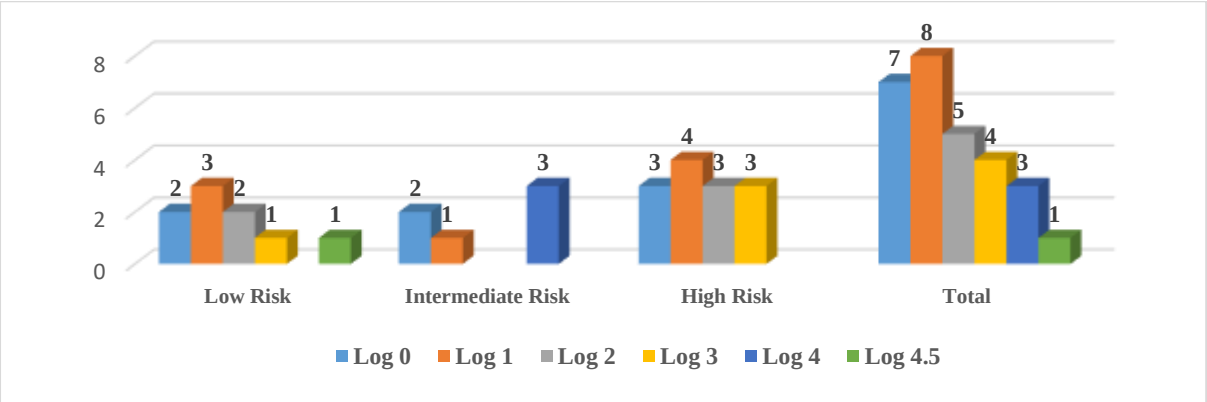

Figure 2: Distribution of BCR-ABL1 at 12 Months after Imatinib Therapy (N=28)

Figure 2 summarized the distribution of BCR-ABL1 at 12 Months after Imatinib Therapy (N=28)

DISCUSSION

Our study, conducted in the Hematology department at BSMMU from January to December 2018, enrolled 28 newly diagnosed, untreated CML patients aged 15-67 years. Participant selection followed specific criteria, resulting in a group with 60.7% (17) males and 39.3% (11) females. The average age was 38.36 years (SD 13.25), mirroring the broad age range. We observed a slight skew towards younger males (mean 38.76 years, SD 14.80) compared to females (mean 37.73 years, SD 11.06). Interestingly, Lavallade et al. (2018) reported similar gender ratios (56.9% male and 43.1% female) in their study of 204 CML patients, albeit with a higher median age of 46.3 years (range 18-79) [15].

Our study revealed a high prevalence of common CML symptoms at diagnosis. Splenomegaly was present in 96.4% (27/28) of patients, followed by hepatomegaly in 57.1% (16/28). Anorexia (60.7%), fatigue (57.1%), and fever (39.3%) were also frequently reported. While less common, weight loss (21.4%) and abdominal lumps (82.1%) were still significantly present. Notably, only 10.7% of patients had bleeding tendencies and 7.1% were asymptomatic. While priapism occurred in only one patient (3.6%), a wider range of symptoms like back pain, flushing, and dyspepsia may occasionally occur. Interestingly, Nasser et al. (2021) observed similar widespread symptom prevalence, with 98.1% of their 191 CML patients presenting with symptoms at diagnosis. Anemia was particularly common (81.7%), followed by splenomegaly (84.2%) and bleeding tendencies (21.5%). These comparisons suggest a consistent pattern of presenting symptoms in CML patients across different populations [16].

Our analysis of hematological parameters revealed average values within expected ranges for CML patients at diagnosis. Mean hemoglobin concentration was 10.22 g/dL (SD 1.67), while mean white blood cell (WBC) count was 168.39 x 10^9/L (SD 94.90) and mean platelet count was 612.96 x 10^9/L (SD 382.54). Basophil percentage averaged 2.78% (SD 1.72) and blast percentage averaged 3.58% (SD 2.46). These findings align with those of Lavallade et al. (2018), who reported an average Hb concentration of 11.6 g/dL (range 3-17.2), average WBC count of 140 x 10^9/L (range 5.8-600), and average platelet count of 393 x 10^9/L (range 112-2267). Additionally, their reported basophil percentages (3%, range 0-18) and blast percentages (1%, range 0-14) were comparable to our results. This consistency suggests similar baseline hematological profiles among CML patients across these populations [15].

Our analysis revealed a distribution of CML risk categories as assessed by the SOKAL Score. High-risk patients, defined by a score of 1.63 (±0.45), comprised 46.4% (13/28) of our cohort. Intermediate-risk (1.02 ± 0.07) and low-risk (0.71 ± 0.05) categories accounted for 21.4% (6/28) and 32.2% (9/28) of patients, respectively. Interestingly, Nasser et al. (2021) observed a contrasting risk profile in their Tanzanian CML population, with a higher proportion of intermediate (49%) and high-risk (41%) individuals compared to our study's distribution. This discrepancy suggests potential geographic or population-specific differences in CML risk profiles, warranting further investigation [16].

Starting from a mean of 77.82 (±22.49) at diagnosis, BCR-ABL1 levels significantly decreased to 15.14 (±20.88) at 6 months and further down to 7.59 (±16.43) at 12 months ($p < 0.05$). This substantial reduction, observed in both time points compared to baseline, signifies a notable response to Imatinib therapy in our CML-CP patients, potentially translating to improved outcomes.

Our analysis revealed varying degrees of BCR-ABL1 reduction in CML patients after 6 months of Imatinib treatment. Among the 28 participants, 11 (39.3%) achieved a reduction exceeding 10%, while 6 (21.4%) had moderate reduction (≤10%). Notably, 10 patients (35.7%) exhibited minimal responses, with 7 falling within the ≤1% range and 3 within the ≤0.1% range. Interestingly, the response distribution mirrored risk stratification. Within the low-risk group, 9 patients (75%) attained Log 0-2 reductions, with only 1 achieving Log 3. Similarly, the high-risk group displayed comparable distribution, with 4 patients reaching Log 0-2 and 1 reaching Log 3. These findings suggest a potential correlation between risk categories and treatment response patterns. Comparing to Lavallade et al.'s (2018) work, where 75% of their CML patients achieved CCyR and 65% MCyR, our data indicates a lower rate of complete responses but similar trends in MCyR achievement. This discrepancy warrants further investigation, potentially considering differences in patient populations or treatment protocols [16].

Our analysis revealed varying degrees of BCR-ABL1 reduction at 12 months post-Imatinib in CML patients, categorized by the Log scale. In the low-risk group, two patients achieved Log 0 reduction (>10%), with three reaching Log 1 (≤10%), two at Log 2 (≤1%), and one each at Log 3 (≤0.1%) and Log 4.5 (≤0.0032%). The intermediate-risk group had all three patients within the Log 4 range (≤0.01%). Notably, the high-risk group showed limited response, with three remaining at Log 0 and three reaching Log 3. Interestingly, these findings differ somewhat from previous studies. While Bilén and Erdem (2009) reported 71% complete cytogenetic response after one year in Turkish CML patients, our data suggests less frequent complete responses at 12 months. Similarly, Hughes et al. (2003) observed BCR-ABL1 reduction in 57% of patients after 12 months, compared to our broader response distribution. These discrepancies warrant further investigation, potentially considering differences in patient populations, treatment protocols, or assessment methods [14].

LIMITATIONS

Our study acknowledges several limitations:

- Relatively small sample size: While statistically determined, the cohort of 28 patients may not fully represent the larger CML population due to its size.
- Limited scope: Focusing solely on the Hematology department at BSMMU, both inpatient and outpatient, restricts the generalizability of our findings to the broader Bangladesh population.
- Lack of follow-up: Without long-term follow-up data, we cannot assess remission rates or the prognostic significance of our observed BCR-ABL1 reduction patterns.

These limitations should be considered when interpreting the

study's results and designing future research in this area.

CONCLUSIONS

Our analysis indicates a statistically significant reduction in BCR-ABL1 levels at both 6 and 12 months post-Imatinib compared to baseline ($p < 0.01$). However, the response to treatment was not uniform. While one-third of patients achieved major molecular response (MMR, ≥ 3 Log reduction), the remaining two-thirds did not. This suggests the need for further investigation into factors influencing treatment response and potential alternative approaches for non-responders. Regular BCR-ABL1 quantification using RT-PCR remains crucial for all CML patients. This monitoring enables early detection of treatment failure, personalized intervention strategies, and potentially, molecular characterization of mutations associated with resistance.

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