Article

Discovery Medicine 2025; 37(203): 2863–2873
https://doi.org/10.24976/Discov.Med.202537203.239

Molecular Evaluation of MDR1 Gene Variations and Their Association With Imatinib Resistance in Chronic Myeloid Leukemia Patients

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Submitted: 19 August 2025 Revised: 9 November 2025 Accepted: 19 November 2025 Published: 20 December 2025

Background: Chronic myeloid leukemia (CML) is a cancer caused by uncontrolled growth of myeloid cells in the bone marrow. Tyrosine kinase inhibitors (TKIs) like imatinib have revolutionized treatment, but resistance remains a challenge, possibly due to genetic variations. Specifically, the 3435TT genotype has been linked to lower event-free survival in CML and B-cell acute lymphoblastic leukemia (B-ALL) patients, with multivariate analysis identifying it as an independent risk factor for imatinib resistance in CML cases. Therefore, the aim of our study was to evaluate the association of multidrug resistance mutation 1 (*MDR1*) C3435T (rs1045642) and G2677T (rs2032581) gene variations with the CML susceptibility and resistance to imatinib mesylate.

Methods: In this case-control study, 50 CML patients and 50 healthy controls from the Saudi population were recruited. DNA was extracted from peripheral blood samples, and the MDR1 C3435T (rs1045642) and G2677T (rs2032581) genotyping were analyzed by using PCR-RFLP analysis to assess the correlation among MDR1 genotypes and the risk of CML.

Results: It has been found that MDR1 C3435T (rs1045642) variation was statistically significant ($p = 0.035$) between CML patients and healthy controls. In addition, strong association was reported for MDR1 G2677T (rs2032581) variation ($p = 0.044$) between the CML patients and healthy controls. The results of MDR1 (rs1045642) show that individuals with the TT genotype were significantly associated with risk of developing CML as evidenced by the odds ratio (OR) is 6.75 (95% CI: 1.3181 to 34.5662), and $p = 0.021$. Similarly in dominant model, CT + TT genotypes vs CC genotype was significantly associated with risk of developing CML as evidenced by the odds ratio is 2.25 (95% CI: 1.010 to 5.008), $p = 0.047$. The allelic comparison highlighted a strong association of the MDR1-T allele with CML risk (OR = 2.26, $p = 0.009$). Under the codominant model, the MDR1 rs2032581-GT genotype showed a substantial link with CML susceptibility, evidenced by an OR of 2.56, $p = 0.041$. Additionally, the MDR1-TT genotype indicated increased susceptibility with an OR of 3.16, $p = 0.049$. The allelic comparison highlighted a strong association of the MDR1-T allele with CML risk OR = 2.04, $p = 0.014$.

Conclusion: It was concluded that MDR1 rs2032581 G>T MDR1 rs1045642 C>T polymorphisms might be a risk factor for imatinib resistance in Saudi CML patients. Significant associations were reported between MDR1 genotypes and molecular responses to imatinib and advanced stage of the disease. Determination of MDR1 polymorphisms MDR1 rs2032581 G>T MDR1 rs1045642 C>T might be useful in response prediction to therapy with imatinib in patients with CML.

Keywords: chronic myeloid leukemia; tyrosine kinase inhibitors; multidrug resistance 1 gene

Introduction

Leukemia is a common malignancy worldwide. In 2018, 437,033 cases and 309,006 deaths were reported, making it the eleventh leading cause of mortality [1]. Chronic myeloid leukemia (CML) is a slowly progressing form of leukemia that develops in three stages, and most individuals receive a diagnosis during the initial chronic phase. During this phase, the body produces excessive numbers of mature, functional granulocytes [2]. CML affects the blood and bone marrow and is characterized by the uncontrolled proliferation of myeloid cells in the bone marrow.

The Philadelphia chromosome is the characteristic genetic abnormality in more than 90% of CML cases. It is also present in approximately 20%–30% of acute lymphoblastic leukemia (ALL) cases and in a smaller proportion of acute

myeloid leukemia cases. The Philadelphia chromosome forms when chromosomes 9 and 22 break and exchange segments, producing a shortened chromosome 22 and new oncogenic instructions for the cells. These altered instructions can lead to the development of chronic myelogenous leukemia. In some cases, multidrug chemotherapy and bone marrow transplantation can eliminate the Philadelphia chromosome and interrupt the natural progression of the disease [3]. Tyrosine kinase inhibitors (TKIs) are widely used in cancer therapy, particularly in tumors caused by abnormal tyrosine kinase activity. TKIs represent a major advance in oncology and remain a focus of active research and drug development [4]. TKIs bind to the ATP-binding site within the tyrosine kinase domain, competing with ATP and preventing the transfer of phosphate groups to tyrosine residues on target proteins. This inhibition disrupts phosphorylation and downstream signaling pathways involved in cell growth and proliferation [5].

TKI resistance arises from mutations in the BCR-ABL1 kinase domain. Multiple clinical studies have examined the significance of these mutations, and the T315I mutation has been identified as the predominant alteration in both CML and Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ALL). CML or Ph+ALL harboring the T315I mutation has shown resistance to several TKIs and responds only to next-generation agents such as ponatinib and asciminib [6].

In approximately half of the cases, TKI resistance results from *BCR-ABL1* gene amplification or overexpression. Increased BCR-ABL1 expression reduces TKI binding efficiency, which often requires higher TKI doses to suppress phosphorylation of downstream targets. Evidence indicates that elevated BCR-ABL1 expression is frequently associated with advanced disease stages and a greater likelihood of *BCR-ABL1* mutations [7]. Although dose escalation can counter increased *BCR-ABL1* expression, it also increases the risk of adverse drug reactions. In such situations, clinicians may consider using a more potent TKI. Treatment failure can also occur due to amino acid substitutions that alter the kinase domain or interfere with TKI binding. Additional resistance mechanisms include drug transporters and alternative signaling pathways [8].

Several studies have evaluated the relationship between mutations in the multidrug resistance (*MDR1*) gene and TKI resistance in CML. Specific *MDR1* polymorphisms, particularly the C3435T and G2677T variants, have been associated with decreased responses to imatinib therapy in patients with CML [9].

The first polymorphism identified in the *ABCB1* gene was the 3435C>T (rs1045642) SNP, which affects mRNA stability and protein folding, leading to changes in P-glycoprotein (P-gp) synthesis without altering its amino acid sequence. The 1236T>C (rs1128503) SNP affects both the expression and function of P-gp. The frequency of this SNP varies across populations, and differences in variant allele distribution provide insight into genetic diversity among demographic groups. These variations can affect the transport of substrates regulated by ABCB1 and highlight the importance of considering ethnic and genetic backgrounds when prescribing medication [10].

The *MDR1* G2677T polymorphism is relevant to treatment response in patients with CML, particularly regarding their response to imatinib, which is widely used as first-line therapy. The *MDR1* gene encodes P-glycoprotein, an efflux transporter that affects drug bioavailability and contributes to resistance by exporting several agents, including imatinib, from cells [11]. The G2677T polymorphism has been associated with a protective effect against primary failure of imatinib therapy in patients with CML [12].

Elghannam *et al.* [13] reported that the TT genotype was significantly less frequent in patients with CML, whereas the frequencies of the GG and GT genotypes did not differ significantly between patients and controls (p = 0.004, 0.138, and 0.210, respectively). Multivariate analysis indicated that the TT genotype was protective against imatinib resistance (p = 0.008), whereas the GT genotype was an independent risk factor for resistance (p = 0.037) [13].

A recent study reported significant associations between the G2677T and C3435T polymorphisms and imatinib response in specific ethnic populations, indicating that these variants may affect drug resistance [14].

According to pooled data, the *MDR1* C1236T polymorphism was significantly associated with an increased likelihood of imatinib resistance among Asian patients with CML. However, the *MDR1* G2677T and C3435T polymorphisms did not show significant correlations with imatinib resistance in either Asian or Caucasian populations in that analysis [15].

Lardo *et al.* [16] further observed that particular MDR1/ABCB1 haplotypes could predict treatment outcomes in patients receiving TKIs, indicating that combinations of variants rather than single nucleotide polymorphisms may affect therapeutic response. This study determined the association between the *MDR1* C3435T (rs1045642) and G2677T (rs2032581) polymorphisms and imatinib resistance in patients with CML.

Methods

Study Design and Sample Collection

The case-control study was adopted on 100 individuals comprising 50 controls and 50 CML cases. 50 control samples obtained from the Saudi population were taken with different hospitals in Tabuk. The study was carried out according to the Declaration of Helsinki, and all participants provided written informed consent. The study was ethically approved from Institutional Ethics Committee University of Tabuk (Approval no. UT-88-19-2019, dated November 24, 2019).

Inclusion and Exclusion Criteria

The case-control study included clinically confirmed cases of CML patients. CML patients positive Ph chromosome. Also included newly diagnosed cases with all three stages Chronic phase (CP), Accelerated phase (AP) and Blast crisis (BC). Both males and females. The study only registered CML patients receiving Imatinib mesylate therapy with dose of 400 mg to 800 mg/day. The exclusion criteria included CML patients with Ph(-ve) chromosome and JAK2 mutation positive cases.

Inclusion Criteria and Exclusion Criteria for Controls

All controls specimens were timed around routine blood draws that are part of routine workout, and hence there was no requirement of additional phlebotomy. All participants were Saudi nationals. The Non-Arab Saudi or recently naturalized Saudi Arabia will be excluded.

Sample Collection

Peripheral blood was collected from all patients and controls in EDTA vials, after obtaining informed consent. The samples were collected, stored, and processed after the Institutional Ethics Committee accepted the study (Approval no. UT-88-19-2019, dated November 24, 2019).

Genotyping Study

The genomic DNA was extracted from blood using a Qiagen DNA extraction kit, (Cat no. / ID. 51126, Qiagen-Germany) following the manufacturer's instructions, and a NanoDropTM (Cat no. / ID. ND-8000-GL, Thermo Scientific 8000, Waltham, MA, USA) was used to determine the amount of isolated DNA. Two primers were used forward outer primer (Fo, 0.25 µL), reverse outer primer (Ro, 0.25 µL), along with 25 pmol of each primer (Sigma-Aldrich, Chemicals Private Limited, Bangalore, India) and 10 µL of green PCR Master Mix (2×) (Cat M712C, Promega, Madison, WI, USA) made up the 11.50 µL reaction volume used for the PCR. Supplementation with nuclease-free water [H_2O] produced a final volume of 22 µL. Finally, 50 ng of template DNA was introduced into the mixture.

Polymerase chain reaction -Restriction Fragment Length Polymorphism (RFLP). PCR-RFLP primers for MDR1 C3435T and G2677T were designed using Primer3 software (version 0.4.0, National Institutes of Health, Howard Hughes Medical Institute, and the University of Tartu, Tartu, Estonia).

PCR Program

The thermocycling conditions optimized for MDR1 C3435T and G2677T amplification are depicted in Table 1. MboI restriction enzyme (FD0814, Thermofisher, India) was used to detect MDR1 C3435T (rs1045642) genotypes and XbaI restriction enzyme [FD0684, Thermofisher, India] was used to detect MDR1 (G2677T) (rs2032582) genotypes in CML as depicted in Table 1.

Statistical Analysis

The statistical program for social science (SPSS) version 16 (IBM Corp., Chicago, USA) was used to analyze the data. The Kolmogorov–Smirnov test was applied to test the normality distribution of the data. A statistical technique for evaluating hypotheses regarding categorical data is the chi-square test, which compares observed and anticipated frequencies to ascertain if two categorical variables are independent or whether there is a statistically significant difference. Chi-square test was employed to assess the allelic and genotypic frequencies between MDR1-rs1045642 and MDR1-rs2032581 and cases. Logistic regression in genetics was used to model the probability of a binary outcome, like having a disease, based on genetic factors. It can predict gene function, analyze associations between genetic variations and diseases (e.g., through case-control studies). The associations between MDR1-rs1045642 and MDR1-rs2032581 genotypes and cases of CML were assessed through estimations of odds ratios (ORs), risk ratios (RRs), and risk differences (RDs) with 95% confidence intervals (CIs). A p-value of <0.05 was considered significant. GraphPad (Prism 8.4.0, Dotmatics, Boston, MA, USA) and SPSS (version 16, IBM Corp., Chicago, IL, USA) were used to conduct all statistical analyses. Our study evaluated the potential associations of MDR1-rs1045642 and rs2032581 genotypes between CML patients and controls by calculating odds ratios, risk ratios, and risk differences with 95% confidence intervals. A p-value below 0.05 was deemed significant.

Results

Demographic and Clinical Characteristics of CML Patients and Healthy Controls

Table 2 presents a comprehensive comparison of demographic and clinical characteristics between a group of 50 patients with Chronic Myeloid Leukemia (CML) and 50 healthy controls. The data reveal significant differences between the two groups, highlighting the profound impact of CML on a patient's physiology. Demographically, the CML patient group was significantly younger, with a median age of 38 years compared to 47 years in the control group. This age difference was statistically highly significant. However, the distribution of gender was similar between the two groups, with no significant difference in the proportion of males and females.

The most striking differences are evident in the common hematological values. CML patients exhibited severe anemia, with a median hemoglobin level of 9.4 g/dL, substantially lower than the 11.9 g/dL in healthy individuals. The disease's hallmark is also clear in the total leucocyte (white blood cell) count, which was drastically elevated in

Table 1. Restriction fragment length polymorphism for MDR1 C3435T (rs1045642).

PCR-RFLP for MDR1 C3435T (rs1045642)		
MDR13435F	5′-GATCTGTGAACTCTT GTT TTCA-3′	244 bp
MDR13435R	5′-GAAGAGAGACTTACATTAGGC-3′	
✓ 95 °C for 10 minutes		
✓ 35 cycles		
✓ 95 °C for 30 seconds		
✓ 60 °C for 35 seconds		
✓ 72 °C for 45 seconds		
✓ 72 °C for 10 minutes		
✓ 4 °C for infinity		
Polymerase chain reaction-restriction fragment length polymorphism by MboI		
5 µL of PCR products were resolved in 2% agarose gel to check the PCR products.		
	1×	19×
BUFFER	2 uL	2 uL
MboI	1 uL	19 uL
DD Water	7 uL	133 uL
Add PCR Product	10 uL	
Incubation	Incubate in water bath at 37 °C	
Gel electrophoresis	2%	
Results		
CC genotype	172 bp, 72 bp	
CT genotype	244, 172 and 72 bp	
TT genotype	244 bp	
PCR RFLP FOR MDR1 (G2677T) (rs2032582)		
MDR12677F	5′-TACCCATCATTGCAATAGCAG-3′	107 bp
MDR12677R	5′-TTTAGTTTGACTCACCTTGCTAG-3′	
✓ 95 °C for 10 minutes		
✓ 35 cycles		
✓ 95 °C for 30 seconds		
✓ 60 °C for 35 seconds		
✓ 72 °C for 45 seconds		
✓ 72 °C for 10 minutes		
✓ 4 °C for infinity		
PCR-RFLP by XbaI restriction enzyme		
5 µL of PCR products will be resolved in 2% agarose gel to check the PCR products.		
	1×	19×
BUFFER	2 uL	2 uL
MboI	1 uL	19 uL
DD Water	7 uL	133 uL
Add PCR Product	10 uL	190 uL
Incubation	Incubate in water bath at 37 °C	
Gel electrophoresis	2%	
Results	MDR1(G2677T) (rs2032582)	
GG genotype	107 bp	
GT genotype	24 bp, 83 and 107 bp	
TT genotype	83 bp	

patients (168.0×10^9/L) compared to the normal range seen in controls (10.0×10^9/L). Additionally, platelet counts were significantly lower in the patient group. The differential white cell count further illustrates the imbalance caused by CML, showing significantly higher percentages of neutrophils, lymphocytes, basophils, and monocytes in patients, reflecting the uncontrolled production of myeloid cells.

Table 2. Demographic and clinical characteristics of CML patients and healthy controls.

Variables	CML patients	Healthy controls	Z/χ^2	*p* value
Age (Years) Median (Min–Max.)	38 (16–80)	47 (26–67)	–3.546	<0.0001
Gender	n (%)	n (%)		
Male	30 (60%)	28 (56%)	0.164	0.685
Female	20 (40%)	22 (44%)		
Common hematological values	Median (Min–Max.)			
Hb (g/dL)	9.4 (3.4–17.2)	11.9 (9.3–13.4)	–5.399	<0.0001
Total Leucocyte count ($\times 10^9$/L)	168.0 (3.46–673.65)	10.0 (8.0–13.0)	–7.603	<0.0001
Platelets ($\times 10^9$/L)	2.55 (0.34–8.84)	3.7 (1.84–4.8)	–3.112	0.002
Neutrophils %	102.5 (82–146)	61.5 (40–80)	–8.621	<0.0001
Lymphocytes %	55.0 (41–69)	33.0 (23–40)	–8.624	<0.0001
Basophils %	9.0 (2–21)	1.1 (0.1–1.6)	–8.626	<0.0001
Monocytes %	16.0 (8–29)	4.0 (1–9)	–8.602	<0.0001
Hematological values of CML patients	Median (Min–Max.)			
Blast cells %	36 (21–50)			
Promyelocyte %	15 (7–45)			
Metamyelocyte %	16 (8–37)			
Stage of the disease	n (%)			
CP-CML	10 (20%)			
AP-CML	15 (30%)			
BC-CML	25 (25%)			
Molecular Responses	n (%)			
Major molecular responses	15 (30%)			
Minor molecular responses	35 (70%)			
Hematological responses	n (%)			
Major Hematological response	11 (22%)			
Minor Hematological response	39 (78%)			

The Table 2 also provides details specific to the CML patient group. It shows the presence of immature cells in their blood, such as blast cells, promyelocytes, and metamyelocytes, which are not typically found in healthy individuals and indicate active disease. The patients were categorized into different stages of CML: 20% in Chronic Phase (CP-CML), 30% in Accelerated Phase (AP-CML), and a notably listed 25% in Blast Crisis (BC-CML). Finally, the treatment responses were documented, showing that 30% of patients achieved a Major Molecular Response, while the majority (70%) had only a Minor Molecular Response. A similar pattern was seen for hematological responses, with a minor response being the most common outcome.

Genotype Distributions and Allele Frequencies of MDR1 (rs1045642) and (rs2032581) in CML Patients

The MDR1 (rs1045642) genotype frequency in CML patients and controls was CC (40%), CT (42%) and CT (18%) and controls CC (60%), CT (36%) and TT (4%) respectively (Table 3). The results for MDR1 C3435T (rs1045642) gene variation were statistically significant $p = 0.035$ between CML patients and controls. It was also noted that the T allele had a higher frequency among CML patients than in healthy individuals (0.39 vs. 0.22).

In addition, the results of MDR1 (rs2032582) genotype frequency in CML patients and controls were GG (26%), GT (50%), and TT (24%), and controls GG (50%), GT (36%) and TT (14%) respectively (Table 4). The results for MDR1 2677G>T (rs2032582) gene variation were statistically significant $p = 0.044$ between CML patients and controls. It was also noted that the T allele had a higher frequency among CML patients than in healthy individuals (0.49 vs. 0.32).

Multivariate Analysis to Estimate the Association Between the MDR1 (rs1045642) Genotype and the Risk of CML

The results of MDR1 (rs1045642) show that individuals with the CT genotype have not been associated with risk of developing the CML as evidenced by the OR of 1.75 (95% CI: (0.750 to 4.079) and RR of 1.30 (95% CI: (0.864 to 1.954) and $p = 0.195$ (Table 5). However, the TT genotype was significantly associated with risk of developing CML as evidenced by the OR is 6.75 (95% CI: 1.318 to 34.566), and the RR is 3.30 (95% CI: 0.923 to 11.796) and $p = 0.021$. In case dominant model, CT + TT genotypes vs CC genotype was significantly associated with risk of developing CML as evidenced by the OR is 2.25 (95% CI: 1.010 to 5.008), and the RR is 1.50 (95% CI: 0.997 to 2.255) and $p = 0.047$. In case recessive model, CC + CT genotypes vs TT

Table 3. Association of MDR1 (rs1045642) genotypes between CML patients and controls.

Subjects	n	CC	CT	TT	DF	χ^2	C	T	*p* value
Cases	50	20 (40%)	21 (42%)	9 (18%)	2	6.69	0.61	0.39	0.035
Controls	50	30 (60%)	18 (36%)	2 (4%)			0.78	0.22	

Table 4. Association of MDR1 (rs2032581) genotypes between CML patients and controls.

Subjects	n	GG	GT	TT	DF	χ^2	G	T	*p* value
Cases	50	13 (26%)	25 (50%)	12 (24%)	2	6.24	0.51	0.49	0.044
Controls	50	25 (50%)	18 (36%)	7 (14%)			0.68	0.32	

Table 5. Association between MDR1 (rs1045642) genotype and the risk to CML.

Genotypes	Healthy controls (N = 50)	CML (N = 50)	β	SE	Wald	OR (95% CI)	Risk ratio (RR)	*p* value
Codominant inheritance model								
MDR1-CC	30	20				1 (ref.)	1 (ref.)	
MDR1-CT	18	21	0.56	0.43	1.69	1.75 (0.750 to 4.079)	1.30 (0.864 to 1.954)	0.195
MDR1-TT	2	9	1.91	0.82	5.38	6.75 (1.318 to 34.566)	3.30 (0.923 to 11.796)	0.021
Dominant inheritance model								
MDR1-CC	30	20				1 (ref.)	1 (ref.)	
MDR1-(CT+TT)	20	30	0.81	0.41	3.96	2.25 (1.010 to 5.008)	1.50 (0.997 to 2.255)	0.047
Recessive inheritance model								
MDR1-(CC+CT)	48	41				1 (ref.)	1 (ref.)	
MDR1-TT	2	9	1.66	0.81	4.20	5.26 (1.076 to 25.779)	2.96 (0.834 to 10.544)	0.040
Allele								
MDR1-C	78	61				1 (ref.)	1 (ref.)	
MTHFR-T	22	39	0.82	0.31	6.81	2.26 (1.218 to 4.217)	1.55 (1.080 to 2.241)	0.009

genotype was significantly associated with risk of developing CML as evidenced by the OR is 5.26 (95% CI: 1.076 to 25.779), and the RR 2.96 (95% CI: 0.834 to 10.544) and $p = 0.040$. The allelic comparison highlighted a strong association of the MDR1-T allele with CML risk OR = 2.26, 95% CI: 1.218 to 4.217; RR = 1.55, 1.080 to 2.2414; $p = 0.009$).

Multivariate Analysis to Estimate the Association Between the MDR1 (rs2032582) Genotype and the Risk of CML

As shown in Table 6, A multivariate analysis based on logistic regression like risk ratio (RR) with 95% CI were calculated for each group to estimate the association between MDR1-rs2032581 genotypes and risk to CML. Under the codominant model, the MDR1-GT genotype showed a substantial link with CML susceptibility, evidenced by an OR of 2.56 (95% CI: 1.035 to 6.351), a risk ratio (RR) of 1.57 (1.032 to 2.392), and $p = 0.041$. Additionally, the MDR1-TT genotype under the same model indicated increased susceptibility with an OR of 3.16 (95% CI: 1.001 to 10.003), RR of 1.78 (0.949 to 3.358), and $p = 0.049$. In the dominant model, the combined MDR1 GT+TT genotypes, as opposed to GG, were associated with CML risk, with an OR of 2.73 (1.174 to 6.357), RR of 1.63 (1.116 to 2.385), and $p = 0.019$. Conversely, in the recessive model, the MDR1-TT genotype, when compared with GG+GT genotypes, showed no association with CML risk OR = 1.93, 95% CI: 0.693 to 5.429; RR = 1.44, 0.772 to 2.687; $p = 0.207$. The allelic comparison highlighted a strong association of the MDR1-T allele with CML risk OR = 2.04, 95% CI: 1.149 to 3.627; RR = 1.44, 1.059 to 1.974; $p = 0.014$.

Association of MDR1 (rs1045642) and (rs2032581) Genotypes With the Clinicopathological Characteristics of CML Patients

A statistically significant difference in the frequencies of MDR1 (rs1045642) genotypes CC, CT and TT was reported with respect to age of CML patients ($p = 0.012$) as depicted in Table 7. Similarly, a statistically significant difference in the frequencies of MDR1 (rs1045642) genotypes CC, CT and TT with respect gender of CML patients was reported ($p = 0.015$). The distribution of MDR1 (rs1045642) genotypes CC, CT and TT was significantly different in different stages of the CML patients 0.028. A statistically significant difference in the frequencies of MDR1 (rs1045642) genotypes among the patients' hematological responses 0.029. The prevalence of MDR1 (rs1045642) genotypes CC, CT and TT in CML patients who displayed hematological molecular resistance to imatinib mesylate was not significant 0.81.

Table 6. Association between MDR1 (rs2032581) genotype and the risk to CML.

Genotypes	Healthy controls (N = 50)	CML (N = 50)	β	SE	Wald	OR (95% CI)	Risk ratio (RR)	*p* value
Codominant inheritance model								
MDR1-GG	25	13				1 (ref.)	1 (ref.)	
MDR1-GT	18	25	0.94	0.46	4.20	2.56 (1.035 to 6.351)	1.57 (1.032 to 2.392)	0.041
MDR1-TT	7	12	1.15	0.58	3.88	3.16 (1.001 to 10.003)	1.78 (0.949 to 3.358)	0.049
Dominant inheritance model								
MDR1-GG	25	13				1 (ref.)	1 (ref.)	
MDR1-(GT+TT)	25	37	1.00	0.43	5.52	2.73 (1.174 to 6.357)	1.63 (1.116 to 2.385)	0.019
Recessive inheritance model								
MDR1-(GG+GT)	43	38				1 (ref.)	1 (ref.)	
MDR1-TT	7	12	0.66	0.52	1.59	1.93 (0.693 to 5.429)	1.44 (0.772 to 2.687)	0.207
Allele								
MDR1-G	68	51				1 (ref.)	1 (ref.)	
MDR1-T	32	49	0.71	0.29	6.10	2.04 (1.149 to 3.627)	1.44 (1.059 to 1.974)	0.014

Table 7. Association of MDR1 (rs1045642) genotype with the clinicopathological characteristics of CML patients.

	N = 50		CC	CT	TT	DF	χ^2	*p* value
Age								
<40	20	40%	4	9	7	2	8.76	0.012
>40	30	60%	16	12	2			
Gender								
Males	32	64%	8	17	7	2	8.36	0.015
Females	18	36%	12	4	2			
Stage of the disease								
CP-CML	10	20%	3	2	5	4	10.86	0.028
AP-CML	15	30%	8	5	2			
BC-CML	25	50%	9	14	2			
Molecular Reponses								
Major molecular responses	15	30%	5	7	3	2	0.4	0.81
Minor molecular responses	35	70%	15	14	6			
Hematological responses								
Major Hematological response	11	22%	6	1	4	2	7.5	0.029
Minor Hematological response	39	78%	14	20	5			

In addition, results demonstrated a statistically significant difference in the frequencies of MDR1 (rs2032581) genotypes GG, GT, and TT with respect the age of CML patients (p = 0.006) as depicted in Table 8. However, a non-significant difference in the frequencies of MDR1-rs2032581 genotypes GG, GT, and TT with respect gender of CML patients was reported (p = 0.156). The distribution of MDR1-rs2032581 genotypes GG, GT and TT was significantly different in different stages of the CML patients (p = 0.004). A statistically significant difference in the frequencies MDR1-rs2032582 genotypes among Major molecular responses with minor molecular responses of chronic myeloid leukemia patients (p = 0.016). A non-significant difference in the frequencies MDR1 (rs2032581) genotypes among Major hematological responses with minor hematological responses of chronic myeloid leukemia patients (p = 0.167).

Discussion

The introduction of TKIs transformed the treatment of CML. Imatinib, the first-generation TKI, targets the BCR-ABL1 kinase and results in marked reductions in disease burden and improvements in survival outcomes. Second-generation TKIs, including dasatinib, nilotinib, and bosutinib, provide therapeutic alternatives for patients who develop resistance or intolerance to imatinib. Response to TKI therapy is monitored through cytogenetic and molecular evaluations, with complete cytogenetic response and major molecular response serving as key indicators linked to long-term survival benefits [17]. TKI resistance in CML remains a significant clinical challenge and involves mechanisms related to the BCR-ABL1 oncoprotein. These mechanisms are broadly categorized into BCR-ABL1–dependent and BCR-ABL1–independent pathways, each contributing to diminished TKI efficacy [18,19]. This

Table 8. Association of MDR1 (rs2032581) genotype with the clinicopathological characteristics of CML patients.

Variables/genotypes	N = 50		GG	GT	TT	DF	χ^2	*p* value
Age								
<40	20	40%	10	7	3	2	10.01	0.006
>40	30	60%	3	18	9			
Gender								
Males	32	64%	10	17	5	2	3.71	0.156
Females	18	36%	3	8	7			
Stage of the disease								
CP-CML	10	20%	2	4	4	2	15.5	0.004
AP-CML	15	30%	9	5	1			
BC-CML	25	50%	2	16	7			
Molecular Reponses								
Major molecular responses	15	30%	7	3	5	2	8.16	0.016
Minor molecular responses	35	70%	6	22	7			
Hematological responses								
Major Hematological response	11	22%	5	3	3	2	3.57	0.167
Minor Hematological response	39	78%	8	22	9			

study examined the association between the *MDR1* C3435T (rs1045642) and *G2677T* (rs2032581) polymorphisms and the clinical response to imatinib in Saudi patients with CML.

Comparative Analysis of MDR1-rs2032582 G>T or (G2677T) in Different Ethnicities

Individuals may respond differently to the same medication. Although the functional effects of the mutation at position 2677 remain under discussion, MDR1 polymorphisms may influence P-gp expression and activity toward specific anticancer agents, which can affect therapeutic efficacy [20]. The *G2677T* SNP in exon 21 (codon 893) results in the substitution of alanine with serine or threonine. This change replaces a lipophilic residue (Ala) with a hydrophilic residue (Ser or Thr), a modification associated with increased resistance to several drugs, including vinblastine and Adriamycin [21].

In addition, CML patients with the 3435 TT or CT genotypes have demonstrated higher resistance compared with those carrying the CC genotype (59.4% vs 25%, $p = 0.023$). Based on these findings, several studies concluded that the MDR1 1236T, C3435T, and G2677T polymorphisms may assist in predicting response to imatinib therapy in patients with CML [22,23].

The frequency of the G2677T genotypes in our investigation was comparable to the distribution reported by Dulucq *et al.* [24]. Their study showed a significant association between specific MDR1 polymorphisms and major molecular response (MMR) in patients with CML treated with standard-dose imatinib [24]. In our analysis, the MDR1-rs2032582 GT genotype was more common among patients with CML than the TT genotype (50% vs 4%). The polymorphic T allele was also more frequent in patients with CML than in healthy individuals (0.49 vs 0.32). A statistically significant difference in allele and genotype distributions between cases and controls was observed for the MDR1-rs2032582 G>T polymorphism ($p = 0.044$).

Notable differences in allele and genotype frequencies of the *ABCB1* G2677T/A SNP have been reported across ethnic groups [20]. The distribution of the G, T, and A alleles varies substantially among populations, contributing to inter-individual differences in drug response and disease susceptibility. The minor T allele is least common in African populations, with reported frequencies as low as 14% [20]. In American and Caucasian groups, the T-allele frequency ranges from approximately 40% to 55.8%. In Asian populations, the frequency of the *G2677T* SNP among Ashkenazi Jews is comparable to that of the United States population, with an estimated combined G2677T/A/C allele frequency of around 64.4%. In a Jordanian population, no A alleles were detected in the study referenced, and the frequencies of the G and T alleles were reported as 65% and 32%, respectively [20].

In our study, the GT genotype was more common during blast crisis, consistent with the findings of Sailaja *et al.* [23], who reported a higher frequency of the heterozygous 2677GT genotype in blast crisis than in other disease stages. Sailaja *et al.* [23] also observed that the GG genotype was associated with limited cytogenetic response, while the GT genotype was linked to partial hematologic response and minor cytogenetic response. The TT genotype was associated with complete cytogenetic response (CCR). Ni *et al.* [22] reported that the GT genotype was associated with higher CCR (complete cytogenetic response). Dulucq *et al.* [24] found that the TT genotype was associated with higher molecular response, and patients with this genotype achieved a major molecular response MMR.

Our results indicated that the *MDR1* GT genotype was significantly associated with increased susceptibility

to CML, with an odds ratio (OR) of 2.56 and a risk ratio (RR) of 1.57 (p = 0.041). The MDR1 TT genotype, assessed under the codominant model, also demonstrated increased susceptibility, with an OR of 3.16 and an RR of 1.78 (p = 0.049). In contrast, another study found no relationship between the *G2677T* polymorphism and MMR in patients with CML [25]. Similar to findings reported by Ni *et al*. [22], we observed significant differences in the distribution of G2677T genotypes between imatinib-sensitive and imatinib-resistant groups during the chronic phase [24,26].

We reported a strong association with CML risk observed under the dominant model (GT+TT vs GG), with an OR of 2.73 and a RR of 1.63 (p = 0.019) besides our analysis showed that TT genotype was associated with both favorable imatinib response .Allelic comparison also demonstrated a significant association between the T allele and CML susceptibility (Table 5).

Comparative Analysis of MDR1-rs1045642 G>T or C3435T in Different Ethnicities

The *ABCB1* gene contains the rs1045642 SNP, also known as C3435T, which is often examined together with rs2032582. ABCB1 encodes P-glycoprotein, a membrane transporter responsible for exporting medications from cells. The rs1045642 variant can alter P-gp activity and may influence therapeutic responses in patients with CML [27,28]. Because imatinib is a P-gp substrate, P-gp–mediated efflux can contribute to imatinib resistance. Identification of these SNPs may therefore help predict how patients with CML respond to imatinib and how they metabolize the drug. The objective of this study was to characterize the distribution of the C3435T variants and examine their association with imatinib effectiveness in our cohort of patients with CML.

The MDR1 C3435T polymorphism is associated with increased plasma concentrations of P-gp substrates, reduced intestinal P-gp expression, and decreased P-gp function in peripheral blood cells. Digoxin is one example of a drug affected by this variation. The rs1045642 SNP in the ABCB1 (MDR1) gene has also been linked to treatment outcomes in patients with CML. Individuals with the wild-type CC genotype may be more susceptible to imatinib treatment failure, whereas those with the TT genotype may experience more favorable outcomes, although these associations vary across populations [25,29]. Because TKIs such as imatinib target the BCR-ABL oncoprotein, patient response may be affected by rs1045642 genotypes [30].

Genotype C/C: Research on newly diagnosed patients with CML has shown that individuals carrying the C/C genotype of rs1045642 have a higher likelihood of imatinib treatment failure, possibly due to lower plasma concentrations of the drug. In contrast, patients with the T/T genotype may demonstrate better molecular responses, which may reflect higher circulating levels of imatinib [31,32].

The 3435C>T *ABCB1* (MDR1) gene polymorphism has no bearing on the production of P-glycoprotein in blast cells or the risk of adult acute myeloid leukemia [33]. No such correlation was seen in AML, suggesting that the MDR1 C3435 polymorphism did not seem to have any important clinical consequences in AML [34]. Polymorphisms in imatinib influx/efflux transporters have been reported to influence response to imatinib therapy and progression free survival [35]. Several imatinib independent mechanisms of resistance have also been reported including overexpression of efflux transporters, decreased expression of influx transporters, decreased plasma levels, binding to plasma proteins and genetic polymorphisms in the enzymes and transporters involved in imatinib transport or biotransformation [36].

Our results indicated that the frequencies of MDR1 C3435T genotypes vary significantly among patients' hematological responses, with a p = 0.029 confirming that C3435T can serve as a diagnostic marker for cases of CML and can be used to monitor treatment success by observing changes in this gene and other genes. Compared to patients with CT/TT and CT genotypes, individuals with the CC genotype in our patient sample had noticeably higher CCyR rates. Since racial differences can be observed in the frequencies of MDR1 gene polymorphisms, more research in larger series is required to identify the genetic polymorphisms with therapeutic relevance in patients on imatinib [30,32]. Finally, it was reported that *MDR1* 3435TT gene polymorphism is significantly associated with a reduced imatinib response in our CML patients. For these individuals, we propose that this polymorphic variation in MDR1 might serve as an extra criterion for starting nilotinib as the first line of treatment rather than imatinib. To demonstrate the resistance impact of the MDR1 3435TT genotype on imatinib and its therapeutic significance for newly diagnosed CP-CML Saudi patients, we must extend our investigation on a broader cohort.

Conclusions

It was concluded that MDR1 rs2032581 G>T MDR1-rs1045642 C>T polymorphisms might be a risk factor for imatinib resistance in Saudi CML patients. Significant associations were reported between MDR1 genotypes and molecular responses to imatinib and advanced stage of the disease. Determination of MDR1 polymorphisms MDR1 rs2032581 G>T MDR1 rs1045642 C>T might be useful in response prediction to therapy with imatinib in patients with CML. These findings warrant further validation through larger case-control studies and functional protein analysis.

Availability of Data and Materials

All data are available from the corresponding author upon reasonable request.

Author Contributions

Conceptualization: OMA, RM. Methodology: OMA, NTA, NFA, RM. Analysis: FJT, MM, MIA, AH, JB, AAAO, RM, SM. Writing original manuscript: OMA, NTA, NFA, RM. Reviewing and editing manuscript: OMA, NTA, NFA, FJT, MM, MIA, AH, JB, AAAO, RM, SM. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Experiments were approved by the University of Tabuk Ethical Committee (Approval no. UT-88-19-2019, Dated 24/11/2019). Informed consent was obtained from all participants for publication.

Acknowledgment

The authors would like to thank the University of Tabuk.

Funding

The authors extend their appreciation to the Deanship of Scientific Research, University of Tabuk for funding this research through project number S-1441-0034.

Conflict of Interest

The authors declare no conflict of interest.

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