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Genetic Variants of Human Organic Cation Transporter1 (hOCT1) -M408V and M420del- Are Not Associated with Imatinib Response in Chronic Myeloid Leukemia

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Abstract

Background: Human organic cation transporter 1 (hOCT1) encoded by the *SLC22A1* gene, mediates uptake of imatinib (a tyrosine kinase inhibitor) into chronic myeloid leukemia (CML) cells. Variants in hOCT1 genes have been proposed to influence treatment outcomes. This study aimed to determine whether the hOCT1 variants M408V (rs628031) and M420del (rs35191146) are associated with early molecular response to imatinib in patients with CML.

Method: This cohort study included 60 CML patients who had received imatinib therapy for six months. Genotyping of M408V was performed using real-time polymerase chain reaction (PCR), while M420del was analyzed by allele-specific PCR. Patients were stratified according to Sokal and ELTS risk scores, and molecular response was assessed using quantitative BCR::ABL1 transcript levels. Statistical analysis was performed using International Business Machines-Statistical Package for the Social Sciences (IBM SPSS) version 28. Associations between genotypes and treatment response were evaluated using the Chi-square test or Fisher's exact test, and logistic regression analysis was used to estimate odds ratios and 95% confidence intervals. A *P*-value <0.05 was considered to be statistically significant.

Results: At six months of therapy, 38.33% of patients were classified as optimal responders, while 61.67% were suboptimal/non-responders. No statistically significant association was found between M408V or M420del genotypes and early molecular response to imatinib. However, both Sokal and ELTS scores were predictive of response, with the Sokal score showing superior performance in identifying non-responders.

Conclusion: The M408V and M420del variants of hOCT1 were not associated with early molecular response to imatinib therapy in this cohort of CML patients. Risk stratification scores, particularly the Sokal score, remain valuable predictors of treatment response.

Keywords: Organic cation transporter 1, Chronic myeloid leukemia, Imatinib, Single nucleotide polymorphism, Treatment outcome

Introduction

Chronic myeloid leukemia (CML) is a disease that resulted from reciprocal translocation between chromosomes 9 and 22, t(9;22)(q34;q11.2). This chromosomal rearrangement produces the Philadelphia chromosome, which carries the BCR::ABL1 fusion gene. This gene encodes a constitutively active tyrosine kinase that drives the uncontrolled proliferation of leukemic cells. As a result, myeloid cells proliferate excessively, leading to the development and progression of CML.[1] The advent of tyrosine kinase inhibitors (TKIs), particularly imatinib, has significantly improved the prognosis of patients with CML. Once considered a fatal disease, CML is now regarded as a manageable chronic condition with survival rates nearing those of the general population.[2] Imatinib, a first-generation TKI, targets the BCR::ABL1 oncoprotein and remains the standard first-line therapy for CML. Treatment response is monitored through hematologic, cytogenetic, and molecular assessments, following the European LeukemiaNet (ELN) guidelines.[3] Although imatinib is highly effective in treating CML, some patients experience resistance-either primary resistance (failure to achieve an adequate initial response) or secondary resistance (loss of response after an initial period of effectiveness).[4] One key factor contributing to this resistance is the activity of the human organic cation transporter 1 (hOCT1), which is encoded by the SLC22A1 gene. hOCT1 plays a crucial role in mediating the cellular uptake of imatinib into leukemic cells.[5,6] Genetic variations in the SLC22A1 gene, such as single nucleotide polymorphisms (SNPs), can impact hOCT1 function and thereby influence drug transport efficiency. Among these, the M408V (rs628031) and M420del (rs35191146) variants have been identified as potentially affecting imatinib uptake and therapeutic response.[7] The present study aimed to investigate the association between the M408V and M420del variants in the hOCT1 gene and early molecular response to imatinib therapy in patients with CML.

Patients and Methods

Patients

This cohort study included 60 adult patients diagnosed with chronic phase CML who were tested positive for BCR::ABL1 fusion gene and had been receiving first generation TKI, imatinib (Gleevec; Novartis), for a minimum duration of six months. These patients were diagnosed and treated at the Hematology department, Kasr Al-Ainy Faculty of Medicine, Cairo University, a tertiary referral center that serves patients from Cairo and other regions of Egypt. Consequently, the study population reflects the demographic and clinical characteristics of patients treated at this institution.

The study protocol was approved by the Research Ethics Committee (REC) of Faculty of Medicine, Cairo University (Code. MD-58-2022) and written informed consent was obtained from all participants prior to enrollment.

Sample size calculation

The sample size was calculated using a clinical sample size calculator for analytical studies. Based on data reported by Bhutani et al. (2020),[8] patients carrying the normal homozygous genotype for M408V together with mutant homozygous or heterozygous genotypes for M420del showed a higher tendency toward imatinib resistance compared with patients carrying normal homozygous

genotypes for both polymorphisms. Using a significance level (α) of 0.05 and a study power of 80% (β = 0.20), the minimum required sample size was estimated to be 60 patients with CML.

Demographics, clinical and laboratory data

Medical records were reviewed to collect data for demographics (age and sex), spleen size, initial complete blood count (CBC), bone marrow examination results and quantitative BCR::ABL1 transcript levels at diagnosis, as well as after six months of imatinib therapy.

Risk stratification and assessment of therapeutic response

At diagnosis, risk stratification was performed using the Sokal score[9] and European Treatment and Outcome Study for CML (EUTOS) Long-Term Survival (ELTS) score.[10] Therapeutic response was assessed in accordance with the 2020 European LeukemiaNet (ELN) guidelines. Based on molecular response, patients were classified into three categories: optimal responders, suboptimal responders and non-responders. This classification was determined by the results of quantitative real time polymerase chain reaction (PCR) for BCR::ABL1 transcript levels, using international scale (IS), at six months following initiation of imatinib therapy.[11]

Genotyping

Genomic DNA was extracted from whole blood samples using the GeneJET Whole Blood Genomic DNA Purification Mini Kit (#K0781), following the manufacturer's protocol (Thermo Scientific, USA. 2012).

Genotyping of M408V (rs628031) SNP was performed using Real-time PCR allelic discrimination assays with Taq-Man SNP Genotyping Assays (Applied Biosystems, Foster City, CA, USA). Fluorogenic probes specific for the alleles-each labeled with a fluorescent reporter dye (FAM or VIC)-were used to distinguish between the different genotypes. Primer sequence used was: CGTGGGCCGCATCTACCCCATGG CC[G/A]TGTCAAATTTGTTGGCG GGGGCAGC, where [G/A] denotes the SNP site. PCR amplification was carried out using the following thermal cycling conditions: initial denaturation at 95 °C for 10 min; 50 cycles of amplification at 92 °C for 15 sec and 60 °C for 1 min.

Genotyping of M420del (rs35191146) SNP was performed using Allele-Specific PCR (AS-PCR), following the method described by Bhutani et al., 2020 [8]. A total of three primers were used to amplify a 135bp amplicon, including two allele specific forward primers and a common reverse primer:

Forward primer-Wild (G): 5'-GCAGCCTGCCTCGTCATG-3'

Forward primer-Mutant (del): 5'-GCAGCCTGCCTCGTCATA-3'

Common Reverse primer: 5'-CATCTTTGTTCTCATTCCAGAGG C-3'

Thermal cycling conditions were as follows: Initial denaturation at 95°C for 15 min followed by 30 cycles of denaturation at 94°C for 30 s, annealing at 52.5°C for 60 s and extension at 72°C for 90 s, followed by 60°C for 30 min and a final hold at 4°C.

PCR products were analysed by 2% agarose gel electrophoresis and visualized under UV light.

Statistical analysis

Data were coded and analyzed using IBM SPSS Statistics version 28 (IBM Corp., Armonk, NY, USA). Quantitative variables are summarized as mean ± standard deviation (SD) or median (range), according to data distribution. Categorical variables are presented as frequencies and percentages. Comparisons between quantitative variables were performed using the non-parametric Mann–Whitney U test or Kruskal–Wallis test, as appropriate. Associations between

categorical variables were assessed using the Chi-square test or Fisher's exact test when expected cell counts were less than 5. Logistic regression analysis was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between hOCT1 polymorphisms and treatment response. Hardy–Weinberg equilibrium (HWE) was assessed for each polymorphism using the Chi-square goodness-of-fit test. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of risk scores to predict non-response, and the area under the curve (AUC) was calculated. Optimal cutoff values were determined using the Youden index (sensitivity + specificity − 1). Given the exploratory design of the study and the limited sample size, multiple subgroup analyses and ROC-based evaluations were performed without formal adjustment for multiple comparisons; therefore, *P*-values should be interpreted cautiously. A two-sided *P*-value < 0.05 was considered to be statistically significant.

Results

A total of 60 patients diagnosed with CML were included in this study. Table 1 summarizes their demographic characteristics, initial CBC data, and Sokal and ELTS risk scores at diagnosis. At six months following imatinib therapy, 23 patients (38.33%) achieved a BCR::ABL level < 1% (optimal responders), 16 patients (26.67%) had a BCR::ABL level between 1%-10% (suboptimal responders) and 21 patients (35.0%) had a BCR::ABL level >10% (non-responders). Genotype and allele frequencies for the studied SNPs, M408V (rs628031) and M420del (rs35191146), are summarized in Table 2. For M408V (rs628031), the wild homozygous genotype (AA) was the most frequent, observed in 39 patients (65.0%), followed by the heterozygous genotype (AG) in 19 patients (31.67%) and the mutant homozygous genotype (GG) in two patients (3.33%). The frequencies of the A and G alleles were 80.83% and 19.17%, respectively. For M420del (rs35191146), the heterozygous genotype (G/del) was the most common, detected in 50 patients (83.33%), whereas the wild homozygous genotype (GG) and mutant homozygous genotype (del/del) were identified in 9 (15.0%) and 1 (1.67%) patients, respectively. The frequencies of the G and del alleles were 56.67% and 43.33%, respectively. Hardy–Weinberg equilibrium analysis demonstrated that the genotype distribution of M408V was consistent with equilibrium, whereas M420del showed a significant deviation from Hardy–Weinberg equilibrium which may reflect small sample size or biological variability across different cohorts.

Sokal and ELTS risk scores were compared among the three patient groups categorized according to their molecular response at six months of imatinib therapy. The Sokal score was significantly lower in the responder group (median = 0.7) compared with both the suboptimal responder group (median = 0.85) and the non-responder group (median = 0.9), with a *P*-value of 0.038 (Table 3). Similarly, the ELTS score was significantly lower in the responder group (median = 1.07) compared with the suboptimal responder group (median = 1.45) and the non-responder group (median = 1.5), with a *P*-value of 0.021 (Table 3). The diagnostic performance of the Sokal and ELTS Scores for predicting non-responders was assessed. The Sokal score at diagnosis had a best cut-off value of 0.825 for identifying non-responders, with a sensitivity of 61.9%, specificity of 66.7%, and an area under the curve (AUC) of 0.676 (*P* = 0.012).

The 95% confidence interval for the cut-off was between 0.539 and 0.814 (Figure 1). In contrast, the ELTS score did not demonstrate significant predictive ability for non-responders, with a 95% confidence interval of 0.161 to 0.743, an AUC of 0.601, and a *P*-value of 0.161 (Figure 1).

The relationship between M408V (rs628031) genotypes and molecular response to imatinib at six months was assessed. No statistically significant association was found at this time point, with *P*-values of 0.353 (Table 4). Similarly, analysis of M420del (rs35191146) genotypes revealed no statistically significant correlation with molecular response to imatinib at six months, with *P*-values of 0.499 (Table 4). To further evaluate the association between hOCT1 polymorphisms and treatment response, logistic regression analysis was performed using a dominant genetic model, in which optimal responders were compared with the combined group of suboptimal responders and non-responders. For M408V (rs628031), carriers of the mutant allele (AG + GG) did not show a significantly different likelihood of achieving an optimal response compared with patients carrying the wild-type genotype (AA) (OR = 1.16, 95% CI: 0.40–3.35, *P* = 0.58). Similarly, for M420del (rs35191146), carriers of the deletion allele (G/del + del/del) showed no significant association with treatment response compared with patients carrying the wild-type genotype (GG) (OR = 1.09, 95% CI: 0.27–4.40, *P* = 0.88) (Table 5). Patients were stratified into four groups to assess the potential combined effect of the M408V and M420del variants on early molecular response to imatinib therapy, group A: wild-type for both M408V (A/A) and M420del (G/G), group B: M420del wild-type (G/G) with M408V mutant genotypes (A/G or G/G), group C: M408V wild-type (A/A) with M420del mutant genotypes (G/del or del/del), group D: mutant genotypes for both M408V (A/G or G/G) and M420del (G/del or del/del). Molecular response at six months (classified as optimal, suboptimal, or non-responders) was compared among the four groups. No statistically significant differences were observed between any of the groups (Table 6).

Discussion

In the present study, we investigated the association between two hOCT1 polymorphisms, M408V (rs628031) and M420del (rs35191146), and early molecular response to imatinib therapy in patients with chronic phase CML. No significant association was observed between either polymorphism and achievement of optimal molecular response at six months. Similarly, combined genotype analysis did not demonstrate a significant effect on treatment outcome. In contrast, both the Sokal and ELTS risk scores were associated with treatment response, with the Sokal score showing better predictive performance for identifying non-responders in our cohort. These findings suggest that the studied hOCT1 variants are not reliable predictors of early molecular response to imatinib, whereas established clinical risk stratification tools retain prognostic value.

For the M408V SNP, no significant differences were observed in the distribution of M408V genotypes among responders, suboptimal responders, and non-responders after six months of imatinib therapy in our cohort. This finding is consistent with several previous studies that failed to demonstrate a significant association between M408V and treatment response to imatinib. Bhutani et al., (2020) reported that 55.55% of cases with normal homozygous genotype and 57.14 % of cases with the mutant allele

had an optimal response to imatinib, with no statistically significant difference.[8] Similarly, Maffioli et al., (2011) found no correlation between M408V genotypes and response to imatinib treatment in 59 CML patients.[12] White et al., (2010) also failed to demonstrate an association between M408V genotypes and achievement of major molecular response (MMR) or progression to advanced phase in 136 newly diagnosed CML patients.[13] Furthermore, Giannoudis et al., (2013) reported no association between M408V genotypes and the achievement of MMR at either 12 or 24 months nor with disease outcome like progression free survival (PFS) and event free survival (EFS).[14]

Regarding M420del SNP, no significant difference was observed in the frequency of M420del genotypes among responders, suboptimal responders and non-responders at six months following imatinib therapy in our cohort. This finding is consistent with Bhutani et al., (2020) who reported that 59.09% of the cases with normal homozygous genotype and 50% of cases with mutant allele achieved an optimal response to imatinib and this difference was not statistically significant.[8] Similarly, Maffioli et al., (2011)[12] found no correlation between M420del genotypes and response to imatinib in 65 CML patients and White et al., (2010) also failed to demonstrate any association between M420del genotypes and achievement of MMR or progression to advanced phase in 136 newly diagnosed CML patients.[13] In contrast, Giannoudis et al., (2013) reported significant association between M420del and a higher risk of imatinib failure due to unsatisfactory response. They found that M420del was significantly associated with time to treatment failure (TTF), defined as a treatment change because of either unsatisfactory response or intolerance. However, no association was observed with other disease outcomes such as PFS and EFS.[14] It has been proposed that M420del SNP may alter the pharmacodynamics of imatinib, thereby reducing its efficacy in target leukemic cells. However, this does not necessarily translate into worse survival outcomes, since patients who fail imatinib therapy are usually switched to alternative TKIs that are unaffected by this SNP. This hypothesis was further supported by functional studies examining the impact of both M420del and M408V SNP on imatinib uptake in a transfected CML cell line model. They demonstrated that cells carrying the mutant M420del allele and wild allele of M408V exhibited a significant reduction in imatinib uptake compared with cells harbouring both wild alleles. Interestingly, in cells carrying both mutant M420del/M408V alleles, uptake did not differ from the wild type reference cells, suggesting that the mutant allele of M408V SNP can counteract the effect of the mutant allele of M420del.[14] Bhutani et al.,(2020) reported that patients with the wild homozygous genotype for M408V combined with mutant genotypes for M420del had a higher tendency towards imatinib resistance compared with those carrying wild homozygous genotype for both polymorphisms.[8] These results further support that detected by Giannoudis et al., (2013) who confirmed in a functional assay that mutant allele of M420del decreased imatinib uptake by CML cell lines whereas M408V counteracted this effect.[14]

The present study focused on the M408V (rs628031) and M420del (rs35191146) polymorphisms because they are among the most extensively studied functional variants of the SLC22A1 gene and have previously been implicated in altered hOCT1-mediated imatinib transport.[7]

Nevertheless, imatinib response is a multifactorial process that cannot be explained by individual hOCT1 variants alone. Additional genetic factors, including other SLC22A1 polymorphisms, efflux transporter genes, drug-metabolizing enzymes, BCR::ABL1-dependent resistance mechanisms, treatment adherence, and baseline disease characteristics, may all contribute to variability in treatment outcomes. Therefore, the absence of significant associations in the present study should be interpreted within the context of this broader biological complexity. The results of our study add to the growing body of evidence that no single hOCT1 genetic variant has consistently been shown, even in large patient cohorts with long-term follow-up, to reliably predict molecular response to imatinib therapy in CML patients. Therefore, the prediction of clinical response may be better addressed through functional assessment of hOCT1 activity, which remains the only prognostic indicator that has been successfully validated in independent clinical trials.[15] Since hOCT1 activity was not measured in the present study, the functional consequences of the investigated variants could not be directly evaluated in our cohort. As a result, it remains unclear whether the studied polymorphisms had a measurable effect on transporter function in our patients.

In terms of clinical risk stratification, the Sokal score classified 38.33% of patients as low-risk, 55.0% as intermediate-risk, and 6.67% as high-risk. Using the ELTS score, 68.33% of patients were categorized as low-risk, 25.0% as intermediate-risk, and 6.67% as high-risk. In our cohort, the Sokal score demonstrated better predictive performance for identifying non-responders than the ELTS score, with an optimal cutoff value of 0.825, corresponding to a sensitivity of 61.9% and a specificity of 66.7%. However, these findings should be interpreted with caution given the limited sample size and exploratory nature of the analysis. Furthermore, the observed predictive performance of the risk scores requires validation in larger, independent cohorts with adequate statistical power. Pfirrmann et al. (2020)[16] and Zhang et al. (2022)[17] reported that the ELTS score provides superior predictive accuracy for patients treated with TKIs, particularly second-generation TKIs. Similarly, Sato et al. (2020) compared four scoring systems (Sokal, Hasford, EUTOS, ELTS) and found ELTS to have the highest prognostic value for predicting treatment outcomes and deep molecular response.[18] Geelen et al. (2018) further supported the utility of ELTS in stratifying patients according to long-term survival, especially in those treated with second-generation TKIs.[19]

Several limitations of the present study should be acknowledged. First, the relatively small sample size (n = 60) may have limited the statistical power to detect modest associations between hOCT1 polymorphisms and molecular response to imatinib. Second, the study was conducted at a single center which may limit the generalizability of the findings. Therefore, caution should be exercised when extrapolating these results to other populations. The relatively short follow-up period represents another limitation of the present study. Molecular response was assessed only at 6 months after initiation of imatinib therapy, which reflects an early treatment outcome while being clinically relevant and prognostically informative. Consequently, this study could not evaluate the potential impact of M408V and M420del polymorphisms on deeper molecular responses, including major molecular response and deep molecular

response, nor on long-term clinical endpoints such as treatment failure, progression-free survival, event-free survival, and overall survival. Furthermore, long-term outcome assessment was limited by inconsistent treatment adherence and loss to follow-up among a proportion of patients during routine clinical care, which reduced the availability of reliable longitudinal data beyond the 6-month time point. Finally, functional hOCT1 activity and intracellular imatinib concentrations were not measured. This limitation is particularly relevant because previous studies have suggested that functional hOCT1 activity may be a stronger predictor of imatinib response than individual genetic variants.

Conclusion

We found that the M408V (rs628031) and M420del (rs35191146) variants of hOCT1 were not associated with early molecular response to imatinib therapy at the 6-month assessment in this cohort of patients with CML. Taken together with the variability reported across different studies, it is concluded that these hOCT1 SNPs cannot be reliably used to predict treatment outcomes or guide therapeutic decisions. Instead, established clinical risk stratification tools such as the Sokal and ELTS scores appear to offer greater prognostic value in this setting. Larger multicenter prospective studies involving diverse patient populations with longer follow-up periods and integrating genetic, functional, and pharmacokinetic analyses may provide a more comprehensive evaluation of the role of hOCT1 genetic variants in predicting response to imatinib therapy.

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Authors' Contributions

E.N: Study design, data gathering, data analysis, laboratory work and reviewing the manuscript; K.S.: Study design, supervision and reviewing the manuscript; M.S.M: Study design, data analysis, drafting and reviewing the manuscript; E.H.N: Study design, data gathering and data analysis; M.Sh.M: Data analysis and drafting the manuscript; F.M: Study design, data analysis and drafting the manuscript; All authors have read and approved the final manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

None declared.

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Table 1. Baseline demographic, clinical, and hematological characteristics, and risk stratification of patients with CML at diagnosis (N = 60)

Age (years)	
Mean ± SD	46.28 ± 11.69
Sex (N, %)	
Male	33 (55.0%)
Female	27 (45.0%)
Splenomegaly (N, %)	
Yes	35 (58.33%)
No	25 (41.67%)
Hemoglobin (g/dL)	
Mean ± SD	10.49 ± 2.14
WBC count (10^9 /L)	
Mean ± SD	221.31 ± 126.49
Platelet count (10^9 /L)	
Mean ± SD	408 ± 353.59
Sokal risk score (N, %)	
Low	23 (38.33%)
Intermediate	33 (55.0%)
High	4 (6.67%)
ELTS risk score (N, %)	
Low	41 (68.33%)
Intermediate	15 (25.0%)
High	4 (6.67%)

CML: Chronic myeloid leukemia; N: Number; WBC: White blood cell; SD: Standard deviation

Table 2. Genotypes and allele frequencies of M408V and M420del SNPs in patients with CML (N=60)

SNP	**N (%)**
M408V	
Wild (A/A)	39 (65.0%)
Heterozygous (A/G)	19 (31.67%)
Mutant (G/G)	2 (3.33%)
Wild allele (A)	97 (80.83%)
Mutant allele (G)	23 (19.17%)
Allele A frequency	0.808
Allele G frequency	0.192
M420del	
Wild (G/G)	9 (15.0%)
Heterozygous (G/del)	50 (83.33%)
Mutant (del/del)	1 (1.67%)
Wild allele (G)	68 (56.67%)
Mutant allele (del)	52 (43.33%)
Allele G frequency	0.567
Allele del frequency	0.433

SNPs: Single nucleotide polymorphisms; CML: Chronic myeloid leukemia; N: Number

Table 3. Association between baseline Sokal and ELTS risk scores and molecular response to imatinib therapy at six months in patients with CML (N = 60)

	Molecular response at 6 months			***P* value**
	Responders N = 23	**suboptimal N = 16**	**Non-responders N = 21**	
Sokal score median (range)	0.70 (0.49-4.60)	0.85 (0.50-1.50)	0.90 (0.57-2.40)	0.038
ELTS score median (range)	1.07 (0.56-2.07)	1.45 (0.80-3.80)	1.50 (0.90-2.20)	0.021

CML: Chronic myeloid leukemia; N: Number

Table 4. Association between M408V and M420del genotypes and molecular response to imatinib at six months in patients with CML (N=60)

Treatment response at 6 months	**M408V**				**M420del**			
	Wild (A/A) N (%)	**Heterozygous(A/G) N (%)**	**Mutant (G/G) N (%)**	***P* value**	**Wild (G/G) N (%)**	**Heterozygous(G/del) N (%)**	**Mutant (del/del) N (%)**	***P* value**
Responders N = 23	12 (52.17%)	9 (39.13%)	2 (8.70%)	0.353	5 (21.74%)	17 (73.91%)	1 (4.35%)	0.499
Suboptimal responders N = 16	11 (68.75%)	5 (31.25%)	0 (0%)		1 (6.25%)	15 (93.75%)	0 (0%)	
Non-responders N = 21	16 (76.19%)	5 (23.81%)	0 (0%)		3 (14.29%)	18 (85.71%)	0 (0%)	

CML: Chronic myeloid leukemia; N: Number

Table 5. Logistic regression analysis of the association between hOCT1 polymorphisms and molecular response to imatinib at six months under a dominant genetic model in patients with CML (N = 60)

Genotype	**Responders N = 23**	**Suboptimal/Non-responders N = 37**	**OR (95% CI)**	***P* value**
M408V				
AA N (%)	12 (52.17%)	27 (72.97%)	Reference	—
AG + GG N (%)	11 (47.83%)	10 (27.03%)	1.16 (0.40–3.35)	0.58
M420del				
GG N (%)	5 (21.7%)	4 (10.8%)	Reference	—
G/del + del/del N (%)	18 (78.3%)	33 (89.2%)	1.09 (0.27–4.40)	0.88

CML: Chronic myeloid leukemia; N: Number; OR: Odds ratio; CI: Confidence interval

Table 6. Combined effect of M408V and M420del genotypes on the molecular response to imatinib at six months in patients with CML

Patients' groups		Responders N (%)	Suboptimal N (%)	Non-responders N (%)	*P* value
A (N = 6) vs. B (N = 3)	A (wild both)	3 (50.0%)	1 (16.67%)	2 (33.33%)	1.00
	B (wild M420del, mutant M408V)	2 (66.67%)	0 (0.0%)	1 (33.33%)	
A (N = 6) vs. C (N = 33)	A (wild both)	3 (50.0%)	1 (16.67%)	2 (33.33%)	0.629
	C (wild M408V, mutant M420del)	9 (27.27%)	10 (30.30%)	14 (42.43%)	
A (N = 6) vs. D (N = 18)	A (wild both)	3 (50.0%)	1 (16.67%)	2 (33.33%)	1.00
	D (mutant both)	9 (50.0%)	5 (27.78%)	4 (22.22%)	
B (N = 3) vs. C (N = 33)	B (wild M420del, mutant M408V)	2 (66.67%)	0 (0.0%)	1 (33.33%)	0.460
	C (wild M408V, mutant M420del)	9 (27.27%)	10 (30.30%)	14 (42.43%)	
B (N = 3) vs. D (N = 18)	B (wild M420del, mutant M408V)	2 (66.67%)	0 (0.0%)	1 (33.33%)	1.00
	D (mutant both)	9 (50.0%)	5 (27.78%)	4 (22.22%)	
C (N = 33) vs. D (N = 18)	C (wild M408V, mutant M420del)	9 (27.27%)	10 (30.30%)	14 (42.43%)	0.215
	D (mutant both)	9 (50.0%)	5 (27.78%)	4 (22.22%)	

Patients with CML were stratified into four genotype combination groups: A: wild-type for both M408V (A/A) and M420del (G/G); B: M408V mutant (A/G or G/G) with wild-type M420del (G/G); C: wild-type M408V (A/A) with M420del mutant (G/del or del/del); D: mutant genotypes for both M408V and M420del. CML: Chronic myeloid leukemia; N: Number

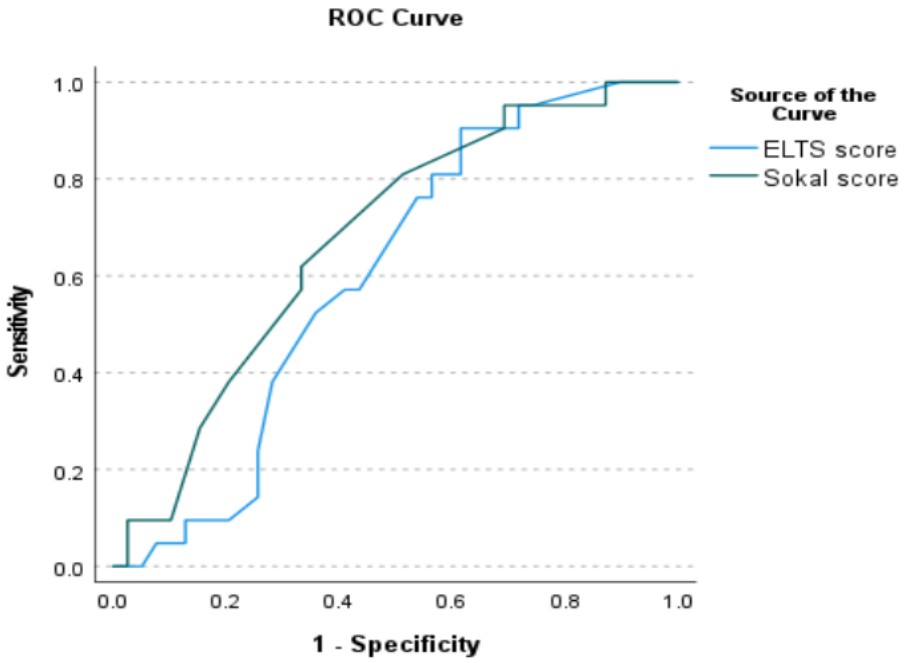

Figure 1. This figure shows the ROC curves of the Sokal and ELTS scores for the prediction of non-response to imatinib therapy at six months.
ROC: Receiver operating characteristic