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Research Article

Efficacy of Imatinib According to BCR-ABL Mutation in Patients with CML; Multi-Centered Analytical Study

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Abstract

Background: Imatinib, a name of assurance in the treatment of CML, not only brings significant prognosis and remission but also improves the quality of life of a patient. The study aimed to evaluate the efficacy of Imatinib in CML patients. Methods: This study was cross-sectional and multi-centered, starting from 2019-2024 from Sylhet, Chittagong, and Rajshahi. In this study, 529 patients were enrolled. Among them, 442 patients were taken, rest of the patients declined as BCR- ABL1 observed copies were <10,000. Sampling was done by convenient technique. *Result:* The patients' ages ranged from under 20 to over 80 years, with the majority falling between 21-30 years (25.71%) and 31-40 years (23.25%). The majority of the patients were male (57.66%). According to the analytical result, 442 patients (83.55%) tested positive. Among the 442 participants who tested positive for BCR-ABL1 mRNA, 155 patients (35.07%) were in remission. In contrast, 287 patients (64.93%) were not in remission, with an IS ratio greater than 0.1%. Among the 155 patients classified as in remission according to the IS ratio (≤0.1%), all 155 (100.00%) were also in remission according to the transcript percent ratio (≤10%). The sensitivity of the transcript percent ratio in identifying patients in remission was 100.00%, indicating that all patients in remission according to the IS categorization were also identified as in remission by the transcript percent ratio. The specificity was 36.60%, reflecting a lower ability to correctly identify patients not in remission. *Conclusion:* In the case of specificity, International-scale and large-scale clinical studies with long-term patient outcomes are more recommended.

Keywords

CML, Efficacy, Mutation, Remission

1. Introduction

In chronic myeloid leukemia (CML), a clonal mylo-proliferative disorder of the hematopoietic stem, 95% cases are characterized by Philadelphia chromosome as the sole genetic abnormality into blast crisis. From previous studies, it is evident that, 1 to 2 cases per 100000 per year are affected with CML annually [1]. Without early diagnosis and proper treatment, the chronic phase (CP) of CML undergoes blast crisis (BC) whereas, the prognosis is poor [2]. The deleted chromosome 22 is pro-duced by the reciprocal (but not fully balanced) translocation between the long arms of chromosomes 9 and 22. During this

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event, two genes, Abelson 1 (*ABL1*), located on chromosome 9, and the Breakpoint Cluster Region (*BCR*), on chromosome 22, generate a fusion gene called BCR-ABL1, that, along with the Philadelphia chromosome, which is the main diagnostic marker of CML [3].

There are three phases of CML. 90% of patients are diagnosed in the chronic phase (CP), and the other two phases are the accelerated phase (AP) and the blast phase (BP) [4]. In previous studies, we have found that the average age of CML is around 64 years. Almost half of cases are diagnosed in people 65 and older. Children are rarely affected by this disease [5].

Most of the CML patients do not have significant diagnostic symptoms. Some of common complaints from the patients are fatigue, weight loss, malaise and anemia. On laboratory findings, leukocytosis is a common finding, whereas platelet count can be high or low [6]. In 20-40 cases of CML, Splenomegaly is a common clinical manifestation. In case of prognosis of CML, it depends on the early diagnosis. The greatest diagnostic difficulty is patients having splenomegaly and leukocytosis but who do not have the Ph chromosome. Blood test and other laboratory tests are not able to clear the arising confusion. In these cases, the *BCR-ABL1* hybrid gene can be recommended as a diagnostic tool. Patients achieving Ph negative and *BCR-ABL1* negative are considered to be Ph-negative CML or chronic myelomonocytic leukemia [7].

Imatinib, a pioneer drug of CML, recommended by FDA (Food Drug Administration) in the year of 2001, is recognized as the first signal transduction inhibitor (STI), to decline the oncologic pathway from BCR-ABL protein. It directly inhibits the constitutive tyrosine kinase activity. Once Imatinib is started, there is a significant decrease rate of mutation. The ultimate outcome of this drug is, modification of the function of various genes involved in the control of the cell cycle, cell adhesion, cytoskeleton organization and finally in the apoptotic death of Ph (+) cells. The oral bioavailability and terminal half-life are 98% and 18 hours respectively [8]. From the last 15 years of clinical studies, Imatinib and second-generation TKIs dramatically improved the prognosis of the disease [9].

In spite of having a high response of Imatinib in CML, there is a possibility of recurrence of CML if the drug is discontinued. Among the 3 phases of CML, Imatinib responds in CP, compared to the other phases. For a satisfactory prognosis of CML patients, 400 mg Imatinib is recommended [10]. By the BCR-ABL test, we can detect abnormal genes from the blood or bone marrow in CML patients. Real-time PCR has become the most acceptable method for monitoring BCR-ABL transcript levels of patients treated with kinase inhibitors [11]. This study aimed to evaluate the efficacy of Imatinib in CML patients.

2. Methods

This study was cross-sectional and multi-centered, starting from 2019-2024 from Sylhet, Chittagong and Rajshahi. In this study, 529 patients were enrolled. Among them, 442 patients were taken, rest of the patients are declined as BCR-ABL1 observed copies were <10,000. Sampling was done by convenient technique.

Collecting all the information by using a data collection sheet that contained a structured Questionnaire along with baseline, demographic and clinical data. All information regarding clinical features were recorded in the information collection sheets with written consent from the respondents.

All the information were entered in SPSS for analysis (version 25.0; IBM Corp). We performed frequency analysis as an analytic study to observe the age, gender and the remission status of the respondents (Chi-square).

Inclusion Criteria:

1) Patients with CML.
2) Patient with written consent.

Exclusion Criteria:

1) Other malignancies.
2) Refuse to give consent.
3) Mentally unstable patients.

3. Result

Table 1. *Distribution of the Respondents according to the Age.*

Age Range (year)	Frequency	Percentage
≤20	59	11.15%
21-30	136	25.71%
31-40	123	23.25%
41-50	93	17.58%
51-60	91	17.20%
61-70	19	3.59%
71-80	6	1.13%
>80	2	0.38%
Mean±SD Age	37.92±14.63	

Table 1 resembled distribution of the respondents according to the age. The patients' ages ranged from under 20 to over 80 years, with the majority falling between 21-30 years (25.71%) and 31-40 years (23.25%).

Table 2. *Distribution of the Respondents according to the Gender.*

Gender	Frequency	Percentage
Male	305	57.66%
Female	224	42.34%

Table 2 resembled distribution of the respondents according to the gender. Majority of the patients were male (57.66%).

Table 3. *Distribution of the Respondents according to the analytical result.*

Result	Frequency	Percentage
Negative	87	16.45%
Positive	442	83.55%

Table 3 shows distribution of the respondents according to the analytical result. It is evident that, 442 patients (83.55%) tested positive.

Figure 1 showed majority of patients had a lower number of observed copies, with a steep decline as the number of copies increased. The mean number of BCR-ABL1 observed copies was 17,553.69, with a standard deviation of 116,005.69, indicating a high variability among the patients.

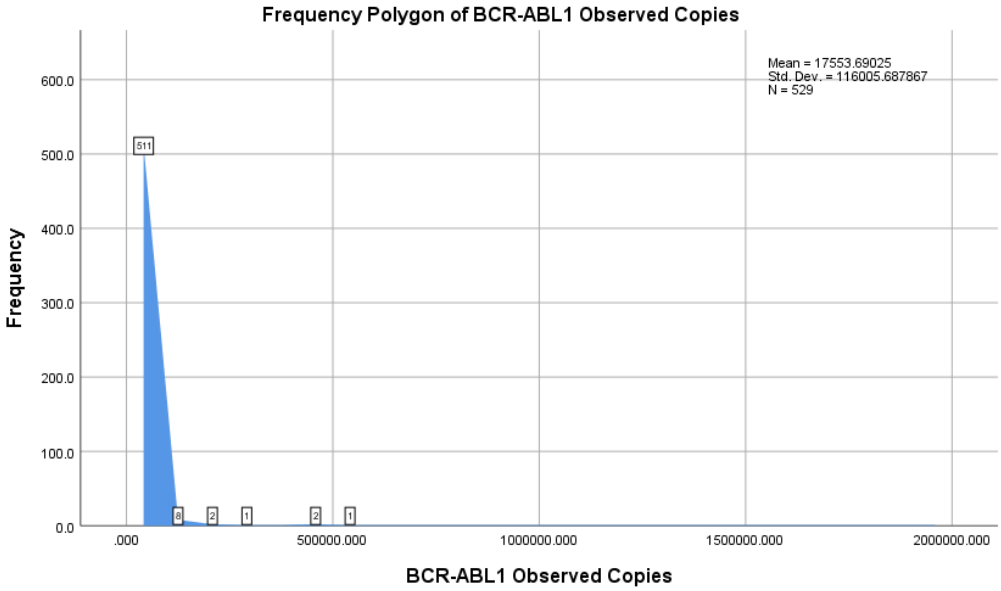

Figure 1. *Frequency polygon of BCR-ABL Observed copies.*

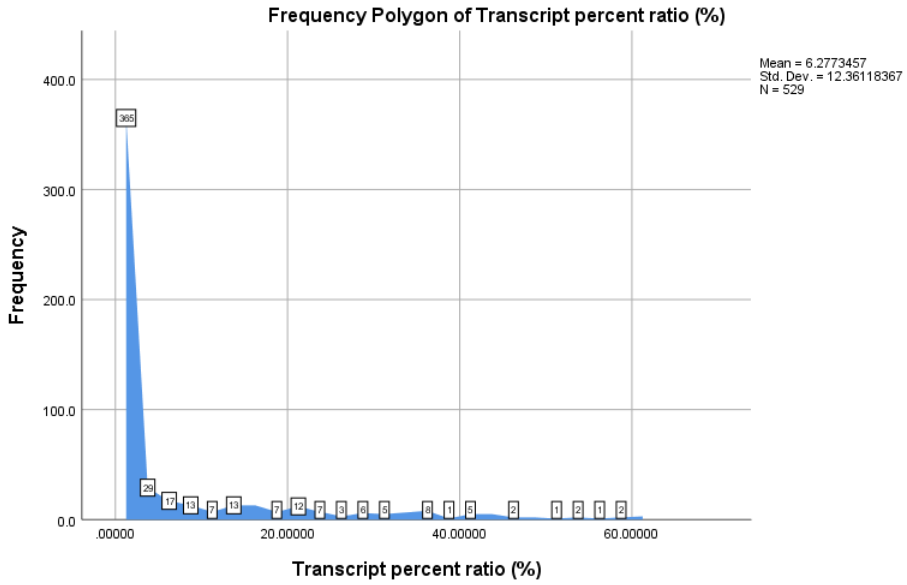

Figure 2. *Frequency polygon of Transcript percent ratio.*

Similar to the observed copies, the transcript percent ratio also showed a high frequency of lower values, with the majority of patients having a ratio close to zero. The mean transcript percent ratio was 6.28%, with a standard deviation of 12.36%, again indicating significant variability.

Table 3. *Observation of patient remission status according to transcript percent ratio (n=442).*

BCR-ABL1/ABL1 Transcript Percent Ratio	Frequency	Percentage
In remission (≤10%)	337	76.24%
No Remission (>10%)	105	23.76%
Mean±SD	7.51±13.18	

Table 3 illustrated observation of patient remission status according to transcript percent ratio. Out of the 442 positive cases, 337 patients (76.24%) were in remission, defined as having a BCR-ABL1/ABL1 transcript percent ratio of ≤10%. Conversely, 105 patients (23.76%) were not in remission, with a transcript percent ratio greater than 10%. The mean transcript percent ratio for this group was 7.51%, with a standard deviation of 13.18%.

Table 4. *Observation of patient remission status according to International Scale.*

BCR-ABL1/ABL1 IS Ratio	Frequency	Percentage
In remission (≤0.1%)	155	35.07%
No Remission (>0.1%)	287	64.93%
Mean±SD	4.93±8.67	

Table 4 showed observation of patient remission status according to international scale. Among the 442 participants who tested positive for BCR-ABL1 mRNA, 155 patients (35.07%) were in remission, defined as having a BCR-ABL1/ABL1 IS ratio of ≤0.1%. In contrast, 287 patients (64.93%) were not in remission, with an IS ratio greater than 0.1%. The mean IS ratio for this group was 4.93, with a standard deviation of 8.67.

Table 5 above showed correlation between IS and transcript percent ratio categorizations. Among the 155 patients classified as in remission according to the IS ratio (≤0.1%), all 155 (100.00%) were also in remission according to the transcript percent ratio (≤10%). In contrast, among the 287 patients classified as not in remission according to the IS ratio (>0.1%), 182 (63.41%) were in remission according to the transcript percent ratio, while 105 (36.59%) were not in remission according to the transcript percent ratio. The chi-square test revealed a significant correlation between the IS ratio and the transcript percent ratio (p-value <0.001).

Table 5. *Correlation between IS and Transcript percent ratio categorizations.*

Transcript Percent Ratio	International Scale				p-value (Chi-square test)
	In Remission (n=155)		No Remission (n=287)		
	n	%	n	%	
In Remission	155	100.00%	182	63.41%	<0.001
No Remission	0	0.00%	105	36.59%	

Table 6. *International Scale (IS) categorization as the gold standard.*

Transcript Percent Ratio	International Scale		Total
	In Remission	No Remission	
In Remission	155 (TP)	182 (FP)	337
No Remission	0 (FN)	105 (TN)	105
Total	155	287	442

Table 6 showed Using the International Scale (IS) categorization as the gold standard, we evaluated the correlation between patient remission status as defined by the IS ratio and the transcript percent ratio. Among the 442 participants, 155 patients were correctly identified as in remission by both the transcript percent ratio and the IS categorization (True Positives, TP), while 182 patients were incorrectly identified as in remission by the transcript percent ratio but were not in remission according to the IS categorization (False Positives, FP). There were no patients incorrectly identified as not in remission by the transcript percent ratio but in remission according to the IS categorization (False Negatives, FN). Additionally, 105 patients were correctly identified as not in remission by both the transcript percent ratio and the IS categorization (True Negatives, TN). This analysis revealed a significant correlation between the IS ratio and the transcript percent ratio (p-value <0.001), indicating a strong association between the two measures. These findings highlight the specificity and sensitivity of the transcript percent ratio in identifying patient remission status when using the IS categorization as the gold standard.

Table 7. *Sensitivity, Specificity, Accuracy, PPV, and NPV according to respondents.*

Metric	Value	Simplified Formula
Sensitivity	100.00%	"TP / (TP + FN) * 100"
Specificity	36.60%	"TN / (TN + FP) * 100"
Accuracy	58.80%	"(TP + TN) / Total * 100"
Positive Predictive Value (PPV)	46.00%	"TP / (TP + FP) * 100"
Negative Predictive Value (NPV)	100.00%	"TN / (TN + FN) * 100"

Table 7 showed Sensitivity, Specificity, Accuracy, PPV, and NPV according to respondents. The sensitivity of the transcript percent ratio in identifying patients in remission was 100.00%, indicating that all patients in remission according to the IS categorization were also identified as in remission by the transcript percent ratio. The specificity was 36.60%, reflecting a lower ability to correctly identify patients not in remission. The accuracy of the transcript percent ratio was 58.80%, showing the overall correctness of the test. The positive predictive value (PPV) was 46.00%, indicating that less than half of the patients identified as in remission by the transcript percent ratio were correctly identified. The negative predictive value (NPV) was 100.00%, showing that all patients identified as not in remission by the transcript percent ratio were indeed not in remission according to the IS categorization.

4. Discussion

This cross-sectional multi-centered study, starting from 2019-2024 from Sylhet, Chittagong and Rajshahi. In this study, 529 patients were enrolled. Among them, 442 patients were taken, rest of the patients are declined as BCR- ABL1 observed copies were <10,000. Sampling was done by convenient technique.

In Ethopia, there was a study that occurred among 962 cases of CML diagnosis, the median age was 33 years and the majority presented with features of advanced-phase disease [12]. another similar study showed The mean age of respondents was 39.75 ±1.76 years [13]. In our study, the majority of patients fell between 21-30 years (25.71%) and 31-40 years (23.25%).

In this study, Out of the 442 positive cases, 337 patients (76.24%) were in remission, defined as having a BCR-ABL1/ABL1 transcript percent ratio of ≤10%. All 155 (100.00%) were also in remission according to the transcript percent ratio (≤10%). In contrast, among the 287 patients classified as not in remission according to the IS ratio (>0.1%), 182 (63.41%) were in remission according to the transcript percent ratio, while 105 (36.59%) were not in remission according to the transcript percent ratio. The chi-square test revealed a significant correlation between the IS ratio and the transcript percent ratio (p-value <0.001). Similarly, there is an Iris trial whereas for 106 patients, the estimated PFS rates at 12 months and 36 months after the dose escalation were 94% and 89%, respectively. Complete molecular response (CMR) rates were 0% versus 43.8% respectively (p = 0.002), and no molecular responses were observed when adherence rates were 80% or lower. Lower adherence rates have been described in younger patients, those who experience adverse events (AEs) related to therapy, and those who require dose escalations [14]. In the year of 2014, there was a similar study, where all outcomes were significantly superior for the 410 patients with BCR-ABL1 ≤10% which strongly indicated remission at 3 months (P <.001) [15].

Imatinib, a magical hope in CML, not only helps in satisfactory remission but also improve the quality of life of patients, that may help people to lead a nearly normal lifespan. In previous cases, Undetectable BCR-ABL patients who have stopped treatment had a minimum chance of recurrence of the disease. There was only 10% chance of their disease coming back after the cessation of the treatment [16]. Overall, only efficacy and safety are not the concern in case of treatment, it is also mandatory to maintain the quality of life.

5. Limitation of the Study

105 patients were correctly identified as not in remission by both the transcript percent ratio and the IS categorization (True Negatives, TN). After 6 months of treatment, they might be in remission. Moreover, at the beginning of the study, only the *Transcript percent ratio* was available. So there may be some technological errors.

6. Conclusion

In this study, the transcript percentage ratio is not an ideal scale as the specificity percentage is low. However, limited data and lack of funding for treatment and lab equipment are some of the biggest obstacles to improving quality of life (HRQoL), especially in our country. More clinical trials and social awareness will be expected for better outcomes.

Abbreviations

BCR-ABL	Breakpoint Cluster Region-Abelson Proto-Oncogene
CML	Chronic Myeloid Leukemia
CP	Chronic Phase
SD	Standard Deviation
TKI	Tyrosine Kinase Inhibitor

Conflicts of Interest

The authors declare no conflicts of interest.

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