https://doi.org/10.29309/TPMJ/2025.32.10.9812

The Professional Medical Journal
www.theprofesional.com
2025, Volume, 32 Issue, 10

ORIGINAL ARTICLE

Age, Gender and Genetic Code: Exploring imatinib Mesylate therapeutic response with the role of rs683369 in chronic myeloid leukemia.

Asma Khan[1], Zabiullah[2], Faizan Rasheed[3], Zarafshan Bader[4], Imrana Aamir[5]

Article Citation: Khan A, Zabiullah, Rasheed F, Bader Z, Aamir I. Age, Gender and Genetic Code: Exploring imatinib Mesylate therapeutic response with the role of rs683369 in chronic myeloid leukemia. Professional Med J 2025; 32(10):1280-1287. https://doi.org/10.29309/TPMJ/2025.32.10.9812

ABSTRACT… Objective: To evaluate the impact of demographic (age, gender) and genetic (rs683369) factors on the therapeutic response to Imatinib Mesylate. **Study Design:** Prospective, Non-interventional Observational Study. **Setting:** Islamic International Medical College and Holy Family Hospital, with Genetic Testing at KRL Hospital, Islamabad. **Period:** January 2019 to December 2022. **Methods:** Included 106 CML patients aged 18–75 years, receiving 400 mg/day of Imatinib Mesylate. Response was assessed after three months based on hematological markers and Philadelphia chromosome presence. rs683369 genotyping was performed using PCR-RFLP, and plasma Imatinib levels were measured after one month. Statistical analysis included chi-square tests and binary logistic regression using SPSS. **Results:** Gender was significantly associated with treatment response, with females showing a higher response rate ($p < 0.001$). Older patients (≥51 years) exhibited higher plasma drug levels. The CC genotype of rs683369 was significantly associated with a favorable response compared to CG and GG genotypes ($p = 0.04$). **Conclusion:** Age, gender, and rs683369 genotype significantly influence Imatinib response in Pakistani CML patients. These findings support the application of pharmacogenetics in developing personalized treatment strategies.

Key words: Chronic Myeloid Leukemia, HPLC, Imatinib.

INTRODUCTION

Chronic myeloid leukemia (CML) is characterized by an abnormal rise of clonal hematopoietic stem cells as a consequence of the Philadelphia chromosome. Philadelphia chromosome is an abnormal chromosome that is produced by a specific chromosomal translocation between chromosomes 9 & 22.[1] In this, the Abelson murine Leukemia (ABL) gene from Chromosome 9 joins to the Breakpoint Cluster Region (BCR) gene from chromosome 22 to form a BCR–ABL fusion gene. Under the influence of this fusion gene, there would be sustained activation of tyrosine kinase with ineffective deactivating mechanism.[2] This uncontrolled constitutively active tyrosine kinase leads to cytokine signal transduction that stimulates growth and inhibits apoptosis in hematopoietic cells. The novel drug Imatinib Mesylate (IM) is the primary treatment for CML. It is a tyrosine kinase inhibitor that effectively targets the BCR-ABL-stimulated protein kinase and stops disease progression across all stages. It also modifies gene function associated with adhesion, cytoskeleton organization, and cell cycle control.[3] The interaction between IM and the inactive kinase domain of the BCR-ABL protein is the mechanism by which it causes apoptosis in Ph(+) cells. By selectively attaching to this dormant domain, IM efficiently prevents phosphate from being transferred to the protein's tyrosine residues.[4] This barrier prevents downstream proteins from being activated, which in turn causes Ph(+) cells to begin apoptosis.[5]

The development of resistance in a substantial portion of CML patients receiving IM therapy has emerged as a significant therapeutic problem with the shift to alternate therapies that may not be cost-effective.[6]

1. MBBS, M.Phil, Ph.D, Associate Professor Pharmacology & Therapeutics, HITEC Institute of Medical Sciences, Taxila.
2. MBBS, Research Associate, Rawalpindi Medical University, Rawalpindi.
3. MBBS, Research Associate, Rawalpindi Medical University, Rawalpindi.
4. MBBS, M.Phil, Associate Professor Pharmacology & Therapeutics, Fauji Foundation Medical College.
5. MBBS, M.Phil, Professor Pharmacology & Therapeutics, Fazaia Medical College, Islamabad.

Correspondence Address:
Dr. Asma Khan
Department of Pharmacology & Therapeutics,
HITEC Institute of Medical Sciences, Taxila.
asmazeb26@yahoo.com

Article received on: 23/04/2025
Date of revision: 26/05/2025
Accepted for publication: 27/06/2025

Due to TKI resistance, 20–40% of patients initially given IM will ultimately require an alternative.[7] Both Pharmacokinetic and Pharmacodynamics mechanisms could be involved in this acquired resistance. Mutations in the BCR-ABL kinase binding domain of IM are the basic mechanism for Pharmacodynamic resistance in CML. This hinders drug binding and affects its ability to block oncogenic signaling.[8] Alternatively, activation of alternative oncogenic pathways may circumvent the need for BCR-ABL signaling, reducing the therapeutic response of IM therapy and promoting leukemia cell survival. In chronic myeloid leukemia, variability in the pharmacokinetics of the drug also plays an important role in the development of therapeutic resistance to Imatinib.[9] Variations in absorption due to gastrointestinal factors, altered tissue distribution, changes in metabolism mediated by enzymes like CYP3A4, and enhanced drug efflux by transporters like P-glycoprotein or reduced expression of uptake transporter can result in suboptimal drug levels with diminishing therapeutic efficacy.[10] Human organic cation transporter 1 (hOCT1) is considered the main IM uptake transporter. The SLC22A1 gene, which spans roughly 37.41 kb and has eleven exons and ten introns, encodes the hOCT1 transporter. It is found inside a cluster on chromosome 6q25-q27. The 12 α-helical transmembrane domains (TMDs) that comprise the 554 amino acid OCT1 protein have their N and C termini inside cells.[11]

Individuals with CML who exhibit reduced hOCT1 activity are less likely to respond to IM therapy in terms of major molecular response (MMR). On the other hand, people with higher hOCT1 mRNA levels usually had better MMR or complete cytogenetic response (CCyR).[12] There is a common single nucleotide polymorphism (SNP) in the SLC22A1 gene known as rs683369(C480G). It includes changing the nucleotide sequence by converting cytosine (C) to guanine (G). This alteration results in an amino acid substitution at codon 160, where leucine (abbreviated as phe160Leu) takes the place of phenylalanine. The structure and functionality of the protein that the SLC22A1 gene encodes are affected by this change in the amino acid content of the protein caused by the SNP. Individuals with CML who had either the SLC22A1 rs683369 G allele (CG+GG vs CC) or the SLC22A1 rs628031A allele (GA+AA vs GG) showed a reduced main molecular response rate to IM. It raises the possibility that variations rs628031 and rs683369 are related to reduced IM concentration.[13] An inadequate response to treatment could result from the C to G genetic mutation, according to a study, which also implies that it may contribute to a decrease in transporter activity. Altered therapeutic response to the treatment may likely develop in people who inherit the G allele in selected SNP rs 683369 of SLC22A1.

This study aims to explore the impact of the SLC22A1 C480G polymorphism on therapeutic response in CML patients, a topic not previously investigated in Pakistan.

METHODS

The Institutional Review Committee approved before this study could be carried out according to the Declaration of Helsinki with Ref#Riphah/IIMC/ERC/18/0265 of Islamic International Medical College affiliated with Riphah International University. 106 newly diagnosed CML patients from the CML clinic in Holy Family Hospital, Rawalpindi with Ph chromosome-positive BCR-ABL were included in this study who had been receiving 400 mg IM daily for less than 03 months and had no comorbidities and were not taking any enzyme inducers or inhibitors. These patients ranged from 18-70 in age. Before the commencement of the study, every person had given written informed consent.[14] Leukemia net guidelines were adhered to regarding the prognosis of treatment.[15] After three months of CML treatment, a portion of patients achieved a complete haematological response. These patients were assigned to the group of responders. These patients were observed for an additional three months to ascertain the response to the same dose of Imatinib. The group that was labelled as non-responders were those who did not achieve a full haematological response after three months of treatments with Imatinib (400 mg/day/oral) with Ph chromosome > 95%.

Three milliliters of peripheral blood were collected in EDTA tubes for DNA analysis. Genomic DNA was extracted using the Whole Blood Genomic DNA Purification Mini Kit (Thermo Fisher Scientific), which consistently provided high yields of quality DNA.[16] The SLC22A1 rs683369 polymorphism was identified using the PCR-RFLP method. Specific primers—5′-GAT ACC GAG TTT GAT GAA CTG-3′ (forward) and 5′-ACT CTG AAA CAC ACC TCA AAT C-3′ (reverse)—amplified a 424 bp DNA fragment. The 25 µL PCR reaction contained PCR buffer, 2.0 µM $MgCl_2$, 0.2 µM dNTPs, 0.4 µM of each primer, 1.0 U Taq polymerase, 50 ng of DNA, and distilled water. The thermal cycling involved 40 cycles of denaturation (95°C, 2 min), annealing (56°C), extension (72°C, 30 sec)[17], and a final extension (72°C, 10 min). The PCR product underwent electrophoresis in 2% agarose gel and digestion with MboII.[18] Genotypes were determined by electrophoresis band patterns: CC (240, 132, 52 bp), CG (372, 240, 132, 52 bp), and GG (372, 52 bp).

For measuring IM plasma levels, peripheral venous blood samples were obtained 0.5 hours before the daily IM dose. As all participants were taking IM 400 mg for at least 04 weeks, it was assumed that plasma Imatinib levels had already reached a steady state concentration.[19] For the analysis, reverse-phase high-performance liquid chromatography (HPLC) was employed. An e2695 separation module, integrated with a 2489 UV/VIS detector and an automated sampler, was used. The separation was performed over 10 minutes using a C18 column with a 5 μm particle size, and 1 ml/min was the flow rate for the mobile phase. The mobile phase was an aqueous buffer solution consisting of acetonitrile in a 90:10 v/v ratio, KH2PO4 (0.094 M) and KH2PO4 (0.0058 M). 210 nm was selected as the detector's wavelength.[20]

Statistical Analysis

Microsoft SPSS-23 and SPSS software version 22.0 were used for statistical analysis. For descriptive statistics, standard errors and means of each group were presented. For the comparison of categorical variables, the chi-square test was used. The distribution of genotypes adhered to the expectations set by Hardy-Weinberg equilibrium for that locus (p value>0.05). To determine the effect of genotypes on therapeutic response, binary logistic regression analysis was done.[21] Using analysis of variance (ANOVA), Plasma Imatinib levels were compared between all genotypes. Sub-group analysis was also done to analyze other potential factors like age and gender. For values to be considered statistically significant, the p-value should be less than 0.05.

There were notable gender differences in the distribution of respondents and non-responders. Of the male population, 21 were responders, and 37 were non-responders. On the other hand, of the female participants, 38 were found to be responders, while 10 were non-responders. The plasma Imatinib levels differed significantly, with females showing greater levels at 1151 ng/ml compared to males at 875 ng/ml ($p < 0.001$), according to statistical analysis. (Table-I)

The study population was categorized into four age groups: 18–30, 31–40, 41–50, and 51 and above. The distribution of responders and non-responders was different for each group. It is noteworthy that the percentage of responders increased with age, with the group of those 51 years and older showing the largest percentage. The plasma IM levels also differed by age group, with those 51 years of age and above exhibiting the highest levels (1205 ng/ml), followed by those 41 to 50 years old (1013 ng/ml). Significant variations in trough levels were seen between age groups, according to statistical analysis ($p = 0.021$). (Table-I, Figure-1)

The genotype distribution of rs683369 in this study showed that different genotypes have varied frequencies. The most common genotype among the individuals is CC, which made up 44.3% of the sample. Next in line were the CG and GG genotypes, with 37.8% and 17.9%, respectively. Out of a total of 47 patients, those with the CC genotype demonstrated a strong correlation in their response to treatment, with 31 of them responding and 16 not responding.

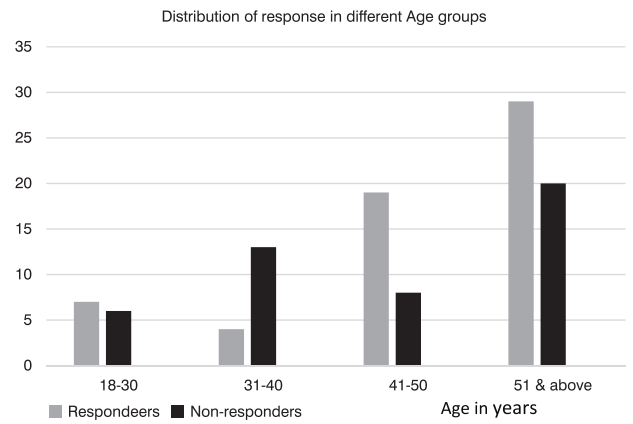

Figure-1. Distribution of Responders and non-responders in different age groups

Among bearers of the CC genotype, the average plasma IM levels were measured at 1178 ng/ml, with a significant p-value of 0.04. In comparison, out of 40 individuals, the CG genotype revealed 22 responders and 18 non-responders, whereas out of 19 individuals, the GG genotype showed 6 responders and 13 non-responders. The average plasma IM levels were 747 ng/ml for the GG genotype and 1021 ng/ml for the CG genotype. These results, point to a possible relationship between the rs683369 genotype and treatment response. The odds ratio(OR) for Gender indicates a significant association which reflects that females exhibit a 6.695 times higher likelihood of response when compared to males which is also evident by the wide CI ranging from 2.781 to 16.119. It highlights a potential gender-specific response to Imatinib treatment among CML patients warranting further detailed exploration into the underlying mechanisms. These findings reveal the potential utility of Genetic Polymorphism such as SLC22A1 C480G as prognostic indicators for the treatment response in CML patients undergoing Imatinib therapy. (Table-II)

Table-III provides a detailed analysis of the relationship between therapeutic response and SLC22A1 C480G polymorphism genotypes in enrolled patients in various genetic models. GG genotype had the lowest chances of response (OR = 0.014, 95% CI: 0.076-0.745) in the Co-dominant model, which compares each genotype separately. This suggests that the individuals with GG genotype have a measurably lower capacity to respond to Imatinib than the CC genotype.

	Responders n = 59	Non-Responders n =47	Total n =106	Test Value	IM Trough Levels (ng/ml)	P-Value
Gender				19.64 (Chi-Square)		<0.001**
Female	38	10	48		1151	
Male	21	37	58		875	
Age		9.623 (Fisher's exact test)				0.02*
Group 1(18-30)	7	6	13		763	
Group 2(31-40)	4	13	17		830	
Group 3(41-50)	19	8	27		1013	
Group 4 (51 and above)	29	20	49		1205	
rs683369		6.49 (Chi-Square)				0.04*
CC	31	16	47		1178	
CG	22	18	40		1021	
GG	06	13	19		747	

Table-I. Demographic features of CML patients

On the other hand, the CG genotype showed an intermediate effect on treatment response (OR = 0.298, 95% CI: 0.265-1.502), suggesting that treatment effectiveness may have a dose-relative relationship. When the CG and GG genotypes were merged to create the dominant model, carriers of the variant allele showed a lower response (OR = 0.059, 95% CI: 0.211-1.028), barely reaching statistical significance. However, the GG genotype was counterbalanced against a combination of CC and CG genotypes under the recessive model where the G allele's recessive effect on treatment response was evident with the lower odds ratio and decreased therapeutic response shown by individuals with the GG genotype. Furthermore, heterozygotes (CG) showed negligible correlation with treatment response when compared to both homozygotes (CC and GG) in the Over-Dominant Model. In the end, each more copy of the G allele leads to decreased therapeutic response as evidenced by the additive model (OR = 0.007, 95% CI: 0.261-0.812). (Table-III)

Genotype	Frequencies (%)	Alleles	Allele Frequency	Test Value (Chi square)	HWE P-Value
CC	47(44.3%)	C	134(63.2%)	3.77	0.15
CG	40(37.8%)	G	78(36.8%)		
GG	19(17.9%)				
Total	106		212		

Table-II. Genotype and allele frequencies for rs693369 (SLC22A1)

Parameter	Odds Ratio	95% Confidence Interval (Lower)	95% Confidence Interval (Upper)
Odds Ratio for Gender (Male vs. Female)	6.695	2.781	16.119
Total Valid Cases	106		

Table-III. Risk estimates with 95% confidence intervals

Genetic Model	Genotype (rs683369)	Non Responders Total n =47	Responders Total n =59	OR	95% CI		P-Value
					Lower	Upper	
Codominant	CC	16	31	1			0.039*
	CG	18	22	0.631	0.265	1.502	
	GG	13	06	0.238	0.076	0.745	
Dominant	CC	16	31				0.057
	CGGG	31	28	0.466	0.211	1.028	
Recessive	GG	34	53				0.020*
	CCCG	13	06	0.296	0.103	0.854	
Over Dominant	CG	29	37				0.915
	CCGG	18	22	1.044	0.474	2.300	
Additive	C G	50 44	84 34	0.460	0.261	0.812	0.007*

Table-IV. Genetic models in responders and non-responders

DISCUSSION

A major obstacle in the therapeutic care of individuals with chronic myeloid leukemia (CML) is the emergence of decreased therapeutic response to Imatinib (IM) therapy in a considerable proportion. Numerous mechanisms, including genetic differences affecting drug transporters and metabolizing enzymes that contribute to interpatient pharmacokinetic variability, have been discovered by studies as potential mechanisms for altered clinical response. This study is an innovative attempt to investigate how genetic differences, specifically in the entry transporter gene SLC22A1, affect the therapeutic response of Imatinib.[21]

We found that individuals with the GG genotype had shown reduced therapeutic response when compared to those with the CC genotype. Moreover, the CG genotype was associated with reduced treatment response (OR = 0.298, $p < 0.05$) relative to the CC genotype. These results underscore the importance of genetic factors, specifically SLC22A1 C480G, in predicting Imatinib treatment outcomes in CML patients. In 2022, a study was conducted on CML patients which found that the homozygous variant (GG) genotype was more common in the group of patients who had an inadequate cytogenetic response than in the group that had a complete hematologic response.[22] This difference, though, did not become statistically significant. Additionally, they looked at the genotype distribution of those who achieved major molecular response (MMR) against those who did not. The homozygous variation (GG) genotype was more common in the non-MMR group. Another study was done on Malaysian Patients with chronic myeloid leukemia (CML) receiving Imatinib (IM) therapy with SLC22A1 gene polymorphisms.[23] The IM-resistant group had notably greater rates of homozygous variant (GG) and heterozygous genotype (CG) in comparison to the favorable response group, according to the results. Furthermore, these genotypes were linked to a noticeably increased risk of becoming resistant to immunomodulatory medication (IM), underscoring the significance of SLC22A1 C480G SNP genotyping for IM therapy optimization in patients with CML.

In addition to genetic variations, our study explored gender-based and age-based differences in IM response. Interestingly, we observed a significant gender-specific effect, with female patients exhibiting a higher likelihood of response compared to males.[24] This gender disparity in treatment outcomes warrants further investigation into potential sex-specific factors influencing IM response. It agrees with the study done by Shin H et al in 2020 which states that females achieve MMR earlier as compared to males on the same dose.[25] This could be attributed to differences in hormonal status and better compliance. Furthermore, age-related variations in treatment response were observed, with older patients demonstrating higher response rates compared to younger individuals. This age-related influence on treatment outcomes suggests the importance of dose adjustment based on age. This study may provide the basis for the pharmacokinetic studies measuring plasma IM levels adjusted for age, gender, and population ethnicity.[26]

Regarding the effect of entry transporters in modifying treatment responses to IM, numerous investigations conducted on a variety of populations have produced a variety of results. Furthermore, additional studies have shown that hOCT1 expression levels may play a critical role in the effectiveness of IM treatment in CML patients; decreased expression of hOCT1 was seen in the peripheral blood of CML patients compared to healthy controls.[27]

The findings of this study contribute to our understanding of the mechanisms underlying IM resistance in CML and provide a basis for the development of personalized treatment strategies tailored to individual genetic profiles. By identifying genetic markers associated with treatment response, clinicians can optimize therapeutic regimens and improve outcomes for CML patients.[28] However, further research is required to validate these findings in larger cohorts and explore potential interactions between genetic variants and other clinical factors that may influence treatment responses.

CONCLUSION

In conclusion, the investigation into the impact of the SLC22A1 C480G polymorphism on IM treatment responses in CML patients represents a significant advancement in precision medicine approaches for cancer therapy. By elucidating the role of genetic variations in drug response, this study paves the way for the implementation of personalized treatment strategies aimed at improving outcomes and overcoming therapeutic challenges in CML management.

ACKNOWLEDGMENTS

Grammerly software was used for better writing and to avoid grammatical mistakes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Copyright© 27 June, 2025.

REFERENCES

1. Mojtahedi H, Yazdanpanah N, Rezaei N. **Chronic myeloid leukemia stem cells: Targeting therapeutic implications.** Stem Cell Research & Therapy. 2021; 12(1):603. DOI: https://doi.org/10.1186/s13287-021-02659-1

2. Yung Y, Lee E, Chu H-T, Yip P-K, Gill H. **Targeting abnormal hematopoietic stem cells in chronic myeloid leukemia and philadelphia chromosome-negative classical myeloproliferative neoplasms.** International Journal of Molecular Sciences. 2021; 22(2):659. DOI: https://doi.org/10.3390/ijms22020659

3. Kumar R, Krause DS. **Recent advances in understanding chronic myeloid leukemia: where do we stand?** Faculty Reviews. 2021; 10. DOI:10.12703/r/10-35. PMID: 33977288; PMCID: PMC8103906.

4. Poudel G, Tolland MG, Hughes TP, Pagani IS. **Mechanisms of resistance and implications for treatment strategies in chronic myeloid leukaemia.** Cancers. 2022 Jul 6; 14(14):3300. DOI: 10.3390/cancers14143300

5. Saleh K, Fernandez A, Pasquier F. **Treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia in adults.** Cancers. 2022; 14(7):1805. https://doi.org/10.3390/cancers14071805

6. Hofmann WK, Trumpp A, Müller-Tidow C. **Therapy resistance mechanisms in hematological malignancies.** International Journal of Cancer. 2023 Feb 1; 152(3):340-7. https://doi.org/10.1002/ijc.34243

7. Alves R, Gonçalves AC, Rutella S, Almeida AM, De Las Rivas J, Trougakos IP, et al. **Resistance to tyrosine kinase inhibitors in chronic myeloid leukemia—from molecular mechanisms to clinical relevance.** Cancers. 2021; 13(19):4820. https://doi.org/10.3390/cancers13194820

8. Liu J, Yang H, Xu X, Yi S, Meng L. **Mutations in the BCR-ABL1 kinase domain in patients with chronic myeloid leukemia treated with TKIs or at diagnosis.** Oncology letters. 2020; 20(2):1071-6. https://doi.org/10.3892/ol.2020.11650

9. Batcha JSD, Gota V, Matcha S, Raju AP, Rao M, Udupa KS, et al. **Predictive performance of population pharmacokinetic models of imatinib in chronic myeloid leukemia patients.** Cancer Chemotherapy and Pharmacology. 2024; 94(1):35. doi: 10.1007/s00280-024-04644-w

10. Pena MÁ, Muriel J, Saiz-Rodríguez M, Borobia AM, Abad-Santos F, Frías J, et al. **Effect of cytochrome P450 and ABCB1 polymorphisms on imatinib pharmacokinetics after single-dose administration to healthy subjects.** Clinical Drug Investigation. 2020; 40(7):617-28. https://doi.org/10.1007/s40261-020-00921-7

11. Manvi AA, Rodrigues EC, Afreen M, Padmapriyan SGG. **Effect of 1022C> T and 1222A> G genetic polymorphisms of SLC22A1 gene on substrates binding to human organic cation transporter 1.** Journal of Applied Pharmaceutical Science. 2020; 10(9):072-81. DOI: 10.7324/JAPS.2020.10909

12. Giacomini K, Yee SW. **Emerging Roles of the Human Solute Carrier 22 Family.** Drug Metabolism and Disposition. 2021; 50(9). https://doi.org/10.1124/dmd.121.000702

13. Franczyk B, Rysz J, Gluba-Brzózka A. **Pharmacogenetics of drugs used in the treatment of cancers.** Genes. 2022; 13(2):311. https://doi.org/10.3390/genes13020311

14. Kurihara C, Kerpel-Fronius S, Becker S, Chan A, Nagaty Y, Naseem S, et al. **Declaration of Helsinki: Ethical norm in pursuit of common global goals.** Frontiers in Medicine. 2024; 11:1360653. https://doi.org/10.3389/fmed.2024.1360653

15. Hochhaus A, Baccarani M, Silver RT, Schiffer C, Apperley JF, Cervantes F, et al. **European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia.** Leukemia. 2020; 34(4):966-84. https://doi.org/10.1038/s41375-020-0776-2

16. Wulan DT, Sutanta M, Sophian A. **Comparison of two commercial DNA extraction kit to obtain high quality porcine DNA.** Asian Journal of Tropical Biotechnology. 2021; 18(2).69-72. DOI: 10.13057/biotek/c180203

17. Zhu H, Zhang H, Xu Y, Laššáková S, Korabečná M, Neužil P. **PCR past, present and future**. Biotechniques. 2020; 69(4):317-25. https://doi.org/10.2144/btn-2020-0057

18. Meiser LC, Antkowiak PL, Koch J, Chen WD, Kohll AX, Stark WJ, et al. **Reading and writing digital data in DNA.** Nature protocols. 2020; 15(1):86-101. https://doi.org/10.1038/s41596-019-0244-5

19. Roosendaal J, Groenland SL, Rosing H, Lucas L, Venekamp N, Nuijen B, et al. **Determination of the absolute bioavailability of oral imatinib using a stable isotopically labeled intravenous imatinib-d8 microdose.** European Journal of Clinical Pharmacology. 2020; 76:1075-82. https://doi.org/10.1007/s00228-020-02888-y

20. Coşkun GP, Demirbolat GM. **Development and validation of an HPLC method for simultaneous determination of Imatinib and rifampicin.** Journal of Research in Pharmacy. 2022; 26(5). DOI:10.29228/jrp.237

21. Pranckeviciene E, Gineviciene V, Jakaitiene A, Januska L, Utkus A. **Total genotype score modelling of polygenic endurance-power profiles in Lithuanian elite athletes**. Genes. 2021; 12(7):1067. https://doi.org/10.3390/genes12071067

22. Jiang X, Fu Q, Kong Y, Liu H, Rexiti K, Wei X, et al. **Genetic polymorphisms are associated with imatinib plasma levels and periorbital edema in Chinese patients with gastrointestinal stromal tumors receiving adjuvant imatinib.** 2022. https://doi.org/10.21203/rs.3.rs-1994623/v1

23. Ullah A, Ali F, AunMuhammad S, Hassan SSU. **A review of the genetic variants affecting efficacy and adverse effects of standard of care treatment in patients with chronic myelogenous leukemia.** Precision Medicine Communications. 2022; 2(1):43-58. https://doi.org/10.55627/pmc.002.01.0045

24. Stiehler S, Sembill S, Schleicher O, Marx M, Rauh M, Krumbholz M, et al. **Imatinib treatment and longitudinal growth in pediatric patients with chronic myeloid leukemia: influence of demographic, pharmacological, and genetic factors in the German CML-PAED cohort.** Haematologica. 2024; 109(8):2555. DOI: 10.3324/haematol.2023.284668

25. Shin H, Choi SY, Kee K-M, Kim S-H, Yang S-Y, Jung SY, et al. **Comprehensive analyses of safety and efficacy toward individualizing imatinib dosage in patients with chronic myeloid leukemia.** International Journal of Hematology. 2020; 111:417-26. https://doi.org/10.1007/s12185-019-02805-9

26. Gao D, Wang G, Wu H, Wu J, Zhao X. **Prediction for plasma trough concentration and optimal dosing of imatinib under multiple clinical situations using physiologically based pharmacokinetic modeling.** ACS omega. 2023; 8(15):13741-53. https://doi.org/10.1021/acsomega.2c07967

27. Cheng F, Cui Z, Li Q, Chen S, Li W, Zhang Y. **Influence of genetic polymorphisms on imatinib concentration and therapeutic response in patients with chronic-phase chronic myeloid leukemia.** International Immunopharmacology. 2024; 133:112090. https://doi.org/10.1016/j.intimp.2024.112090

28. Goutelle S, Guidi M, Gotta V, Csajka C, Buclin T, Widmer N. **From personalized to precision medicine in oncology: A model-based dosing approach to optimize achievement of imatinib target exposure.** Pharmaceutics. 2023 Apr; 15(4):1081. https://doi.org/10.3390/pharmaceutics15041081

AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Asma Khan:** Conception, design, acquisition, analysis, drafting, final approval.
2	**Zabiullah:** Drafting work, reviewing, critically for important intellectual content.
3	**Faizan Rasheed:** Drafting work, reviewing, critically for important intellectual content.
4	**Zarafshan Bader:** Final approval of the version to be published.
5	**Imrana Aamir:** Final approval of the version to be published.