

# Determination of the Cut-off Value for Imatinib Plasma Levels Linked to Occurrence of Bone Pain in CML Patients

Marwa S Hamza <sup>1</sup>, Samia A Shouman <sup>2</sup>, Raafat Abdelfattah<sup>3</sup>, Heba S Moussa<sup>4</sup>, Mervat M Omran <sup>2</sup>

<sup>1</sup>Clinical Pharmacy Practice Department, Faculty of Pharmacy, The British University in Egypt, El-Sherouk City, Cairo, Egypt; <sup>2</sup>Pharmacology Unit, Cancer Biology Department, National Cancer Institute, Cairo University, Cairo, Egypt; <sup>3</sup>Medical Oncology Department, National Cancer Institute, Cairo University, Cairo, Egypt; <sup>4</sup>Clinical Pathology Department, National Cancer Institute, Cairo University, Cairo, Egypt

Correspondence: Marwa S Hamza, Clinical Pharmacy Practice Department, Faculty of Pharmacy, The British University in Egypt, El-Sherouk City, Cairo, Egypt, Email [marwa.hamza@bue.edu.eg](mailto:marwa.hamza@bue.edu.eg)

**Background:** Imatinib is used to treat chronic myelogenous leukemia (CML). Variations in imatinib pharmacokinetics have been linked to genetic variations. That has an impact on imatinib response and adverse effects. Therefore, the aim of the study was to study bone pain as an adverse effect that occurs with imatinib and to investigate the risk factors for bone pain.

**Methods:** The relationship between the peak and trough plasma concentrations of imatinib with bone pain as one of the most frequently occurring adverse effects was examined. Multiple linear regression analysis and binary logistic regression analysis were used to measure the impact of various patients' characteristics on both peak and trough imatinib concentrations and the risk of the occurrence of imatinib-induced bone pain.

**Results:** As a side effect of imatinib, approximately 15% of patients with CML who were taking it experienced bone pain. This side effect was linked to the imatinib peak and trough plasma levels. Imatinib trough concentration was also linked to gender and the gene *SLCO1B3-334T > G (TT)*. There were significant associations between peak concentrations and gender as well as patient weight.

**Conclusion:** Higher peak and trough plasma concentrations of imatinib are linked with the risk of the occurrence of bone pain as a side effect of imatinib. Monitoring plasma concentrations of imatinib is useful to predict the bone pain of imatinib and to support quality of life in patients with CML.

**Keywords:** imatinib, tyrosine kinase inhibitor, chronic myelogenous leukemia, trough plasma concentration, bone pain

## Introduction

Nearly 1–2 of every 100,000 persons in the world are diagnosed with chronic myelogenous leukemia (CML).<sup>1–3</sup> Tyrosine-kinase inhibitors (TKIs) are typically used as first-line therapy for CML patients.<sup>4</sup> Imatinib mesylate is the gold standard for first-line therapy.<sup>3,5–7</sup> The standard dose of imatinib is 400 mg/day for patients with chronic phase CML.<sup>8,9</sup> This dose is well tolerated by most patients.<sup>10</sup> Prioritizing criteria including toxicity, age, risk score, and patients' ability to tolerate TKI therapy should be utilized while selecting treatment.<sup>11</sup> Despite the fact that TKIs for CML are far superior to traditional chemotherapy, a case report study stated that they have a variety of side effects, such as bone pain and growth attenuation.<sup>12</sup> Also, imatinib is linked to toxicity; most of them occur within the first two years after commencing treatment, and some reverse with continuous use of the drug at the same dose. In the vast majority of cases, toxicity is minimal or non-existent, and it is easy to control and even reverse. Fluid retention as a side effect of imatinib can cause weight gain in some people, notably in those with infraorbital edema, but it can also be more widespread. As previously stated, imatinib can cause bone pain, which can be quite severe.<sup>13</sup>

According to prior research, pain in patients treated with imatinib can occur everywhere in the body, including the shoulders, hips, hands, and feet. At other times, it can also be described as muscle soreness or seem like polymyalgia rheumatica.<sup>14</sup> It is possible that imatinib is the cause of the pain syndrome because of the quick disappearance of

symptoms after discontinuing imatinib and the rapid return of symptoms after restarting the medication.<sup>15</sup> While severe leg and arm pain has been linked to imatinib-induced bone edema in the past, these studies focus on situations where the edema is predominantly in the long shaft bones.<sup>15</sup> Other examples of imatinib-induced bone toxicity, such as osteonecrosis in the diaphysis of the tibia, the femoral head, and the jaw, have been documented in the literature.<sup>16–18</sup>

Single nucleotide polymorphisms (SNPs) in genes are linked to imatinib absorption, distribution, metabolism, and excretion. SNPs are likely to have a role in the reported variations in imatinib pharmacokinetics. The human organic anionic transporter OATP1B3 is involved in imatinib absorption.<sup>19</sup> Transporter polymorphisms may alter how much of a medication is able to reach the target cells, which can have an impact on imatinib response and adverse effects. Until now, SNP variations in closely related transporters have not been studied in relation to imatinib-induced bone pain as a side effect. Therefore, this study investigated whether bone pain is an adverse effect that occurs with imatinib in patients with CML. Also, find out what causes bone pain so that best practices can be developed.

## Methods

### Design

This study was based on data from 102 patients, obtained from our previously published dataset.<sup>20</sup> This study was conducted at the Hematological Outpatient Clinic of the National Cancer Institute at Cairo University. Patients were diagnosed with CML, at least 18 years old, and were receiving imatinib therapy for at least 30 days (to reach a steady state). Patients with documented imatinib sensitivities and those with serious medical conditions were excluded from the study.

### Drug Administration, Blood Sampling and Assay

As mentioned in our previous work,<sup>20</sup> whole blood samples were drawn and placed in tubes that contained EDTA just prior to administering the medication (trough samples) and 2 hours after imatinib administration (peak sample). Injecting 10  $\mu$ L of plasma into the LC/MS/MS system after it was analyzed using HPLC autosampler bottles.<sup>21</sup> Pharmacogenetic analysis requires preparation of DNA for polymorphism determination using the Gentra Puregene Blood Kit (Qiagen Inc., Minneapolis, MN, USA) following the manufacturer's instructions. The whole-cell pellet was used for the extraction of genomic DNA. Until the analysis, the DNA was kept at a temperature of  $-80^{\circ}\text{C}$ . For the genotyping of ABCG2 SNPs 34 G > A and 421C > A and the solute carriers SLCO1B3 SNPs 334T > G, the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method was used.<sup>22,23</sup>

### Evaluation of Bone Pain as an Adverse Effect of Imatinib

Bone pain was reported during imatinib therapy. According to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, bone pain is defined as a disorder characterized by a sensation of marked discomfort in the bones.<sup>24</sup> The patients were considered to be suffering from bone pain, either in grade 1, 2 or 3 according to the CTCAE.

### Data Collection

All patients' data was collected, such as age, gender, other diseases other than CML, body weight, height, concomitant medications, serum albumin, total bilirubin, aspartate aminotransferase, alanine aminotransferase, hemoglobin, urea, and serum creatinine. As well as the previous genetic polymorphism data for those patients that was extracted from our previous study.<sup>20</sup>

### Statistical Analysis

The baseline features and events throughout imatinib therapy were described using descriptive statistics. Statistical information was summarized using percentages and numbers to represent the qualitative data. Proportion independence was evaluated using a chi-squared test or a Fisher exact test. A Student's *t*-test and an ANOVA test were done between both trough as well as peak imatinib plasma concentration and different categorical variables. A Spearman's rank correlation test was used to confirm that they were employed to compare the average results of two different groups.

A Spearman's rank correlation test was carried out for the confirmation of the association between peak and trough plasma concentration, patient characteristics, genetic polymorphism, and laboratory data. Multiple linear regression analysis was used to determine the role of various genetic polymorphisms and other factors in the fluctuation of imatinib plasma concentrations.

Binary logistic regression analysis was used to characterize the effects of variables on bone pain in order to compare the incidence of bone pain as a side effect of imatinib. Varieties of genotypes had different chances of adverse responses, as shown by the odds ratio (OR) and its 95% confidence interval (95% CI). In addition, ROC curves were used to find the imatinib trough and peak plasma concentration cut-off values for the incidence of bone pain in patients. The cut-off value was considered to be the maximum of the sum of sensitivity and specificity. The Statistical Package for Social Science (SPSS) (version 23.0; SPSS, Chicago, USA) was used to conduct the statistical analysis. *p* values less than 0.05 were considered statistically significant differences.

## Results

### Demographic and Clinical Characteristics

There were 102 CML patients in the present study. Forty-seven of them were men, and 55 of them were women, with a mean age of  $40.6 \pm 11$  years and normal liver and kidney laboratory results. The imatinib dose was 400 mg/day. It was found that plasma imatinib levels peaked at  $2884 \pm 1063$  ng/mL while the trough plasma level was  $1416 \pm 701$  ng/mL (Figure 1). Fifteen patients (14.7%) were suffering from bone pain. This cohort's demographical, clinical, and pharmacokinetic features are shown in Table 1 and Figure 1.

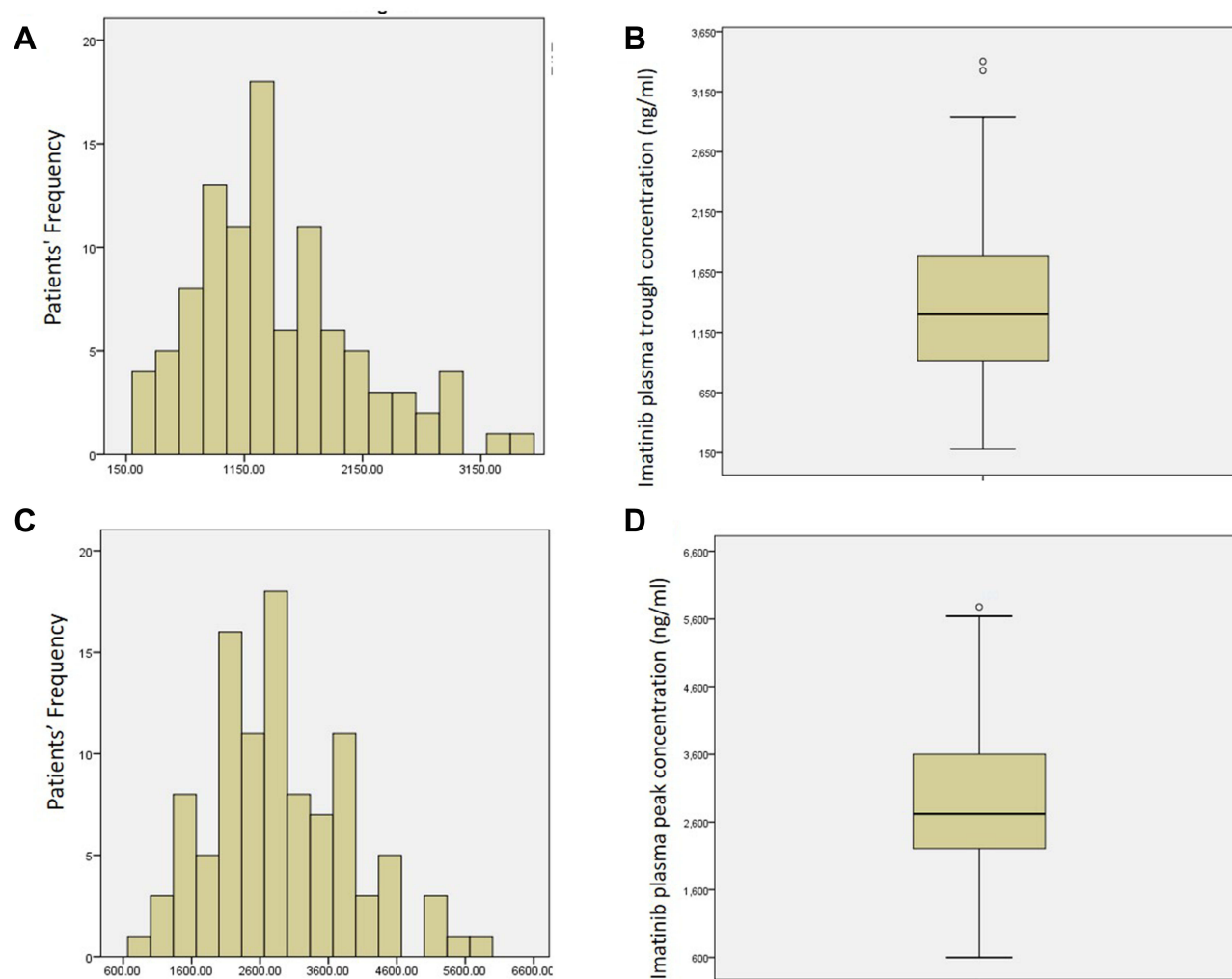
### Association Between Imatinib Peak and Trough Plasma Concentration and Certain Patients' Features

A Student's *t*-test test was done to examine the relationship between both trough and peak imatinib plasma concentration and gender. Interestingly, it was found that males had lower imatinib plasma levels where the mean values of the trough and peak levels were  $1168 \pm 613$ ,  $2529 \pm 959$  ng/mL for males vs  $1628 \pm 707$ ,  $3187 \pm 1062$  ng/mL for females, respectively ( $P < 0.001$ ).

Then an ANOVA test was done, and it was found that there was no significant association between both trough and peak imatinib plasma concentration and different gene categories. The Spearman's rank correlation test was used to confirm whether patient characteristics or laboratory data were correlating with imatinib trough and peak plasma concentration. Hemoglobin level ( $r = -0.28$ ,  $r = -0.29$ ,  $P < 0.05$ ) and the alpha-1-acid glycoprotein ( $r = -0.23$ ,  $r = 0.2$ ,  $P < 0.05$ ) were the only factors found to be significantly but weakly correlated with the trough and peak imatinib plasma concentrations, respectively. Imatinib trough plasma concentration was not correlated with several laboratory data, such as height, body weight, total protein, total bilirubin, aspartate aminotransferase, alanine aminotransferase and serum creatinine.

Multiple linear regression analysis was done where the imatinib trough concentration was used as the dependent variable and age, sex, laboratory data, as well as gene polymorphism as prognostic variables (Table 2). There were significant associations between trough concentrations with the gender, and SLCO1B3-334T>G (TT). For females, the trough concentration increased by 445 ng/mL (95% confidence interval [CI], 185 to 705). The trough plasma concentration of imatinib decreased by 520 ng/mL in patients with SLCO1B3-334T>G homozygous wild type TT allele rather than in patients with the variant type GG (95% confidence interval [CI]: -985.8 to -56.2) (Table 2).

Another multiple linear regression analysis was done where the imatinib peak concentration was used as the dependent variable while age, sex, laboratory data, and gene polymorphism were used as prognostic variables (Table 3). There were significant associations between peak concentrations and the gender, as well as patients' weight. For females, the peak concentration increased by 826 ng/mL (95% confidence interval [CI], 420 to 1232). The peak plasma concentration of imatinib increased by 11.8 ng/mL for every 1 kg increase in the patients' weight (95% confidence interval [CI], 0.126 to 23.4) (Table 3).



**Figure 1** Histogram and boxplot of the Imatinib trough and peak plasma concentration. **(A)** Histogram for the trough plasma concentration of Imatinib. **(B)** Boxplot of distribution for the trough plasma concentration of Imatinib. **(C)** Histogram for the peak plasma concentration of Imatinib. **(D)** Boxplot of distribution for the peak plasma concentration of Imatinib.

## Association Between Bone Pain and Trough and Peak Plasma Concentration of Imatinib, Patient Characteristics, Laboratory Data

The mean of the peak and trough plasma concentrations of imatinib in patients who did not suffer from bone pain were 2620839 and 1239571 respectively. Whereas the mean of peak and trough plasma concentrations of imatinib in patients who suffered from bone pain were  $4414 \pm 942$ ,  $2440 \pm 479$ , respectively. (Figure 2A and B).

The Spearman's rank correlation test was used to confirm the patient characteristics, laboratory and genetic polymorphism, as well as the peak and trough plasma concentrations of imatinib data that may be correlated with the occurrences of bone pain. Only the trough plasma concentration of imatinib ( $r = 0.547$ ,  $p = 0.001$ ), the peak plasma concentration of imatinib ( $r = 0.517$ ,  $p = 0.001$ ), the weight ( $r = 0.226$ ,  $p = 0.05$ ), and the plasma alpha-1-acid glycoprotein ( $r = 0.242$ ,  $p = 0.05$ ) were found to be significantly and positively correlated with the occurrences of bone pain. Other laboratory data, such as height, body weight, total protein, total bilirubin, aspartate aminotransferase, alanine aminotransferase, and serum creatinine, did not show a connection between the presence of bone pain and these other lab results, which did not show any connection.

Binary logistic regression analysis was done where the occurrences of bone pain were used as the dependent variable and age, sex, laboratory data, and gene polymorphism as well as the imatinib peak and trough concentration as prognostic

**Table 1** Demographic and Clinical Characteristics of CML Patients After Treatment with Imatinib According to Bone Pain

	Whole Cohort	Patients with Bone Pain	Patients without Bone Pain	P-value
<b>Gender</b>	102	15	87	0.026
• Male	47	3	44	
• Female	55	12	43	
<b>Age (years) (mean ± SD)</b>	40.6±11	45±9	39±11	0.54
<b>Weight (kg) (mean ± SD)</b>	83±19	91±12	81±19	0.038
<b>Hg (g/dl) (mean ± SD)</b>	11.7±1.9	11±1.9	12±1.8	0.22
<b>WBC (/mm<sup>3</sup>) Median (range)</b>	5.7 (2–212)	6 (3–212)	5.6 (2–185)	0.71
<b>Platelet (/mm<sup>3</sup>) Median (range)</b>	186.5 (14–934)	189 (100–934)	184 (14–554)	0.57
<b>AST (IU) Median (range)</b>	22 (11–115)	21 (14–44)	22 (11–115)	0.69
<b>ALT (IU) Median (range)</b>	18.2 (7.4–117)	21.6 (10–43)	21 (7.4–117)	0.94
<b>Creatinine (mg/dl) Median (range)</b>	0.9 (0.3–1.4)	0.8 (0.5–1.26)	0.9 (0.3–1.4)	0.26
<b>Imatinib trough concentration (ng/mL) (mean ± SD)</b>	1416±701	2440±479	1239±571	0.001
<b>Imatinib peak concentration (ng/mL) (mean ± SD)</b>	2884 ± 1063	4414±942	2620±839	0.001
<b>Alpha-I glycoprotein (μg/mL) Median (range)</b>	1.5 (0.08–2.86)	2 (0.89–2.7)	1.5 (0.08–2.86)	0.016
<b>Duration of Imatinib therapy (months) Median (range)</b>	22 (1–84)	24 (1–84)	22 (1–72)	0.43

Abbreviation: SD, standard deviation.

**Table 2** Associations Between Imatinib Trough Plasma Level and Patients' Characteristic

Independent Variables	Unstandardized Coefficients		P-value	95% C.I.		Collinearity Statistics	
	B	Std. Error		Lower Bound	Upper Bound	Tolerance	VIF
SLCO1B3.334 T>G (TT)	−520.98	234.2	0.028	−985.8	−56.2	0.95	1.04
Gender (females)	445.59	131.06	<0.001	185	705	0.98	1.01

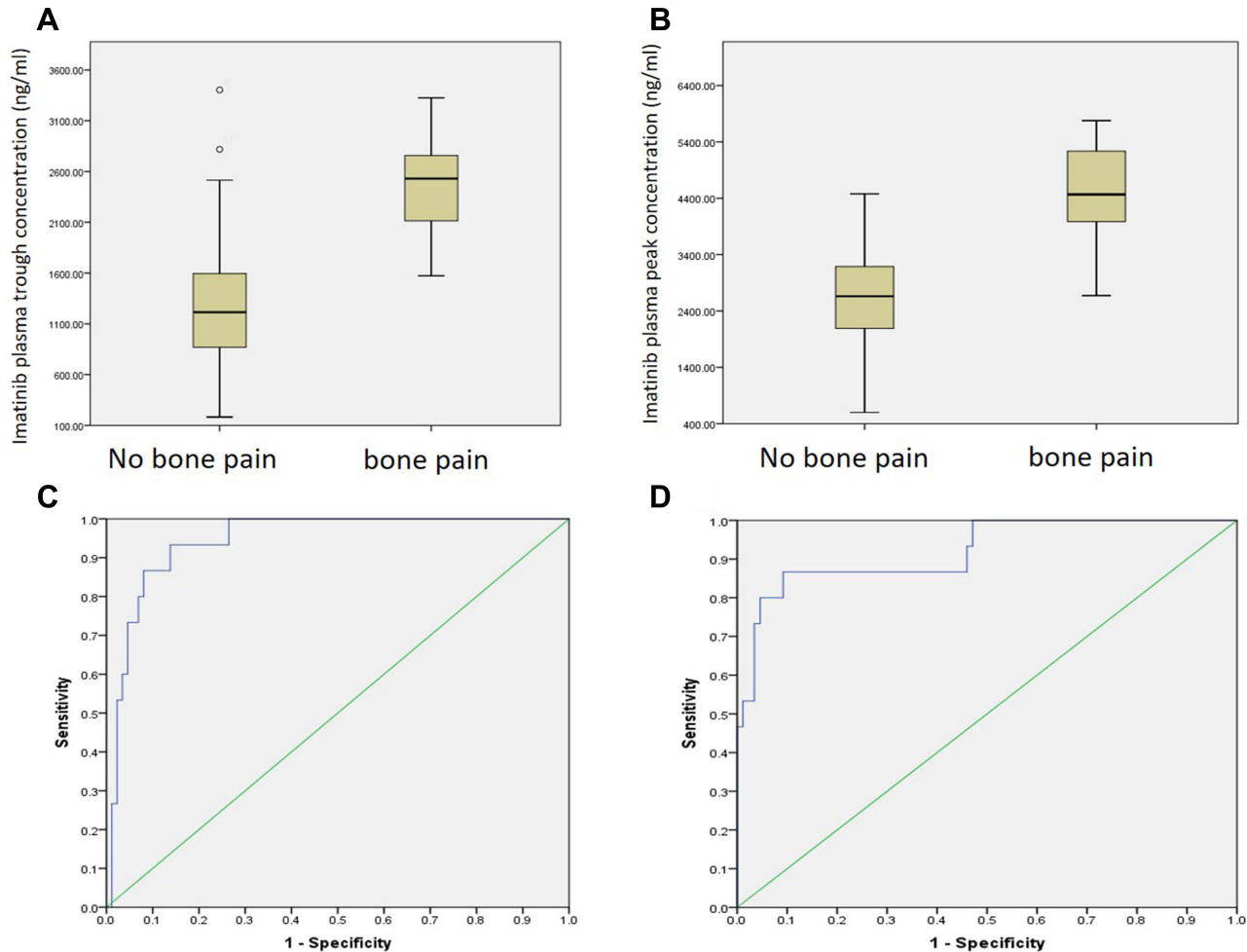
Abbreviations: B, unstandardized coefficients; 95% C.I., 95% confidence interval; VIF, the variance inflation factor.

**Table 3** Associations Between Imatinib Peak Plasma Level and Patients' Characteristic

Independent Variables	Unstandardized Coefficients		Standardized Coefficients	P-value	95.0% CI		Collinearity Statistics	
	B	Std. Error			Lower Bound	Upper Bound	Tolerance	VIF
Gender (female)	826	203	−0.394	<0.001	420	1232	0.99	1.04
Weight (kg)	13	5	0.244	0.015	2.6	24	0.99	1.04

Abbreviations: B, unstandardized coefficients; 95% C.I., 95% confidence interval; VIF, the variance inflation factor.

variables. There was a significant association between the occurrence of bone pain and the imatinib trough and peak plasma levels. The risk of developing bone pain increases by ~ 1 time for every 1 ng/mL increase in imatinib trough concentration (95% CI, 1.001 to 1.004). Also, the risk of bone pain occurrence increases by ~ 1 time for every 1 ng/mL increase in the imatinib peak concentration (95% confidence interval [CI], 1.001 to 1.003) (Table 4).



**Figure 2** Relationship between bone pain with the trough and peak plasma concentration of Imatinib. **(A)** Boxplot of distribution for the trough plasma concentration of Imatinib and bone pain. **(B)** Boxplot of distribution for the peak plasma concentration of Imatinib and bone pain. **(C)** Receiver operating characteristic curve for the trough plasma concentration of Imatinib. **(D)** Receiver operating characteristic curve for the peak plasma concentration of Imatinib.

## Receiver Operating Characteristic (ROC) Curves

The cut-off values for imatinib peak and trough plasma concentrations were 3720 and 1775 ng/mL. The area under the ROC curve (AUC) was 0.92 and 0.94 for the peak and trough curves, respectively. Table 3 summarizes the sensitivity and specificity of this cut-off at 0.93 and 0.15, respectively, for the trough concentration and 0.87 and 0.11 for the peak concentration (Table 5). The ROC curve is shown in Figure 2C and D.

**Table 4** Logistic Regression Analysis to Identify Risk Factors for Bone Pain in CML Patients Treated with Imatinib

Independent Variables	P-value	OR	95% C.I.	
			Lower	Upper
Imatinib Peak concentration (ng/mL)	0.004	1.002	1.001	1.003
Imatinib trough concentration (ng/mL)	0.003	1.003	1.001	1.004

**Abbreviations:** OR, odds ratio; 95% C.I., 95% confidence interval.



**Table 5** The Parameters of the Receiver Operating Characteristic (ROC) Curve for the Cut-off for Trough Plasma Imatinib Concentration in Bone Pain

	p-value	Area Under the ROC Curve	Cut-off Point	Sensitivity	Specificity
Trough Imatinib level (ng/mL)	0.001	0.94	1775	0.93	0.85
Peak Imatinib level (ng/mL)	0.001	0.92	3720	0.86	0.89

## Discussion

Imatinib has been linked to toxicity, but the majority of side effects are seen during the first two years of commencing medication, and some go away with continuous use of the same dose.<sup>13</sup> Some individuals may suffer from skin reactions,<sup>25</sup> interstitial lung disease<sup>26</sup> and edema.<sup>27</sup> Bone discomfort is another devastating side effect.<sup>28</sup> The connection between plasma levels and adverse drug reactions (ADRs) in patients with CML using imatinib has only been studied in small samples till now. According to our research, which included 102 patients with advanced CML, bone pain was the most prevalent side effect after receiving imatinib therapy. Most experts agree that detecting imatinib plasma concentration is critical for drug guidance and dose modification,<sup>29</sup> as imatinib plasma concentration plays a role in the occurrence of imatinib side effects. Therefore, we hypothesized that bone pain is significantly associated with imatinib plasma concentrations.

In this study, the mean imatinib trough plasma levels were  $1199 \pm 506$  ng/mL. This value falls within the imatinib trough plasma concentration range of 181 to 2947 ng/mL, with a mean of 1058 ng/mL for the 400 mg/day dosage.<sup>30</sup> Also, it lies within the range of 363–2900 ng/mL with a mean of 1325.61 in different studies.<sup>31</sup> All these concentrations are greater than 1002 ng/mL, which means there is a higher chance of a major molecular response (MMR).<sup>32</sup>

Multiple linear regression analyses were carried out to verify the link between imatinib trough and peak plasma levels with several patient-specific variables. Gender and weight had strong relationships with imatinib plasma concentrations. Females had imatinib peak and trough plasma levels higher than males. Previous research showed that females had greater imatinib trough plasma levels, which supports this assertion.<sup>33–35</sup> This may be explained by the fact that females have a higher percentage of body fat than males<sup>36</sup> and low-density lipoproteins are inhibited by imatinib, which inhibits glycosaminoglycan production on vascular proteoglycans and reduces their binding to the platelet-derived growth factor receptor both in vitro and in vivo.<sup>37</sup> Besides the fact that fat metabolism is related to the level of low-density lipoproteins.<sup>38</sup> Another study reported that the effective imatinib dose is associated with age as well as body surface area, and a reduced dose of 300 mg/day of imatinib may be sufficient for the treatment of CML patients with smaller body sizes, particularly when intolerability arises.<sup>39</sup> Therefore, in order to avoid inadequate effectiveness at decreased dosages in men, the effective dose of imatinib must be raised.<sup>39</sup> Also, in order to minimize side effects at high dosages of imatinib, the effective dose for females must be reduced.

In addition, interindividual variability in imatinib pharmacokinetics is still debated due to genetic variations and race differences. Our earlier research showed that a high imatinib trough is linked with a strong response to the drug, and that the genotypes ABCG2.34 G > A and SLCO1B3.334 T > G were associated with a good imatinib response in Egyptian CML patients.<sup>20</sup> In this study, for individuals who had the wild homogenous allele TT SLCO1B3.334 T > G, we discovered that the imatinib trough concentration was 520 ng/mL higher in them than in those with the heterozygous GA allele and the variant type. This supports our previous finding that patients with the wild variant of SLCO1B3.334 T > G have favorable response to imatinib.<sup>20</sup> According to earlier research on the immunosuppressant medication Mycophenolic acid, SLCO1B3 334T > G was shown to be strongly linked to adverse outcomes, although heterozygous carriers of SLCO1B3 334T > G had a lower chance of experiencing gastrointestinal side effects than wild-type people.<sup>40</sup>

As a result, patients' dosages should be tailored to their imatinib trough concentration. However, the present study did not examine the relationship between an effective dose of imatinib and other drug-metabolizing enzymes and drug transporter genotypes. In previous studies, Imatinib pharmacokinetics have been shown to be linked to ABC transporters, the human organic cation transporter, and cytochrome P450 isoenzymes.<sup>19,41–43</sup> There is still a lot of debate about how

important genetic variation and body surface area variability are when it comes to the effective dose and pharmacokinetics of imatinib. More research is needed to figure out how important they are.<sup>39</sup>

In the last decade, researchers have argued that an appropriate plasma concentration of imatinib can be linked to a satisfactory clinical response. Following these results, the determination of the trough plasma imatinib concentration is useful for patients with a suboptimal response, treatment failure,<sup>44</sup> unpredicted severe adverse reactions, supratherapeutic levels<sup>45</sup> and drug-drug interactions with imatinib.<sup>46</sup> Despite the fact that plasma concentration measurements may be helpful in these difficult situations, decisions about whether to interrupt treatment, reduce the dose, or change the therapy should always be made based on the overall clinical situation until more data is available.<sup>46</sup>

The relationship between imatinib plasma concentration and therapeutic effects has been extensively studied in clinical trials. However, the relationship between imatinib plasma concentration and toxicity in CML has received far less attention. In this study, it was shown that imatinib trough and peak concentration, as well as certain patient characteristics, were associated with an increased chance of developing bone pain as a side effect. As we mentioned before, the correlation between the occurrence of bone pain and the level of alpha-1 glycoprotein was significantly positive but weak ( $r = 0.242$ ,  $p < 0.05$ ). Since imatinib is predominantly bound to plasma alpha-1-acid glycoprotein, this might dramatically affect the distribution and elimination of imatinib<sup>47</sup> leading to bone pain.

A binary logistic regression analysis was conducted to examine the role of different patients' characteristics that may play a role in the development of bone pain. Imatinib trough and peak plasma levels were shown to be significantly associated with the occurrence of bone pain. For every 1 ng/mL rise in the imatinib either trough or peak plasma level of imatinib, the risk of bone pain rose by 1 time.

Although in this study there was no association between SLCO1B3.334 T > G and the occurrence of bone pain, we confirmed in our previous work that patients with the heterogeneous allele of SLCO1B3.334 T > G (TG) were more likely to respond favorably in earlier studies.<sup>20</sup> Therefore, SLCO1B3 may serve as a diagnostic, therapeutic, and prognostic biomarker.<sup>48</sup>

After carrying out the ROC curve analysis, we found that the cut-off points for the imatinib trough and peak plasma levels are 1775 and 3720 ng/mL, respectively. Above that, the risk of bone pain as a side effect of imatinib increases. According to prior research, patients with CML who receive imatinib at a trough concentration of more than 1002 ng/mL should have their blood tested often.<sup>30</sup> Another study reported that the trough concentration of imatinib that can contribute to the incidence of CML-wide adverse effects is 926 ng/mL.<sup>49</sup> This information lets us formulate the drug regimen in a way that ensures a good response in terms of avoiding or relieving bone pain, as well as continuing therapy as needed.

## Conclusion

Imatinib trough concentration is linked to gender and the intake transporter SLCO1B3.334 T > G. Imatinib peak concentration is linked to the patient's gender and weight. Also, patients with CML using imatinib may experience bone pain as a side effect, which is linked to the imatinib trough and peak plasma levels. Imatinib plasma concentration monitoring may be useful in predicting the likelihood of bone discomfort.

## Ethical Approval

The Institutional Review Board (IRB) of the National Cancer Institute of Cairo University, Egypt, reviewed and approved the study with acceptance number IRB00004025. The study was carried out in accordance with the ethical principles outlined in the Helsinki Declaration of the World Medical Congress and its amendments.

## Informed Consent

All participants included in this study signed informed consent.

## Disclosure

All of the authors declare no conflicts of interest in relation to this work and that there is no conflict of interest associated with this manuscript.



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