Original Article

Access this article online
Quick Response Code:

Website: https://journals.lww.com/ijhm
DOI: 10.4103/ijh.ijh_140_25

Assessment of fragile histidine triad (FHIT) gene expression as a predictive biomarker of therapeutic response in chronic myeloid leukemia

Noor Hashim Ismail, Amal Mohamed Ali[1], Asmaa Amer Almukhtar[1]

Abstract:

BACKGROUND: The accumulation of other abnormalities in both genetic and epigenetic pathways, in addition to the *BCR-ABL1* oncoprotein, affects the overall clinical consequences of chronic myeloid leukemia (CML), including treatment responsiveness.

OBJECTIVES: This study investigated the expression levels of fragile histidine triad (*FHIT*) gene among patients with CML and evaluated its association with the response of patients to imatinib mesylate treatment.

PATIENTS AND METHODS: Samples of blood were provided from sixty CML patients: Thirty responsive and thirty nonresponsive patients to imatinib mesylate treatment, as well as sixty healthy controls matched for age and sex were provided blood samples. The *FHIT* gene expression was estimated using reverse transcription quantitative polymerase chain reaction.

RESULTS: The results indicated that *FHIT* gene expression was significantly lower in CML patients than in the controls ($P < 0.001$). Compared to the responsive CML patients, the nonresponsive CML patients presented a significantly decreased level of *FHIT* gene expression ($P < 0.001$). A significant increase in *FHIT* gene expression was found at a cut-off value of more than 0.0578 for distinguishing responsive from nonresponsive CML patients, as shown by receiver operating characteristic analysis, with 97% sensitivity and 72.4% specificity.

CONCLUSIONS: Reduced *FHIT* gene expression was associated with CML and with changes in hematopoietic patterns observed in the studied patients. Variations in *FHIT* expression were noted between responsive and nonresponsive patients, indicating a potential association with treatment response, suggesting that *FHIT* expression may have value as a complementary predictive biomarker for imatinib mesylate responsiveness, although further validation is required.

Keywords:

Chronic myeloid leukemia, fragile histidine triad gene expression, imatinib mesylate, treatment response

Departments of Cancer Research and [1]Medical Genetics, Iraqi Center for Cancer and Medical Genetics Research, Mustansiriyah University, Baghdad, Iraq

Address for correspondence:
Dr. Noor Hashim Ismail, Department of Cancer Research, Iraqi Center for Cancer and Medical Genetics Research, Mustansiriyah University, Baghdad, Iraq.
E-mail: noor.hi@uomustansiriyah.edu.iq

Submission: 12-10-2025
Revised: 15-02-2026
Accepted: 19-02-2026
Published: 21-03-2026

Introduction

Leukemia ranked the seventh most prevalent cancer in Iraq in 2023, with an overall age-specific rate of 6 per 100,000 people, and Iraqis, fifth most prevalent cause of cancer-related mortality.[1] Chronic myeloid leukemia (CML) represents a malignant disorder affecting hematopoietic stem cells with a high incidence rate in adults and is characterized by accelerated generation of new myeloid blast cells and a reduced rate of apoptosis.[2] This occurs alongside a range of symptoms, including anemia, fatigue, leukocytosis, splenomegaly, thrombocytosis, and basophilia. The disease primarily originates from a genetic

How to cite this article: Ismail NH, Ali AM, Almukhtar AA. Assessment of fragile histidine triad (FHIT) gene expression as a predictive biomarker of therapeutic response in chronic myeloid leukemia. Iraqi J Hematol 2026;15:113-20.

abnormality related to the Philadelphia chromosome due to a chromosomal translocation comprising long arms of chromosomes 9 and 22, specifically t (9;22) (q34;q11.2), resulting in fusion between *BCR* and *ABL1* genes, forming the path-oncogenic driver *BCR-ABL1*, which functions as the persistently active tyrosine kinase implicated in CML and serves as a goal for tyrosine kinase inhibitors (TKIs).[3,4] This disease is defined as a triphasic disorder: Chronic phase (CP), accelerated phase (AP) and blastic phase. Approximately 85% to 90% of patients exhibit a stable phase, the rest, meanwhile, are either in an AP or going through blast crisis. In the absence of therapy, the CP of the disease will ultimately progress to either AP or blast crisis. However, TKIs have been shown to significantly reduce the rate at which the disease progresses to the blast crisis stage.[5] In the context of cancer, such as leukemia, the mechanisms of therapy resistance may be associated with both genetic and epigenetic alterations.[6] Resistance mechanisms to TKIs in CML are often classified into *BCR-ABL1*-dependent and *BCR-ABL1*-independent pathways. Alongside *BCR-ABL1* alterations and overexpression, various pathways are associated with resistance to TKIs. These include anomalous drug transporter activity, alternative signaling pathway activation, genomic instability, leukemia stem cells persistence, immune system malfunction, and impaired epigenetic regulatory mechanisms.[7] Common chromosomal fragile sites refer to genomic regions characterized by susceptibility to breakage, rearrangement, and an increased probability of recombination.[8] The fragile histidine triad *(FHIT)* gene, a large gene located on FRA3B, one of the frequent chromosomal fragile loci, on chromosome 3p14.2, functions as a tumor suppressor gene that is disrupted in several forms of cancer; however, the exact mechanism by which *FHIT* suppresses tumors is not completely understood.[8]

The concept emerged from the observation of common abnormalities in these loci within tumor cells, indicating their possible role in cancer development. FRA3B is one of the most common chromosomal fragile loci and contains *FHIT* gene, which serves as a tumor suppressor implicated in numerous cancers. Its activity is frequently altered by genetic and epigenetic modifications, such as deletions, translocations, and promoter methylation, which often lead to diminished expression of the *FHIT* protein in many types of cancer.[9-11] Studies indicated that *FHIT* frequently downregulated in hematological malignancies, including CML compared to normal hematopoietic cells, and may be associated with disease progression, poorer prognosis, and resistance to therapy.[12-19] *FHIT* has been demonstrated to inhibit tumor development through the initiation of apoptosis and the inhibition of cellular growth.[20,21]

This study aims to assess the association between *FHIT* mRNA gene expression and the progression of CML, along with the treatment response of CML patients to imatinib mesylate treatment, a first-generation TKI.

Patients, Materials, and Methods

Ethical approval

This research was executed in conformity with the ethical rules stated in the Declaration of Helsinki. The approval of this research protocol from our institution's scientific committee carried out in accordance with ethical standards approved according to document no. 1 dated January 15, 2023. The study was conducted following the acquisition of verbal and written informed consent from patients, after which samples and clinical information were collected during the period from January 2023 to December 2023.

Study subjects

A total of sixty CML patients receiving imatinib mesylate treatment for at least 1 year as a first-line therapy, comprising: 30 responsive (taken 400 mg/day of imatinib) and 30 nonresponsive to therapy (20 patients taken 400 mg/day of imatinib and 10 patients taken 600 or 800 mg/day), were included. These patients were in the CP and selected on the basis of molecular (*BCR-ABL*% international scale) and hematological response criteria retrieved from their records, as stated according to the European Leukemia Net 2023 criteria,[22] and collected from Mustansiriyah University/The National Center of Hematology research and treatment. In addition, sixty healthy subjects, matched for sex and age, were assigned as to the control group; their complete blood counts (CBCs) were within normal ranges and had no history of hematologic disorders. Five milliliters of peripheral blood were collected from each participant, including both patients and controls, and divided into two tubes containing K3EDTA (2 ml each): One tube was used for CBC analysis, and the other was used for the extraction of the total RNA to evaluate *FHIT* gene expression.

Extraction of total RNA with subsequent cDNA synthesis

Extraction of complete RNA has been performed by combining 0.25 ml of k3EDTA-treated blood and 0.75 ml of TransZol Up reagent (TransGen Biotech Co., China) according to the manufacturer's protocol with some modifications that focus on the use of cold reagents throughout (chloroform, isopropanol, and ethanol were precooled before use), and extended-low temperature incubation steps, in addition to the use of cooled centrifuge, intended to enhance RNA yield and stability. The NanoDrop spectrophotometer (Quawell, USA) was utilized for the assessment of purity as well

as the quantity of the purified RNA. The cDNA has been produced via reverse transcription of total RNA employing the EasyScript® One-Step gDNA Removal and cDNA Synthesis SuperMix Kit (TransGen Biotech Co., China) using both random hexamer and Oligo dT primers. The execution of this process complied strictly with the manufacturer's directions.

Assessment of fragile histidine triad gene expression

Fluorescent dye-based quantitative real-time polymerase chain reaction (PCR) was performed for the purpose of determining the expression of *FHIT* using the Rotor-Gene® Q (Qiagen, Germany). Primer 3 plus software was used for the designation of the *FHIT* gene primers, whereas the sequence of the reference gene used, *β-Actin*, was obtained from a prior study.[23] The reaction was accomplished by employing 10 μL of TransStartTM Top Green quantitative PCR SuperMix (TransGen Biotech Co., China), 3 μL of cDNA, and 0.5 μLof each of the primers (10 μM) listed in Table 1 and nuclease-free water (6 μL), for a total volume of 20 μL. The following characterizes the thermal profile: holding the temperature at 94° Celsius for 60 s, followed by forty cycles encompassing denaturation at 94° Celsius for 5 s, followed by annealing (at 54° Celsius for both *FHIT* and *β-Actin*) for 15 s and extension at 72° Celsius for 20 s. After that, samples are dissociated from 65° Celsius to 95° Celsius (5 s for 1°). An examination of the melting curve was performed to validate the specificity of the amplified product. The expression of the *FHIT* gene was assessed by relative fold change in gene expression, estimated via the delta-delta Ct method.[24] The data were normalized to the endogenous reference gene (β-Actin) with respect to the controls.

Statistical analysis

Data analysis was conducted via the Statistical Package for Social Sciences, version 22 (SPSS 22; IBM Corporation, Armonk, New York, USA; Released 2013). The Shapiro–Wilk test was employed to assess the normality of the quantitative parameters under study. Data were provided using fundamental statistical measures, including medians, and interquartile ranges (IQRs), frequencies, and percentages, two-sample *t*-test (Parametric approach), along with Mann–Whitney *U*-test (nonparametric approach), have been employed to evaluate the quantitative data of two groups. The frequency and percentage of qualitative data are reported, and any significant changes in distribution that occur within the research groups are measured by implementing Pearson's Chi-square test or Fisher's exact test, depending on which is most suitable. The best cut-off point for *FHIT* gene expression levels in differentiating CML patients according to their responsiveness to therapy was determined using the receiver operating characteristic (ROC) analysis. A probability (P) < 0.05 was considered statistically significant.

Table 1: Primers used for the investigating the expression of the fragile histidine triad gene

Primers sequences for gene expression		
Primer	**Sequence (5′ →3′ direction)**	**Product size (pb)**
FHIT		
Forward	CCCAGTGGGAGGTAACTGAA	142
Reverse	AAAGAGGAGCAAAGCCACA	
β-Actin		
Forward	CCGCAAATGCTTCTAGGCG	78
Reverse	TGTTTTCTGCGCAAGTTAGGT	

FHIT=Fragile histidine triad

Results

The general features of examined cohorts

The general characteristics of the studied groups are presented in Table 2. There were no significant differences (P = 0.871) between the control and the patient groups according to age (mean ± standard deviation), with values of 46.50 ± 10.735 and 46.12 ± 12.501, respectively. In addition, for the responsive and nonresponsive CML patients (P = 0.532), the mean ± standard deviation age was 45 ± 11.310 years for the responsive patients and 47.24 ± 13.73 years for the nonresponsive CML patients. This study revealed that females presented significantly greater nonresponsiveness to therapy than males did (60% vs. 40%; P = 0.02). The findings of this study indicated that patients with CML exhibited significantly lower mean ± standard deviation of hemoglobin levels (11.2860 ± 2.054, P < 0.001) than did the controls (14.084 ± 0.657). In addition, these patients presented a significantly greater (P = 0.03) white blood cell (WBC) counts median (IQR) value 7.3750 (5.45–12.35) than did the controls 6.5500 (4.90–7.65) and had significantly greater (P = 0.008) platelet counts 318 (236.5–480.75) versus 291 224–316.25 in controls. A comparison of responsive and nonresponsive CML patients revealed that those who were nonresponsive to treatment exhibited notably lower hemoglobin levels (9.8 ± 1.48969, P < 0.001), as well as significantly higher WBC counts 12.3 (7.25–19.34); P < 0.001 and platelet counts 479 (378–525); P < 0.001. This study demonstrated a significantly greater median (IQR) *BCR-ABL*% (P < 0.001) in nonresponsive patients 1.1 (0.42–11.185) than in responsive CML patients 0.0032 (0.0001–0.021).

RNA concentration and purity

Table 3 shows acceptable extracted RNA concentrations and purity. The median (IQR) RNA concentration for controls and patients was 865 (640–1613) and 1472 (665–2026), respectively, with a median (IQR) RNA purity (260/280) 2.03 (2–2.1) in controls and 2 (2–2.07) in

Table 2: The general characteristics of the studied groups

Variables	Group		*P*	Group		*P*
	Controls (*n*=60)	CML patients (*n*=60)		Responsive CML patients (*n*=30)	Nonresponsive CML patients (*n*=30)	
Age	46.50±10.735	46.12±12.501	0.871	45±11.310	47.24±13.73	0.532
Sex, *n* (%)						
Male	33 (55)	33 (55)	1	21 (70)	12 (40)	0.02
Female	27 (45)	27 (45)		9 (30)	18 (60)	
Hemoglobin (g/dL)	14.084±0.657	11.2860±2.054	<0.001	12.772±1.338	9.8±1.48969	<0.001
White blood cells ($\times10^3$/mm^3)	6.5500 (4.90–7.65)	7.3750 (5.45–12.35)	0.03	6.6000 (5.65–7.375)	12.3 (7.25–19.34)	<0.001
Platelets ($\times10^3$/mm^3)	291 (224–316.25)	318 (236.5–480.75)	0.008	257 (221.50–285.5)	479 (378–525)	<0.001
BCR-ABL %(IS)	-	-	-	0.0032 (0.0001–0.021)	1.1 (0.42–11.185)	<0.001

CML=Chronic myeloid leukemia, IS=International Scale

Table 3: RNA concentrations and purity of the studied groups

Variables	Group		*P*
	Controls (*n*=60)	CML patients (*n*=60)	
RNA concentration (ng/μL)	865 (640–1613)	1472 (665–2026)	0.183
RNA purity (260/280)	2.03 (2–2.1)	2 (2–2.07)	0.257

patients without significant differences between study groups.

Fragile histidine triad gene expression

The estimation of *FHIT* gene expression revealed significantly downregulated *FHIT* gene expression level among CML patients as opposed to the controls group ($P < 0.001$), with a fold change of 0.0651 and a median (IQR) fold change in *FHIT* gene expression of 0.1090 (0.0254–0.2890). The analysis of CML patient groups on the basis of treatment responsiveness revealed a significant ($P < 0.001$) reduction in *FHIT* mRNA level among the nonresponsive patient group, with a fold change of 0.0197 and a median (IQR) expression of 0.0266 (0.0067–0.1034), compared with responsive patients group, which presented a fold change of 0.215 and a median (IQR) expression of 0.2083 (0.1286–0.3327). Table 4 summarizes the levels of expression *FHIT* gene mRNA within study groups via a $2^{-\Delta\Delta Ct}$ method.[24] Figures 1 and 2 illustrate the amplification plot and the melting curve of the *β-Actin* and *FHIT* genes, respectively.

An analysis of the ROC curve has been conducted for assessing the diagnostic utility of *FHIT* gene expression in predicting treatment responsiveness in patients with CML [Table 5 and Figure 3].

For *FHIT* gene expression, the value for the area under the curve value was recorded at 0.876, with a $P < 0.001$ among responsive CML patients compared with nonresponsive CML patients, indicating its potential as a marker to distinguish responsive CML patients from nonresponsive CML patients. The *FHIT* gene expression fold exhibited 97% sensitivity and 72.4% specificity at a best cut-off value of 0.0578 for differentiating CML patients according to their responsiveness to therapy.

Discussion

The introduction of TKIs, including imatinib mesylate, has markedly enhanced the clinical results for patients with CML. Numerous molecular investigations on Iraqi CML patients have examined the diverse parameters influencing the responsiveness to this therapy.[25-31] This study examined the impact of *FHIT* gene expression level on the responsiveness of CML patients to imatinib mesylate. Results showed that among CML patients enrolled in the present study, 46.12 year was the mean age. This finding is consistent with previous research showing that CML affects younger populations in Asian countries than in Western countries.[32-34] In addition, the failure rate of females to respond to imatinib treatment was substantially greater ($P < 0.05$) than that of males (60% vs. 40%), possibly due to hormonal variations between the sexes.[35,36] Vitamin D insufficiency is common among Iraqi females and may affect how CML patients respond to therapy.[37,38] On the other hand, a number of studies conducted recently have shown that molecular responses tend to be better in females than in males.[39] The results also indicated that CML patients had significantly lower hemoglobin levels and increased WBC, and platelet counts in comparison to those in the control group. In addition, the nonresponsive CML patients exhibited markedly lower hemoglobin levels and increased WBC, and platelet counts than responsive CML patients did. In CML patients who were nonresponsive to therapy, disease progression may lead to a more severe disease phase characterized by bone marrow suppression due to leukemic cell clone expansion.[40] In accordance with the European Leukemia Net (ELN) 2023[22] published criteria for TKI response, this study revealed a considerably high *BCR-ABL*% among nonresponsive CML patients.

This study revealed a significantly lower gene expression level of *FHIT* in CML patients than in

Table 4: Fragile histidine triad gene expression levels across the study groups

Group	Mean Ct *β-Actin*	Mean Ct *FHIT*	Δ Ct	Δ Ct calibrator	ΔΔCt	$2^{-\Delta\Delta Ct}$	Experimental/ control group	*FHIT* mRNAexpression level		*P*
								Fold change	Fold expression level, median (IQR)	
Controls	19.226	24.233	5.007	6.614	−1.607	3.046	3.046/3.046	1	0.7197 (0.4188–2.5135)	<0.001
CML patients	19.422	28.371	8.948	6.614	2.335	0.198	0.198/3.046	0.0651	0.1090 (0.0254–0.2890)	
Responsive CML patients	19.261	26.486	7.225	6.614	0.611	0.655	0.655/3.046	0.215	0.2083 (0.1286–0.3327)	<0.001
Nonresponsive CML patients	19.584	30.255	10.672	6.614	4.058	0.060	0.060/3.046	0.0197	0.0266 (0.0067–0.1034)	

CML=Chronic myeloid leukemia, IQR=Interquartile range, FHIT=Fragile histidine triad

Table 5: Best cut-off value of the fragile histidine triad fold change in gene expression for the assessment of imatinib responsiveness in chronic myeloid leukemia patients

Parameter	AUC	AUC explanation	95% CI of AUC	AUC (*P*)	Best cut-off value	Sensitivity (%)	Specificity (%)
FHIT fold of gene expression	0.876	Good	0.779–0.973	<0.001	>0.0578	97	72.4

FHIT=Fragile histidine triad, CI=Confidence interval, AUC=Area under the curve

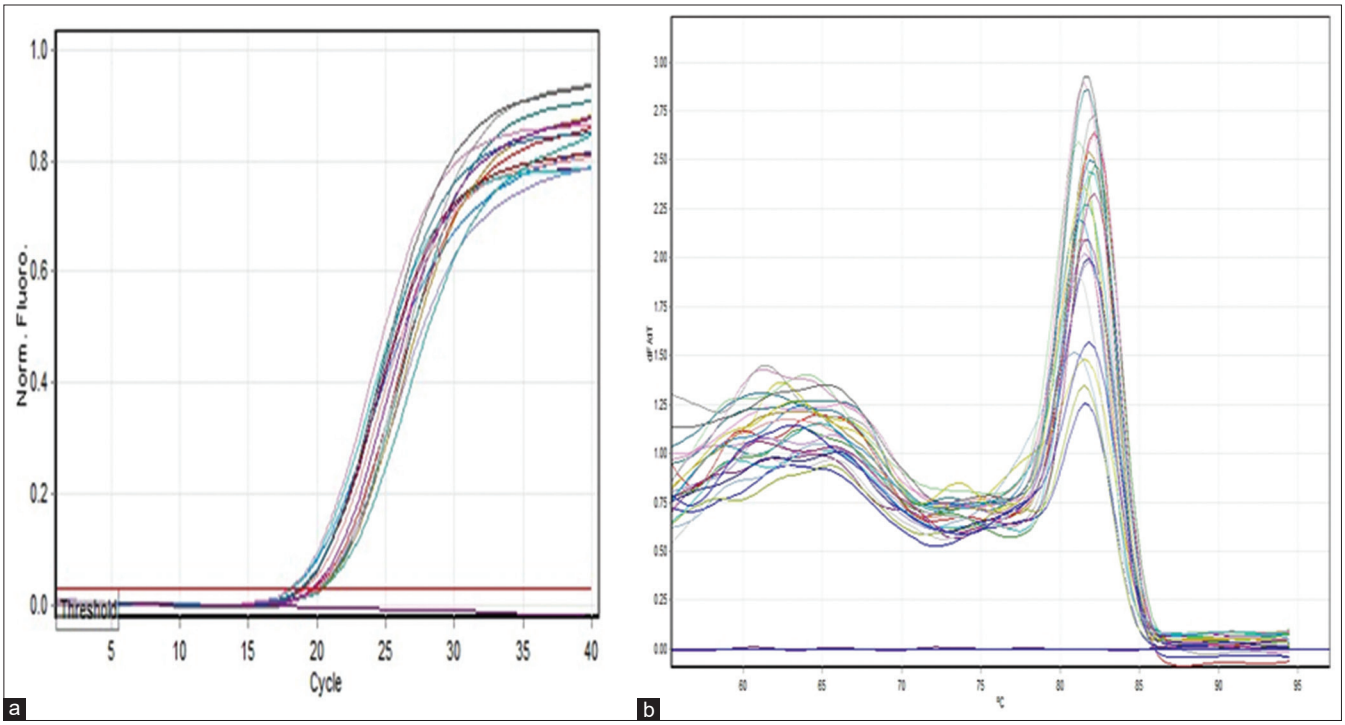

Figure 1: Result of β-actin quantitative polymerase chain reaction of amplification plot (a) and melting curve (b). Images from qiagen rotor gene Q quantitative polymerase chain reaction instrument

controls, with nonresponsive CML patients exhibiting lower levels than responsive CML patients. The results of *FHIT* expression levels in relation to the development of therapy nonresponsiveness in CML patients, which is indicated by the best cut-off point derived from ROC analysis, suggest that *FHIT* expression levels may function as a potential biomarker for predicting imatinib mesylate nonresponsiveness, providing good sensitivity and moderate specificity in distinguishing between responsive and nonresponsive CML patients.

The accumulation of other abnormalities in both genetic and epigenetic pathways, in addition to the *BCR/ABL1* oncoprotein, affects the overall clinical consequences of CML.[22] Identifying these aberrations could enable the development of treatment methods that may halt CML progression and sustain the disease in the CP, hence enhancing prognosis.[7] Multiple studies have demonstrated that an increase in *FHIT* expression results in the stimulation of the extrinsic caspase-8 route and the intrinsic mitochondrial pathway, two main apoptotic pathways.[41-43] Tumorigenesis can occur as a result of the deactivation of programmed cell death, ultimately leading to the expansion of malignant cell clones.[44] Aberrant transcription, deletions, and promoter hypermethylation result in deactivation of the *FHIT* gene, which is documented in many types of cancers, including hematological malignancies.[12-19] The stimulation of caspase-dependent

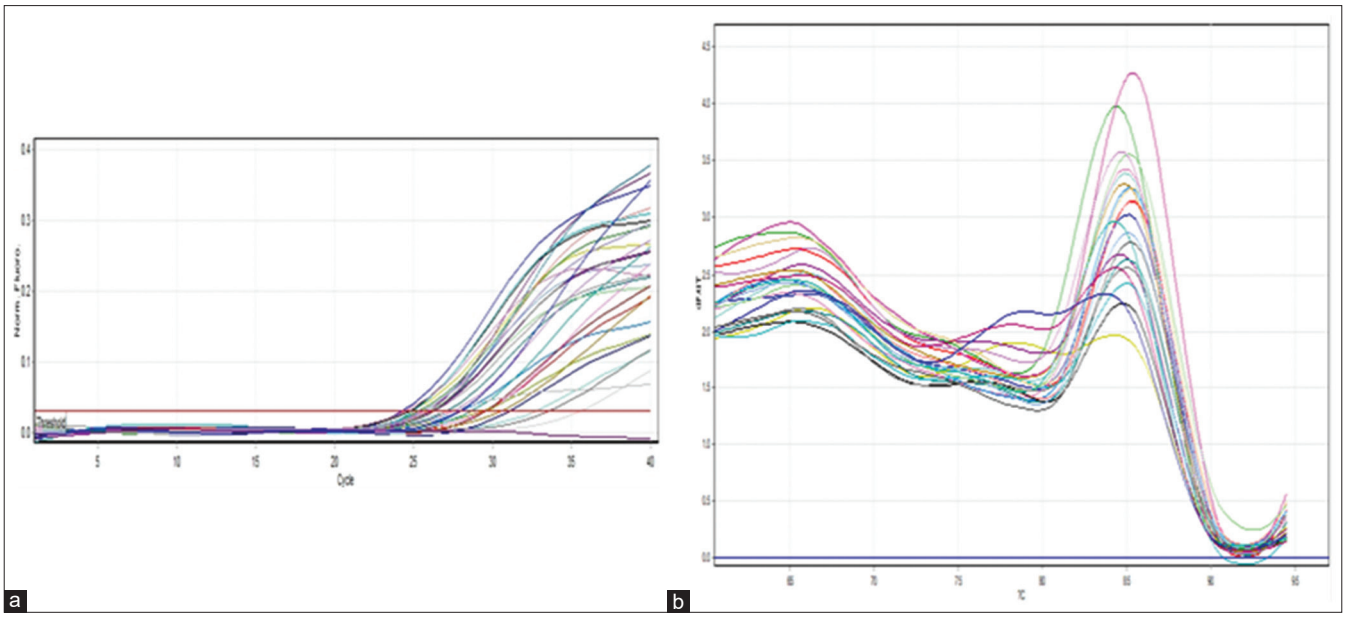

Figure 2: Result of fragile histidine triad quantitative polymerase chain reaction of Amplification Plot (a) and Melting Curve (b). Images from qiagen rotor gene Q quantitative polymerase chain reaction instrument

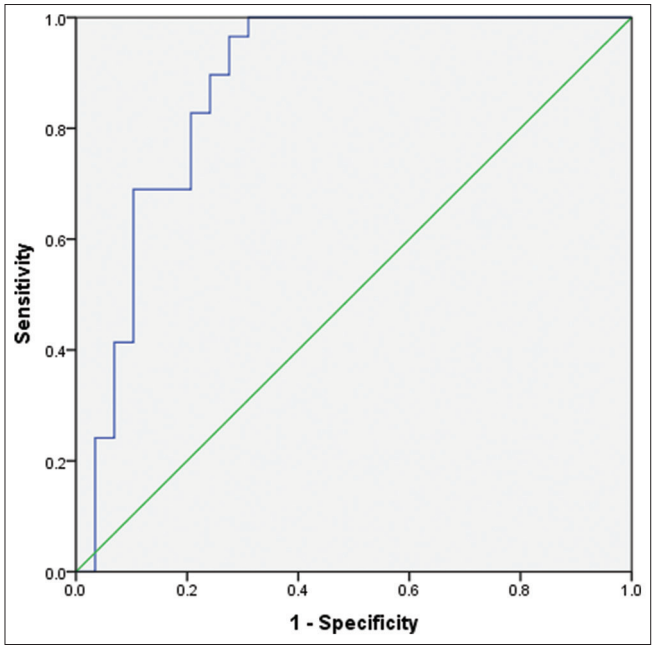

Figure 3: The receiver operating characteristics curve for the fragile histidine triad fold of gene expression level in chronic myeloid leukemia patients who are either responsive or nonresponsive to treatment

apoptosis and the reduction of tumor cell proliferation have been demonstrated to be mechanisms by which the reactivation of *FHIT* inhibits tumorigenesis in mice models and the cancer cell lines.[45,46] Disruption of apoptosis-related genes is associated with advanced CML disease, poor imatinib response, and poor survival.[47] Study limitations include small sample size, single-center study, lack of patients follow-up, and the absence of functional or epigenetic validation.

Conclusions

Reduced *FHIT* gene expression was associated with CML and with changes in hematopoietic patterns observed in the patients studied. Variations in *FHIT* expression were noted between responsive and nonresponsive patients, indicating a potential association with treatment response, suggesting that *FHIT* expression may have value as a complementary predictive biomarker for imatinib mesylate responsiveness, although further validation is required to assess *FHIT* protein expression, the mutational status of the *FHIT* gene, the pattern of promoter methylation, and their impact on protein levels in patients with CML.

Acknowledgment

The authors truly express their profound appreciation to subjects (patients and controls) for their contribution in this study, as well as the staff of Mustansiriyah University/The National Center of Hematology research and treatment, who aid in sample collection.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Ministry of Health and Environment, Iraqi Cancer Board. Annual Report: Iraqi Cancer Registry; 2023.
2. Rinaldi I, Winston K. Chronic myeloid leukemia, from pathophysiology to treatment-free remission: A narrative literature review. J Blood Med 2023;14:261-77.

3. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2025 update on diagnosis, therapy, and monitoring. Am J Hematol 2024;99:2191-212.
4. Yoshimaru R, Minami Y. Genetic landscape of chronic myeloid leukemia and a novel targeted drug for overcoming resistance. Int J Mol Sci 2023;24: 13806.
5. Sicuranza A, Cavalleri A, Bernardi S. The biology of chronic myeloid leukemia: An overview of the new insights and biomarkers. Front Oncol 2025;15:1546813.
6. Khan SU, Fatima K, Aisha S, Malik F. Unveiling the mechanisms and challenges of cancer drug resistance. Cell Commun Signal 2024;22:109.
7. Sun J, Hu R, Han M, Tan Y, Xie M, Gao S, *et al*. Mechanisms underlying therapeutic resistance of tyrosine kinase inhibitors in chronic myeloid leukemia. Int J Biol Sci 2024;20:175-81.
8. Niu Z, Jiang D, Shen J, Liu W, Tan X, Cao G. Potential role of the fragile histidine triad in cancer evo-dev. Cancers (Basel) 2023;15:1144.
9. Saldivar JC, Park D. Mechanisms shaping the mutational landscape of the FRA3B/FHIT-deficient cancer genome. Genes Chromosomes Cancer 2019;58:317-23.
10. Volinia S, Druck T, Paisie CA, Schrock MS, Huebner K. The ubiquitous 'cancer mutational signature' 5 occurs specifically in cancers with deleted FHIT alleles. Oncotarget 2017;8:102199-211.
11. Silveira Zavalhia L, Weber Medeiros A, Oliveira Silva A, Vial Roehe A. Do FHIT gene alterations play a role in human solid tumors? Asia Pac J Clin Oncol 2018;14:e214-23.
12. Ishii H, Vecchione A, Furukawa Y, Sutheesophon K, Han SY, Druck T, *et al*. Expression of FRA16D/WWOX and FRA3B/FHIT genes in hematopoietic malignancies. Mol Cancer Res 2003;1:940-7.
13. Malak CA, Elghanam DM, Elbossaty WF. FHIT gene expression in acute lymphoblastic leukemia and its clinical significance. Asian Pac J Cancer Prev 2015;16:8197-201.
14. Bellon M, Bialuk I, Galli V, Bai XT, Farre L, Bittencourt A, *et al*. Germinal epimutation of fragile histidine triad (FHIT) gene is associated with progression to acute and chronic adult T-cell leukemia diseases. Mol Cancer 2021;20:86.
15. Bahari G, Hashemi M, Naderi M, Sadeghi-Bojd S, Taheri M. FHIT promoter DNA methylation and expression analysis in childhood acute lymphoblastic leukemia. Oncol Lett 2017;14:5034-8.
16. Sugimoto K, Yamada K, Miyagawa K, Hirai H, Oshimi K. Decreased or altered expression of the FHIT gene in human leukemias. Stem Cells 1997;15:223-8.
17. Peters UR, Hasse U, Oppliger E, Tschan M, Ong ST, Rassool FV, *et al*. Aberrant FHIT mRNA transcripts are present in malignant and normal haematopoiesis, but absence of FHIT protein is restricted to leukaemia. Oncogene 1999;18:79-85.
18. Siprashvili Z, Sozzi G, Barnes LD, McCue P, Robinson AK, Eryomin V, *et al*. Replacement of FHIT in cancer cells suppresses tumorigenicity. Proc Natl Acad Sci U S A 1997;94:13771-6.
19. Kantarjian HM, Talpaz M, O'Brien S, Manshouri T, Cortes J, Giles F, *et al*. Significance of FHIT expression in chronic myelogenous leukemia. Clin Cancer Res 1999;5:4059-64.
20. Schrock MS, Karras JR, Guggenbiller MJ, Druck T, Batar B, Huebner K. FHIT and Wwox loss-associated genome instability: A genome caretaker one-two punch. Adv Biol Regul 2017;63:167-76.
21. Karras JR, Schrock MS, Batar B, Huebner K. Fragile genes that are frequently altered in cancer: Players not passengers. Cytogenet Genome Res 2016;150:208-16.
22. Cross NC, Ernst T, Branford S, Cayuela JM, Deininger M, Fabarius A, *et al*. European LeukemiaNet laboratory recommendations for the diagnosis and management of chronic myeloid leukemia. Leukemia 2023;37:2150-67.
23. Mahmood NA, Al-Sudani IM, Al-Sammarraie HK, Jaffar TH. ABCG2 (BCRP) mRNA expression level using real-time PCR and immunohistochemistry associated with clinicopathological features in Iraqi women with stage II-III breast cancer. Iraqi J Cancer Med Genet 2016;9:41-9.
24. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C (T)) Method. Methods 2001;25:402-8.
25. Ismail NH, Abdulhassan IA, Al-Faisal AH. Association of TET2 gene polymorphisms (rs34402524 and rs2454206) and their haplotypes with response to treatment in chronic myeloid leukemia patients. Iraqi J Sci 2023;65:4230-45.
26. Ismail NH, Abdulhassan IA, Al-Faisal AH, Matti BF. Evaluation of HOXA5 methylation-gene expression in response to imatinib mesylate treatment in chronic myeloid leukemia. Biomedicine 2023;43:391-8.
27. Naeem NT, Alsaadi BQ. Role of gene expression hypoxia-inducible factor-1α and serum level monocyte chemoattractant protein-1 in the incidence of chronic myeloid leukemia in Iraqi patients. Iraqi J Hematol 2024;13:50-8.
28. Khaleel AW, Altaee MF. LTB4R gene expression in chronic myeloid leukemia in Iraq. Iraqi J Sci 2023;64:2202-14.
29. Hasan EK, Kasim AA, Matti BF. Impact of MDR-1 gene polymorphism (rs1128503) on response to imatinib or nilotinib in Iraqi patients with chronic myeloid leukemia: An observational study. Al-Rafidain J Med Sci 2024;6:215-21.
30. Radhi KA, Matti BF, Hamzah IH. Role of miRNA-96 and miRNA-150 between different BCR-ABL p210 transcript levels and levels of imatinib optimal response in CML patients. Hum Genet 2023;36:201166. Available from: https://www.sciencedirect.com/science/article/abs/pii/S2773044123000256. [Last accessed on 2026 Mar 13].
31. Sabir SF, Matti BF, Alwatar WM. Assessment of regulatory T cells (Tregs) and Foxp3 methylation level in chronic myeloid leukemia patients on tyrosine kinase inhibitor therapy. Immunogenetics 2023;75:145-53.
32. Jootar S. CML treatment in Asia-Pacific region. Hematology 2012;17 Suppl 1:S72-4.
33. Hasan KM. Evaluation of chronic myeloid leukemia patients and their molecular responses to tyrosine kinase inhibitors in Erbil city, Iraq. Iraqi J Hematol 2018;7:1-7.
34. Mjali A, Obaid MM, Matti BF, Abbas NT. Treatment outcomes of nilotinib as second-line therapy for chronic myeloid leukemia patients in Karbala Province, Iraq. Asian Pac J Cancer Care 2022;7:267-72.
35. Moyer AM, Matey ET, Miller VM. Individualized medicine: Sex, hormones, genetics, and adverse drug reactions. Pharmacol Res Perspect 2019;7:e00541.
36. Tokatli MR, Sisti LG, Marziali E, Nachira L, Rossi MF, Amantea C, *et al*. Hormones and sex-specific medicine in human physiopathology. Biomolecules 2022;12:413.
37. Mulhim AA, Alyahya A, Alarimah YG, Alayed M, Alyahyawi A, Zada AA. Treatment response to tyrosine kinase inhibitors (imatinib versus dasatinib) and its link to Vitamin D deficiency among adult CML patients. Int J Med Dev Ctries 2021;5:1716-21.
38. Hantoosh HA, Mahdi MH, Imran BW, Yahya AA. Prevalence of Vitamin D deficiency in Iraqi females at reproductive age. Med J Babylon 2019;16:119-22.
39. Nachi M, Kihel I, Guella D, Dali-Ali A, Abed A, Boukhatmi Y, *et al*. Sex and major molecular response to imatinib treatment in patients with chronic myeloid leukemia. Biochem Pharmacol 2019;8:263.
40. Senapati J, Sasaki K, Issa GC, Lipton JH, Radich JP, Jabbour E, *et al*. Management of chronic myeloid leukemia in 2023 – Common ground and common sense. Blood Cancer J 2023;13:58.
41. Ishii H, Dumon KR, Vecchione A, Trapasso F, Mimori K, Alder H, *et al*. Effect of adenoviral transduction of the fragile histidine triad gene into esophageal cancer cells. Cancer Res 2001;61:1578-84.
42. Roz L, Gramegna M, Ishii H, Croce CM, Sozzi G. Restoration of

fragile histidine triad (FHIT) expression induces apoptosis and suppresses tumorigenicity in lung and cervical cancer cell lines. Proc Natl Acad Sci U S A 2002;99:3615-20.

43. Dumon KR, Ishii H, Vecchione A, Trapasso F, Baldassarre G, Chakrani F, *et al*. Fragile histidine triad expression delays tumor development and induces apoptosis in human pancreatic cancer. Cancer Res 2001;61:4827-36.
44. Ghavami S, Hashemi M, Ande SR, Yeganeh B, Xiao W, Eshraghi M, *et al*. Apoptosis and cancer: mutations within caspase genes. J Med Genet 2009;46:497-510.
45. Wali A. FHIT: Doubts are clear now. ScientificWorldJournal 2010;10:1142-51.
46. Huebner K, Saldivar JC, Sun J, Shibata H, Druck T. Hits, FHITS and nits: Beyond enzymatic function. Adv Enzyme Regul 2011;51:208-17.
47. Guru SA, Sumi MP, Mir R, Beg MM, Koner BC, Saxena A. Correction: Aberrant hydroxymethylation in promoter CpG regions of genes related to the cell cycle and apoptosis characterizes advanced chronic myeloid leukemia disease, poor imatinib respondents and poor survival. BMC Cancer 2022;22:439.