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Biochemical and breakpoint cluster region-c-ABL oncogene 1 polymorphism study among Iraqi patients with chronic myeloid leukemia

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Abstract:

BACKGROUND: Chronic myeloid leukemia (CML) has been well recognized as an exemplary instance of a malignant disease characterized by a distinctive molecular occurrence, namely the presence of the breakpoint cluster region *(BCR)*-c-ABL oncogene 1 (*ABL1)* oncogene. The Philadelphia chromosome gives rise to an anomalous fusion gene characterized by atypical kinase activity, resulting in the accumulation of reactive oxygen species and genetic instability that holds significance in the advancement of diseases.

OBJECTIVE: The objective of this study was to investigate the detection rate of *BCR-ABL1* polymorphism and *BCR* protein level in a group of Iraqi patients with CML.

MATERIALS AND METHODS: This study has been carried out on 150 specimens, 120 patients subjected to CML included 20 patients diagnosed as newly diagnosis CML and 100 patients treated with CML. In addition to 30 apparently healthy persons as a control group (normal persons) from the National Center of Hematology/Mustansiryiah University/Baghdad, 65 out of 100 patients on imatinib while 35 nonimatinib (nilotinib and bosutinib). Fresh whole blood and serum were obtained from all patients and controls. We used total DNA genomic extraction extracted from ethylenediaminetetraacetic acid blood for genetic detection of *Bcr/Abl* Genes Polymorphism by sequencing technique in patients with CML and apparently control groups and used serum for biochemical tests include urea, lactate dehydrogenase (LDH), aspartate transaminase (AST), alanine transaminase (ALT), and creatinine using biochemicals methods (colorimetric and kinetic), respectively, as well as detection BCR protein level using sandwich enzyme-linked immunosorbent assays technique.

RESULTS: According to age and sex, the patients' groups were matching with the control group. Regarding the biochemical parameters (urea creatinine, ALT, AST, and LDH) serum level, there are no significant differences among new diagnosis CML, patients respond to treatments and failure group except in serum level of creatinine between new diagnosis CML group and failure group, there are significant differences ($P = 0.01$). The present results showed that DNA polymorphism distribution was according to C\C; G\C; A\T; and A\A were 32%, 26%, 18%, and 24%, respectively, in patients with CML and 28%; 20%;12%; and 40%, respectively, in the control group. There are significant statistical differences ($P < 0.05$) between different groups according to the genotyping of *BCR\ABL*, the results obtained from the sequenced 429 bp fragments, and the detailed positions of the observed variations are described in the NCBI reference sequences (rs766724113). The samples were submitted in NCBI, and the accession number of nucleotide sequences of *BCR\ABL* as new recording: LC 775148, LC 775149, and LC 775150, while regarding with BCR protein, there are significant differences in level between new diagnosis CML and CML on treatment and control groups, $P < 0.001$ for each comparison while there are no significant differences between treated group and control group ($P = 0.729$).

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CONCLUSION: The present results indicate that *BCR-ABL1* polymorphism and *BCR* protein level in a group of Iraqi patients with CML may play a role in the tumor biology of the examined subset of CML and may contributed to their development.

Keywords:

Breakpoint cluster region protein level, breakpoint cluster region-c-ABL oncogene 1 polymorphism, chronic myeloid leukemia, polymerase chain reaction, sequencing

Introduction

Chronic myeloid leukemia (CML) is a hematological illness characterized by the clonal expansion of a multipotent hematopoietic stem cell.[1] The c-ABL oncogene 1 (ABL1) gene, which is situated on chromosome 9, translocates to the breakpoint cluster region (BCR) gene, which is located on chromosome 22, to produce *BCR-ABL1*, an oncoprotein with enhanced tyrosine kinase activity.[2]

Before the development of ABL1 tyrosine kinase inhibitors (TKIs), blasts were typically myeloid in about 70% of CML-blastic phase patients and B-lymphoid in about 30% of patients; mixed phenotypes were sporadically observed. The blastic transformation of CML with a heterogeneous phenotype is becoming increasingly more uncommon in the TKI era. Blasts in the myeloid phenotype might be erythroid, megakaryocytic, monocytic, eosinophilic, or basophilic.[3]

The gene *BCR-ABL1* is the most often mutated one in CML. Treatment failure could result from the selection of point mutations within the ABL1 KD by TKI therapy. Imatinib and nilotinib, for example, are unable to recognize the shift from the closed to the open conformation of the kinase that mutations cause in the key contact residues between the TKIs and their target.[4] Imatinib mesylate was the initial TKI to receive approval for the treatment of CML.[5]

Imatinib, a phenylamino-pyrimidine, is effective for *BCR-ABL* signal transduction by gradually inhibiting the ATP-binding site of the *BCR-ABL* protein. This causes the loss of downstream pathways in BCR-ABL transduction activity.[6]

However, it is estimated that approximately 20%–30% of patients would eventually acquire resistance to the treatment. Due to its significant activity and reduced safety profile, the medication imatinib has become a widely used treatment for CML. Doses between 25 and 1000 milligrams were looked at on a daily basis in the first stage of the dosage discovery research of illness patients who were resistant to or did not respond to interferon-alpha treatment. To increase the body's resilience to free radicals, antioxidants are essential.[7]

The current study was designed to unravel the rates of *BCR-ABL1* gene polymorphism in patients with CML.

Materials and Methods

Patients

This study is designed as case–control. This study population included 120 persons diagnosed as CML collected from the National Center of Hematology, 20 CML patients out of 120 were new diagnosed CML and 100 patients were treated with TKIs. Sixty-five patients out of 100 were treated with imatinib and 35 CML patients were nonimatinib. Sixty-nine patients out of 100 showed respond to treatment while 31 patients were failure 30 healthy-looking people considered the control group. The CML group and control were matched age and gender; 5 mL blood samples was collected from patients and control, separated into 2 mL in ethylenediaminetetraacetic acid tube to detection *BCR-ABL1* single nucleotide polymorphism (SNP) and 3 mL sera to detection level of urea, creatinine, alanine transaminase (ALT), aspartate transaminase (AST), and lactate dehydrogenase (LDH) as well as BCR protein level.

Inclusion criteria

New diagnosis CML and treated patients of any sex. The age of patients from 18 to 65 years and the treated patient on TKIs.

Exclusion criteria

The age under 18 years old, pregnant, or lactic women, and patients ongoing active systemic infection.

Methods

Detection of single nucleotide polymorphism of breakpoint cluster region-c-ABL oncogene 1 by sequencing

Total genomic DNA from blood of both patients and control groups was extracted using DNA extraction kit (G-SPIN-INTRON\ KOREA). *BCR-ABL1* SNP detected by sequencing.

Determining the serum level biochemical parameters

Urea, ALT, AST, and LDH using enzymatic colorimetric method (Human, Germany), and creatinine using Kinetic method Human kit, Germany), for all patients and control subjects.

Estimation of breakpoint cluster region protein level

Using diagnostic kit based on quantitative sandwich enzyme-linked Immunosorbent assay (ELISA) (Sandwich ELISA BT LAB COMPANY).

Ethical considerations

Written informed consent was provided by all patients before entry into the study, and the study protocol was approved by Review ethical committee of Dentistry college/ Mustansiriyah university.

Statistical analysis

To assess the significance of the variables under investigation in this study, the Chi-square test was employed. All statistical analyses were conducted using the SPSS version 28 software (IBM, Delaware, Chicago, USA). $P < 0.05$ was deemed to indicate statistical significance.

Results

Age and sex distribution among groups

To age, the patients' groups were matching with the control group ($P = 0.62$). The sex ratio among the new diagnosis group and treated group was 1.5 and 1.08, respectively, which was match with control group ratio 1.5 ($P = 0.56$) [Table 1].

Table 1: Age and sex distribution between patients with chronic myeloid leukemia groups and control groups

Parameters	Patients (*n*=120)		Controls (*n*=30)	*P*
	New diagnosis (*n*=20)	Treated (*n*=100)		
Age±SD	35±12.1	51±11.89	44±13.7	0.62
Sex, *n* (%)				
Male	12 (60)	52 (52)	18 (60)	0.565
Female	8 (40)	48 (48)	12 (40)	
Ratio	1.5:1	1.08	1.5	

SD=Standard deviation

Biochemical parameters among study groups

According to biochemical parameters (urea creatinine, ALT, AST, and LDH) serum level, there are no statistically significant differences among new diagnosis CML, patients respond to treatments, and failure group accept in serum level of creatinine between new diagnosis CML group and failure group, there are statistically significant differences ($P = 0.01$) [Table 2].

The exact position of the breakpoint cluster region-c-ABL oncogene gene

The sequencing chromatogram of the identified variation, as well as its detailed annotations, was documented, and the chromatogram of this sequence was shown according to its position in the polymerase chain reaction amplicon. With regard to GG, it was demonstrated that this SNP was identified in a heterozygous (C > A; G/T) pattern as well as a homozygous variation (A/T) pattern [Table 3].

Genotyping of breakpoint cluster region-c-ABL oncogene polymorphism

The present results showed that DNA polymorphism distribution was according to C\C; G\C; A/T; and A\A were 32%, 26%, 18%, and 24%, respectively, in patients with CML and 28%; 20%;12%; and 40%, respectively, in the control group. There are significant statistical differences ($P < 0.05$) between different groups according to genotyping of *BCR\ABL* [Table 4 and Figure 1a, b].

Samples were submitted in NCBI, and the accession number of nucleotide sequences of *BCR\ABL* as new recording: LC775145.

Table 2: Comparison between new diagnosis chronic myeloid leukemia, treated patients respond to treatment and failure according to biochemical parameters

Parameters	New diagnosis (*n*=20)	Treated (*n*=100)		*P*
		Response to treatment (*n*=69)	Failure (*n*=31)	
Urea±SD (mg/dL)	31.5±7.8	33.3±18.2	30.3±12.1	0.615*
				0.69**
				0.399***
Creatinine±SD (mg/dL)	0.71±0.51	1.0±0.73	0.9±0.33	0.059*
				0.01**
				0.329***
ALT±SD (IU/L)	29.5±10.9	30.5±10.79	28.3±12.3	0.73*
				742**
				418***
AST±SD (IU/L)	33.6±12.6	32.2±12.7	33.2±15.6	0.671*
				931**
				733***
LDH±SD (IU/L)	478±201	485±278	438±20.4	0.909*
				0.49**
				0.39***

*Comparison between new diagnosis CML and response to treatment patients, **Comparison between new diagnosis CML patients and failure patients, ***Response to treatment patients and failure patients. CML=Chronic myeloid leukemia, SD=Standard deviation, LDH=Lactate dehydrogenase, AST=Aspartate transaminase, ALT=Alanine transaminase

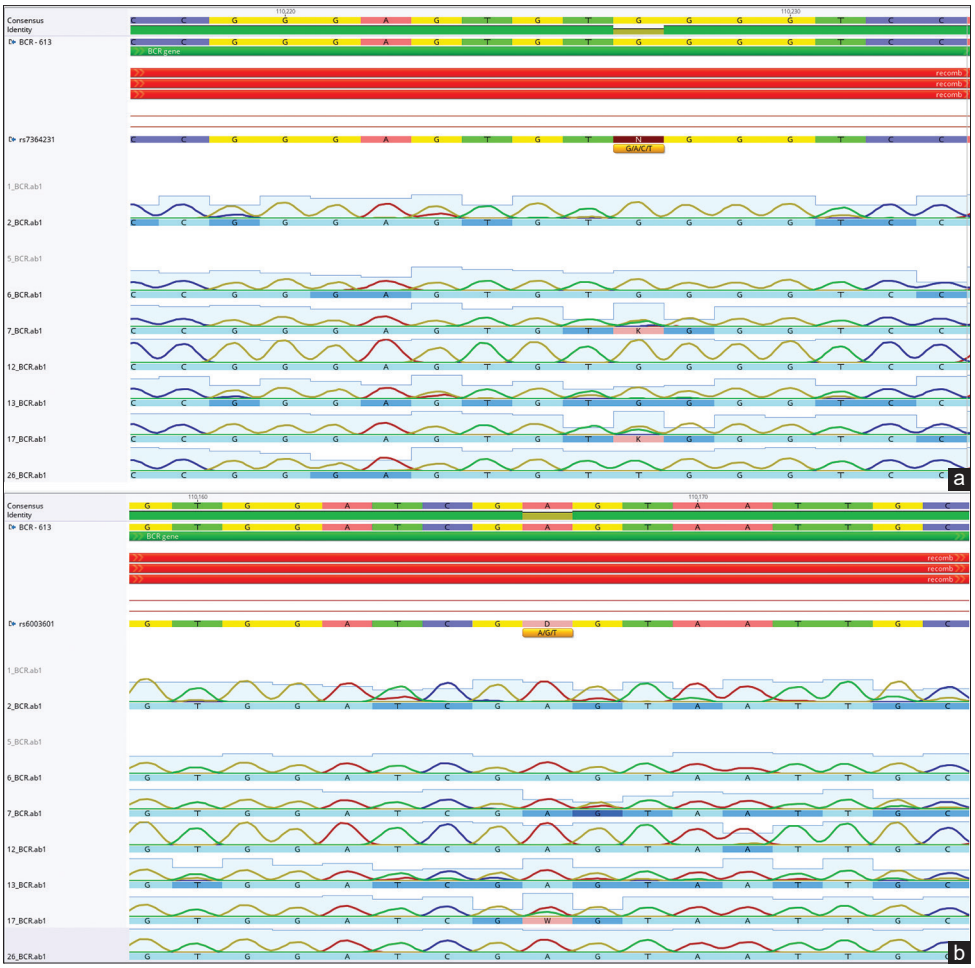

Figure 1: (a and b) The single nucleotide polymorphisms (SNP's) novelty checking of breakpoint cluster region-c-ABL oncogene genetic single nucleotide polymorphisms using the dbSNP server. The identified 613A >T SNP. The GenBank acc. no. NC_ rs7364231 was used in the positioning of the highlighted substitution SNP. The position of the targeted sequences was found in the negative strand

Table 3: Observed DNA sequences of breakpoint cluster region\c-ABL oncogene samples with the retrieved DNA sequences (GenBank acc. rs131677; rs1030813334; rs112463208; rs6003601; rs7364231)

SNPs	rs131677	rs1030813334	rs112463208	rs6003601	rs7364231
Wild	CC	GG	del/del	AA	GG
Variation	C>A	G>C	del/Ins	A>T	G>T
Samples					

SNPs=Single nucleotide polymorphisms

Table 4: Genotyping of breakpoint cluster region\c-ABL oncogene gene (429 bp) gene in comparison with the NCBI referring sequences (GenBank acc. no. rs131677; rs1030813334; rs112463208; rs7364231)

Zygosity status	CML, *n* (%)	Control, *n* (%)	Position in PCR fragment	Position in the reference genome	OR (95%)	SNP type	Significant	Variant summary
C/C	16 (32)	14 (28)		131677	0.98 (0.40–1.22)	3′-UTR	0.05	131677C/C
G/C	13 (26)	10 (20)	613	1030813334	1.55 (0.41–2.45)	3′-UTR	0.04	1030813334C/A
A/T	9 (18)	6 (12)	613	rs73642318	1.08 (0.40–2.43)	3′-UTR	0.04	rs7364231
A/A	12 (24)	20 (40)		6003601	2.98 (0.41–3.77)	3′-UTR	0.02	6003601
Totals	50	50						
Allele								
A	53	40			1.73 (0.65–1.89)		0.029	
T	47	60						

CML=Chronic myeloid leukemia, OR=Odds ratio, PCR=Polymerase chain reaction, SNP=Single nucleotide polymorphism

Comparison between chronic myeloid leukemia groups, controls group according to breakpoint cluster region proteins level

According to BCR protein level, there are statistically significant differences between new diagnosis of CML and CML on the treatment group and control group, ($P < 0.001$) for each comparison while there are no statistically significant differences between the treated group and control group ($P = 0.729$) [Table 5].

Comparison between new diagnosis chronic myeloid leukemia, treated patients respond to treatment and failure in breakpoint cluster region proteins level

According to BCR protein level, there are highly statistically significant differences between the new diagnosis group and the response to treatment group ($P < 0.001$) and also between the new diagnosis group and failure patients group ($P < 0.001$) while nonsignificant differences between respond to treatment and failure group ($P = 0.64$) [Table 6].

Comparison between new diagnosis chronic myeloid leukemia, patients and treated patients according to breakpoint cluster region proteins level

According to BCR protein level, there are statistically significant differences between the new diagnosis group and patients on imatinib and nonimatinib ($P < 0.001$), while there are no significant differences between patients on imatinib and nonimatinib [Table 7].

Table 5: Comparison between new chronic myeloid leukemia, treated patients, and control groups according to breakpoint cluster region - c-ABL oncogene gene expression, breakpoint cluster region proteins level, and ADAR1 enzyme level

Parameters	Patients (*n*=120)		Controls (*n*=30)	*P*
	New diagnosis (*n*=20)	Treated (*n*=100)		
BCR±SD protein	5.3±2.5	8.8±2.7	8.61±3.5	<0.001* <0.001** 0.729***

*Comparison between new diagnosis CML and treated patients, **Comparison between new diagnosis CML patients and control group, ***Comparison between treated patients with CML and control subjects. CML=Chronic myeloid leukemia, SD=Standard deviation, BCR=Breakpoint cluster region

Table 6: Comparison between new diagnosis chronic myeloid leukemia, treated patients respond to treatment, and failure in breakpoint cluster region proteins level

Parameters	New diagnosis (*n*=20)	Treated (*n*=100)		*P*
		Response to treatment (*n*=69)	Nonimatinib (*n*=31)	
BCR±SD protein	5.3±2.5	8.9±2.9	8.63±2.2	<0.001* <0.001** 0.64***

*Comparison between new diagnosis CML and response to treatment patients, **Comparison between new diagnosis CML patients and failure patients, ***Response to treatment patients and failure patients. CML=Chronic myeloid leukemia, SD=Standard deviation, BCR=Breakpoint cluster region

Table 7: Comparison between new diagnosis chronic myeloid leukemia, patients on imatinib, and patients nonimatinib group according to breakpoint cluster region proteins level

Parameters	New diagnosis (*n*=20)	Treated patients (*n*=100)		*P*
		On imatinib (*n*=65)	Nonimatinib (*n*=35)	
BCR±SD protein	5.3±2.5	9.05±3.2	8.4±1.47	<0.001* <0.001** 0.25***

*Comparison between new diagnosis CML and patients on imatinib, **Comparison between new diagnosis CML patients and patients on nonimatinib, ***Comparison between patients on imatinib and patients on nonimatinib. CML=Chronic myeloid leukemia, SD=Standard deviation, BCR=Breakpoint cluster region

Discussion

CML is described as a condition of the clonal progenitor of the hemopoietic tissue, in which the production of new myeloid blast cells is accelerated while the rate of apoptosis is decreased.[8]

In the current study, the average age of patients with a new diagnosis is 35 years, group has an average age of 51 years. However, the $P = 0.62$ suggests that the difference in age between the groups is not statistically significant. In terms of gender, the data indicates a slightly higher proportion of males in the patient groups compared to the control group, although this difference is not statistically significant. The result is compatible with epidemiological data that shows that the CML patient's age differs at the time of analysis depicts the median age ranges among 52–64 years.[9] Another study shows that CML usually presents at a median age (35–45 years) in Asians and the global incidence rate of CML is 15/1,000,000/year with a male-to-female ratio of 1.34.[10,11] The available Indian literature reports that a significant proportion of the patient population consisted of individuals under the age of 60. The present investigation indicates that there exists no statistically significant disparity in diverse clinical parameters among elderly patients diagnosed with CML.[12,13]

The development of TKIs has had a substantial impact on the natural history of CML, resulting in a remarkable improvement in patients' survival.[14] Considering the fact that CML is a neoplasm characterized by molecular abnormalities, it is unlikely that there would be substantial differences in results based on sex. Nevertheless, an examination of research conducted before to the introduction of TKIs uncovers intriguing gender-related disparities in the manifestation and results of individuals diagnosed with CML.

Berger *et al*.[14] conducted an analysis on a cohort of 856 patients diagnosed with CML. The findings of their investigation revealed that female patients had elevated platelet counts and smaller spleen diameters compared to their male counterparts.[14] Furthermore, it was observed that males diagnosed with CML exhibited a greater prevalence of supplementary chromosomal abnormalities and experienced inferior survival rates. The impact of the Sokal score-based risk assessment on the observed outcome was found to be insignificant, with a notable discrepancy detected specifically among those classified as having low or moderate risk.

The results of our study indicate a significant increase in AST and ALT enzyme levels in the pretreatment group of patients aged 12 (20%) and 6 (10%) years, respectively. These elevations were found to be statistically significant compared to the pretreatment group. The *P* values for AST, ALT, and ALP enzymes were 0.0001, 0.001, and 0.03, respectively. In addition, it was observed that the mean levels of ALP enzyme were higher than the normal reference value in both groups. This observation pertains to the metabolic and physiological processes occurring within tumors. In their study conducted in Kinshasa, Mupepe *et al*. investigated the levels of uricemia, fasting blood sugar, and serum creatinine. Uricemia levels ranged from 60 to 108 mg/L, fasting blood sugar levels ranged from 50 to 172 g/dL, and serum creatinine levels ranged from 1.2 to 4.7 mg/dL.[15]

The medication side effects in the treatment of CML commonly involve the administration of TKIs, including imatinib, dasatinib, and nilotinib. Although these medications have demonstrated efficacy in the management of CML, they may also give rise to adverse effects such as hepatotoxicity (damage to the liver) and nephrotoxicity (injury to the kidneys). Elevated liver function tests (such as ALT and AST) and renal function markers might be observed because of drug-induced damage to these organs.[16]

Co-existing conditions: Some CML patients might have other underlying medical conditions that can impact liver and kidney function.

The co-expression of e13a2 and e14a2 transcripts has been documented in specific population cohorts, including 13% of individuals from Mexican descent, 2.5% of Mexican mestizos, 5.36% of individuals of East Indian origin, 4.6% of Sudanese individuals, and 4.38% of those from North Indian ancestry.[17,18] The presence of dual transcripts is not limited to certain phases since it has been documented throughout all stages of the disease. In a previous study conducted by Branford *et al*.,[19] it was demonstrated that the occurrence of an intronic polymorphism in the BCR gene is linked to the activation of a cryptic splice site. This activation is highly likely to lead to a decrease in the efficiency of RNA splicing and the subsequent exclusion of exon 14 in both BCR and BCR-ABL.

Six patients from eastern India with dual transcripts were described by Mondal *et al*.[17] in 2006. All six of the patients had intronic polymorphism, at least in heterozygous form, but not all of the patients had exonic polymorphism. Although the presence of BCR-ABL is sufficient for CML to develop, the development of additional secondary mutations is necessary for the disease to advance from the chronic phase to the lethal blast crisis phase. ABL kinase domain mutations are one of the molecular pathways for medication resistance and illness development, according to reports from a number of research groups.[20] According to a previous report by Kuila *et al*.,[21,22] the incidence of ABL kinase domain mutation in the Indian population is lower than it is in other populations. In a study including 171 Japanese patients, Hashimoto *et al*.[23] found that the N796S polymorphism was substantially related with bipolar II disease. According to a different study,[24] interferon-alpha therapy was linked to bipolar disorder.

Although interferon-alpha was utilized in the treatment of CML, we also discovered this specific polymorphism in control samples. Therefore, there may be no connection between this polymorphism and the use of interferon-alpha or bipolar illness. In addition, one patient had Y910C (rs35537221) polymorphism, according to Nandagopalan *et al*.[25] Although the 1000 genome project indicates that this polymorphism is likely a polymorphism, the mutation taster prediction tool indicated that it may be a polymorphism that causes disease. This polymorphism has not been linked to any known diseases, but Greenman *et al*.[26] reported it as a germline variant. Isokpehi *et al*.[22] have also described it as a nonsynonymous polymorphism that may serve as a possible marker for the responsiveness of protein targets to arsenic.

According to the BCR-ABL gene expression, there are statistically significant variations between the groups ($P = 0.001$). The ratio of the two main transcripts of the M-BCR area, e14a2: e13a2, was determined in an Indian and Bulgarian study to be 1.3:1, which is nearly in agreement with the ratio found in the current study.[27,28]

Studies from Iran and India showed the frequency of e14a2 transcripts to be nearly three times higher than that of e13a2 while reports of e14a2 levels two times higher (ratio 2:1) than e13a2 in CML patients from Brazil, Malaysia, and Korea[29] were also made.

A few studies have also shown that CML patients had a higher frequency of the e13a2 transcript than they do of the more typical e14a2 transcript.[30] Based on the differences in natural genetic factors, environmental factors, and living styles among different ethnic groups, the variation in frequencies of common transcript among different populations and locations of the world can be explained.[31] The prevalence of co-expression in our local population, however, was reported to be very low, which is consistent with the findings of the current investigation.[32]

The clinical characteristics of the two groups of patients with normal transcripts were not significantly different, according to this study. Patients with e14a2 transcripts were found to be younger than patients with e13a2 transcripts when analyzing the difference in means of numerical variables, albeit this difference was not statistically significant. This observation was supported by a study from our local population and a report from the Syrian population.[33] In addition, it is thought that there must be other factors that affect the clinical and hematological characteristics in addition to the kind of transcript for there to be variances between them.[32]

According to BCR protein levels, new diagnosis CML and CML on the treatment group and control group show statistically significant differences, with $P = 0.001$ for each comparison, whereas the treated group and control group show no statistically significant differences, with $P = 0.729$.

In this study, a substantial link between the male gender and the e14a2 transcript was found while looking at a potential relationship between the BCR-ABL variations and clinical parameters in CML patients. This result is consistent with research done in Iran, India, and Iraq.[30]

Other research, however, disputes this finding and states that there is no correlation between the proportion of men and women in any type of fusion gene.[33]

The BCR protein is enriched in neurons and involved in neural activities in healthy individuals. These activities are implicated in cellular processes such as regulation of cell cycle, differentiation, and morphogenesis[34] and because translocation between chromosome 9 and c is associated with BCR protein, there are significant differences in levels between new diagnosis patients, treated patients, and control group.[35]

Conclusion

The present study results showed differences in several parameters between newly diagnosis, treated patients, and controls such as in biochemical parameters (urea, creatinine, ALT, AST, and LDH) has no changes in CML patients except LDH elevated in new diagnosis and treated CML patients, and it has no changes in patients on imatinib or nonimatinib. The protein level was elevated in treated patients and decreased in newly diagnoses. Patients newly and treated (response) and this percentage elevated in failure patients which may play a role in the reprogramming of myeloid progenitor into LSC that derive CML progression.

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Conflicts of interest
There are no conflicts of interest.

References

1. Faderl S, Talpaz M, Estrov Z, O'Brien S, Kurzrock R, Kantarjian HM. The biology of chronic myeloid leukemia. N Engl J Med 1999;341:164-72.
2. Bruns I, Czibere A, Fischer JC, Roels F, Cadeddu RP, Buest S, *et al*. The hematopoietic stem cell in chronic phase CML is characterized by a transcriptional profile resembling normal myeloid progenitor cells and reflecting loss of quiescence. Leukemia 2009;23:892-9.
3. Reid AG, De Melo VA, Elderfield K, Clark I, Marin D, Apperley J, *et al*. Phenotype of blasts in chronic myeloid leukemia in blastic phase-analysis of bone marrow trephine biopsies and correlation with cytogenetics. Leuk Res 2009;33:418-25.
4. Jabbour E, Kantarjian H, Jones D, Talpaz M, Bekele N, O'Brien S, *et al*. Frequency and clinical significance of BCR-ABL mutations in patients with chronic myeloid leukemia treated with Imatinib mesylate. Leukemia 2006;20:1767-73.
5. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2018 update on diagnosis, therapy and monitoring. Am J Hematol 2018;93:442-59.
6. Höglund M, Sandin F, Hellström K, Björeman M, Björkholm M, Brune M, *et al*. Tyrosine kinase inhibitor usage, treatment outcome, and prognostic scores in CML: Report from the population-based Swedish CML registry. Blood 2013;122:1284-92.
7. Pascu VÎnturiŞ EG, GĂman AM. Assessment of oxidative stress in patients with chronic myeloid leukemia depending on associated comorbidities. Curr Health Sci J 2020;46:23-30.
8. Al-Bayati A, Al-Bayti A, Husain V. A short review about chronic myeloid leukemia. J Life Bio Sci Res 2023;4:15-9.
9. Algahtani FH, Alqahtany FS. Evaluation and characterisation of chronic myeloid leukemia and various treatments in Saudi Arabia: A retrospective study. J Infect Public Health 2020;13:295-8.
10. Rohrbacher M, Hasford J. Epidemiology of chronic myeloid leukaemia (CML). Best Pract Res Clin Haematol 2009;22:295-302.
11. Suttorp M, Millot F, Sembill S, Deutsch H, Metzler M. Definition, epidemiology, pathophysiology, and essential criteria for diagnosis of pediatric chronic myeloid leukemia. Cancers (Basel) 2021;13:798.
12. Hochhaus A. Educational session: Managing chronic myeloid leukemia as a chronic disease. Hematology Am Soc Hematol Educ Program 2011;2011:128-35.
13. Latagliata R, Ferrero D, Iurlo A, Cavazzini F, Castagnetti F, Abruzzese E, *et al*. Imatinib in very elderly patients with chronic myeloid leukemia in chronic phase: A retrospective study. Drugs Aging 2013;30:629-37.
14. Berger U, Maywald O, Pfirrmann M, Lahaye T, Hochhaus A, Reiter A, *et al*. Gender aspects in chronic myeloid leukemia:

Long-term results from randomized studies. Leukemia 2005;19:984-9.
15. Coutre L, Philippe D, *et al*. Paterns and management of Selected Adverse Events of adult Patients with Imatinib-Resistant or Intolerant Chronic Myeloid Leukemia (CML) from the Expanding Nilotinib Access in Clinical Trials (ENACT) study. Blood 2009;114:1115.
16. Abruzzese E, Mauro M, Apperley J, Chelysheva E. Tyrosine kinase inhibitors and pregnancy in chronic myeloid leukemia: Opinion, evidence, and recommendations. Ther Adv Hematol 2020;11:1-13.
17. Mondal BC, Bandyopadhyay A, Majumdar S, Mukhopadhyay A, Chandra S, Chaudhuri U, *et al*. Molecular profiling of chronic myeloid leukemia in Eastern India. Am J Hematol 2006;81:845-9.
18. Osman EA, Hamad K, Elmula IM, Ibrahim ME. Frequencies of *BCR-ABL1* fusion transcripts among Sudanese chronic myeloid leukaemia patients. Genet Mol Biol 2010;33:229-31.
19. Branford S, Hughes TP, Rudzki Z. Dual transcription of b2a2 and b3a2 BCR-ABL transcripts in chronic myeloid leukaemia is confined to patients with a linked polymorphism within the BCR gene. Br J Haematol 2002;117:875-7.
20. Ernst T, La Rosée P, Müller MC, Hochhaus A. BCR-ABL mutations in chronic myeloid leukemia. Hematol Oncol Clin North Am 2011;25:997-1008, v-vi.
21. Kuila N, Dash N, Sahoo DP, Pattnayak NC, Biswas G, Chakraborty S. Presence of a new BCR-ABL kinase domain mutation, C330G in an imatinib naive patient with chronic myeloid leukemia: Very low prevalence of BCR-ABL kinase domain mutations in patients with chronic myeloid leukemia from Eastern India. Leuk Lymphoma 2009;50:663-6.
22. Isokpehi RD, Cohly HH, Anyanwu MN, Rajnarayanan RV, Tchounwou PB, Udensi UK, *et al*. Candidate single nucleotide polymorphism markers for arsenic responsiveness of protein targets. Bioinform Biol Insights 2010;4:99-111.
23. Hashimoto R, Okada T, Kato T, Kosuga A, Tatsumi M, Kamijima K, *et al*. The breakpoint cluster region gene on chromosome 22q11 is associated with bipolar disorder. Biol Psychiatry 2005;57:1097-102.
24. Iancu I, Sverdlik A, Dannon PN, Lepkifker E. Bipolar disorder associated with interferon-alpha treatment. Postgrad Med J 1997;73:834-5.
25. Nandagopalan SR, Kuila N, Biswas S, Pattnayak NC, Biswas G, Chakraborty S. Dual transcripts of BCR-ABL & different polymorphisms in chronic myeloid leukaemia patients. Indian J Med Res 2016;143:S136-41.
26. Greenman C, Stephens P, Smith R, Dalgliesh GL, Hunter C, Bignell G, *et al*. Patterns of somatic mutation in human cancer genomes. Nature 2007;446:153-8.
27. Balatzenko G, Vundinti BR, Margarita G. Correlation between the type of bcr-abl transcripts and blood cell counts in chronic myeloid leukemia – A possible influence of mdr1 gene expression. Hematol Rep 2011;3:e3.
28. Deb P, Chakrabarti P, Chakrabarty S, Aich R, Nath U, Ray SS, *et al*. Incidence of BCR-ABL transcript variants in patients with chronic myeloid leukemia: Their correlation with presenting features, risk scores and response to treatment with imatinib mesylate. Indian J Med Paediatr Oncol 2014;35:26-30.
29. Vasconcelos AP, Azevedo IF, Melo FCBC, Neves WB, Azevedo ACAC, Melo RAM. BCR-ABL1 transcript types showed distinct laboratory characteristics in patients with Chronic Meyloid Leukemia. Genet Mol Res 2017;16:541.
30. Mir R, Ahmad I, Javid J, Zuberi M, Yadav P, Shazia R, *et al*. Simple multiplex RT-PCR for identifying common fusion BCR-ABL transcript types and evaluation of molecular response of the a2b2 and a2b3 transcripts to imatinib resistance in North Indian chronic myeloid leukemia patients. Indian J Cancer 2015;52:314-8.
31. de Almeida Filho TP, Maia Filho PA, Barbosa MC, Dutra LL, Castro MF, Duarte FB, *et al*. Does BCR-ABL transcript type influence the prognosis of patients in chronic myelogenous leukemia chronic phase? Hematol Transfus Cell Ther 2019;41:114-8.
32. Javed A, Mukhtar H, Kubra KT, Lodhi S, Abaidullah S. Detection of BCR-ABL fusion gene and its transcript variants in chronic myeloid leukaemia patients – A multi-comparison study. J Pak Med Assoc 2020;70:1748-11752.
33. Al-Achkar W, Moassass F, Youssef N, Wafa A. Correlation of p210 BCR-ABL transcript variants with clinical, parameters and disease outcome in 45 chronic myeloid leukemia patients. J BUON 2016;21:444-9.
34. Modranka J, Jakubowski R, Różalski M, Krajewska U, Janecka A, Gach K, *et al*. Design, synthesis and cytotoxic evaluation of 4-methylidenepyrazolidin-3-ones. Eur J Med Chem 2015;92:565-74.
35. Park AR, Oh D, Lim SH, Choi J, Moon J, Yu DY, *et al*. Regulation of dendritic arborization by BCR Rac1 GTPase-activating protein, a substrate of PTPRT. J Cell Sci 2012;125:4518-31.