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Comparative Analysis of Ankle-Brachial Index in Chronic Myeloid Leukemia Patients Treated with Imatinib versus Nilotinib at Adam Malik Hospital

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ABSTRACT

Introduction: Chronic myeloid leukemia (CML) is commonly managed with tyrosine kinase inhibitors (TKIs) such as imatinib and nilotinib. However, these therapies are associated with cardiovascular risks, including peripheral arterial disease (PAD). This study compares the Ankle-Brachial Index (ABI), a non-invasive measure of PAD, in CML patients receiving imatinib or nilotinib at Adam Malik Hospital, Medan.

Methods: A cross-sectional study was conducted from December 2023 to February 2024 at Adam Malik Hospital. Forty-eight CML patients (34 on imatinib, 14 on nilotinib) were enrolled using consecutive sampling. ABI was measured to assess PAD prevalence, with values <0.9 indicating abnormality. Data were analyzed using independent t-tests and chi-square tests, with significance set at $p<0.05$.

Results: The mean age was 42.9 years (imatinib) and 49.1 years (nilotinib). Abnormal ABI values were observed in 20.6% (7/34) of imatinib-treated patients and 50% (7/14) of nilotinib-treated patients. The mean ABI for the left leg was significantly lower in the nilotinib group (0.91 ± 0.12) compared to the imatinib group (1.06 ± 0.11, $p=0.017$). A significant difference in ABI values between groups was confirmed ($p=0.042$, odds ratio 3.857), indicating a higher PAD risk with nilotinib.

Conclusion: Nilotinib therapy is associated with a higher incidence of PAD compared to imatinib in CML patients. These findings underscore the need for routine cardiovascular monitoring in TKI-treated patients and further research into the vascular effects of TKIs.

Keywords

Chronic Myeloid Leukemia, Tyrosine Kinase Inhibitors, Imatinib, Nilotinib, Ankle-Brachial Index, Peripheral Arterial Disease

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INTRODUCTION

Chronic myeloid leukemia (CML) is a rare hematologic malignancy characterized by the Philadelphia chromosome (t(9;22)(q34;q11.2)), resulting in the BCR-ABL fusion gene, which drives excessive myeloid cell proliferation [1,2]. With an annual incidence of 1–2 cases per 100,000, CML accounts for approximately 0.5% of all cancers [3,4]. The advent of tyrosine kinase inhibitors (TKIs), such as imatinib, nilotinib, and dasatinib, has revolutionized CML treatment, significantly improving patient outcomes [5]. However, these therapies are associated with cardiovascular complications, notably peripheral arterial disease (PAD), which poses a significant challenge to long-term management [6].

PAD, characterized by reduced blood flow to the limbs due to arterial narrowing or occlusion from atherosclerotic plaque buildup, is associated with increased morbidity and mortality [6]. Studies have reported a 9% prevalence of PAD in CML patients on TKI therapy, with variations depending on the specific TKI used

[7]. Although TKIs are effective against CML, they may contribute to vascular dysfunction through mechanisms such as endothelial damage, platelet aggregation, and accelerated atherosclerosis [7,8]. Notably, nilotinib is associated with a higher PAD incidence (30.8%) than imatinib (4.9%) [7]. Another study reported a 14.6-fold increased PAD risk with nilotinib compared to that with imatinib [8].

Mechanistically, nilotinib promotes atherosclerosis by inhibiting discoidin domain receptor 1 (DDR1) and upregulating proatherogenic cell surface adhesion molecules [9,10]. Imatinib, which targets c-KIT, DDR1, and platelet-derived growth factor receptor (PDGF-R), may also accelerate atherosclerosis and endothelial damage [9]. Dasatinib, though less studied, is linked to pulmonary arterial hypertension in some cases [11]. These findings highlight the diverse cardiovascular risks associated with TKIs use. In Indonesia, data on PAD prevalence in patients with CML are scarce, and routine ankle-brachial index (ABI) assessments, a non-invasive measure of peripheral vascular health, are not standard. Given the global variations in disease epidemiology and treatment responses, this study evaluated ABI values in patients with CML treated with imatinib versus nilotinib at Adam Malik Hospital, Medan. By examining PAD prevalence and its association with TKI therapy, this study aims to provide novel insights into the cardiovascular health of patients with CML in Indonesia, informing future therapeutic strategies.

METHODS

Study Design and Setting This cross-sectional analytical study was conducted at Adam Malik Hospital, Medan, Indonesia, from December 2023 to February 2024, to compare Ankle-Brachial Index (ABI) values in chronic myeloid leukemia (CML) patients treated with imatinib or nilotinib. Ethical approval was obtained from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara.

Study Design and Setting This cross-sectional analytical study was conducted at Adam Malik Hospital, Medan, Indonesia, from December 2023 to February 2024, to compare Ankle-Brachial Index (ABI) values in chronic myeloid leukemia (CML) patients treated with imatinib or nilotinib. Ethical approval was obtained from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara. The inclusion criteria were patients with CML aged ≥18 years who were receiving imatinib or nilotinib therapy. Patients with diabetes mellitus, hypertension, heavy smoking (Brinkman Index >600), prior lower limb amputation, severe peripheral arterial disease unrelated to CML therapy, significant cardiovascular conditions, or comorbidities affecting ABI were excluded to minimize confounding factors.

Table 1. ABI classifications are presented in

ABI Score	Classification
<0.9	Abnormal
0.91–0.99	Borderline
1.0–1.4	Normal
>1.4	Noncompressible vessels

Notes: ABI classifications for patients with CML, calculated as the ratio of the highest ankle to brachial systolic pressure: abnormal (<0.9), borderline (0.91–0.99), normal (1.0–1.4), and noncompressible vessels (>1.4).

After explaining the study's objectives, procedures, and benefits, informed consent was obtained from the participants. Baseline demographic data, including age, sex, residence, occupation, and phone number, were collected at the Hematology and Medical Oncology Polyclinic. Additional variables included ABI scores, Brinkman Index, and history of diabetes mellitus or hypertension. Data collection involved patient observation sheets, informed consent forms, Doppler ultrasound, conductive jelly, and writing tools. ABI measurements were performed using a standardized Doppler ultrasound device by trained researchers, with the results verified by staff from the Endocrinology, Metabolism, and Diabetes Division, Department of Internal Medicine, Universitas Sumatera Utara. Following ethical clearance, consecutive sampling was used to recruit participants. Resting ABI measurements were conducted after the patients rested in the supine position for 10 min. Systolic pressure was measured in the brachial arteries (both arms) and dorsalis pedis and posterior tibial arteries (both legs) using Doppler ultrasound. The ABI score for each leg was calculated by dividing the highest ankle systolic pressure by the highest brachial systolic pressure

Descriptive statistics were used to summarize the demographic characteristics and frequency distributions. ABI values between the imatinib and nilotinib groups were compared using inferential statistics. Independent t-tests were used to analyze numerical data, and chi-square tests were used to evaluate categorical data. Fisher's exact test was applied when the chi-square assumptions were unmet. Statistical significance was set at $p<0.05$, and analyses were conducted using appropriate statistical software to ensure systematic and accurate results.

RESULTS

Patient Characteristics This study included 48 patients with chronic myeloid leukemia (CML) from the Hematology and Medical Oncology Polyclinic at Adam Malik Hospital, Medan, who fulfilled the inclusion and exclusion criteria. The sampling process is depicted in Figure 1 (placed below the paragraph). Of the participants, 62.5% (n=30) were male. Patients were allocated into two groups based on treatment: 34 (70.8%) received imatinib, and 14 (29.2%) received nilotinib treatment. The mean age was 42.9 ± 14.9 years in the imatinib group and 49.1 ± 12.3 years in the nilotinib group. Comprehensive patient characteristics are presented in Table 1 (placed at the end of this section). None of the patients had diabetes mellitus, hypertension, or heavy smoking (Brinkman Index >600), minimizing potential confounders.

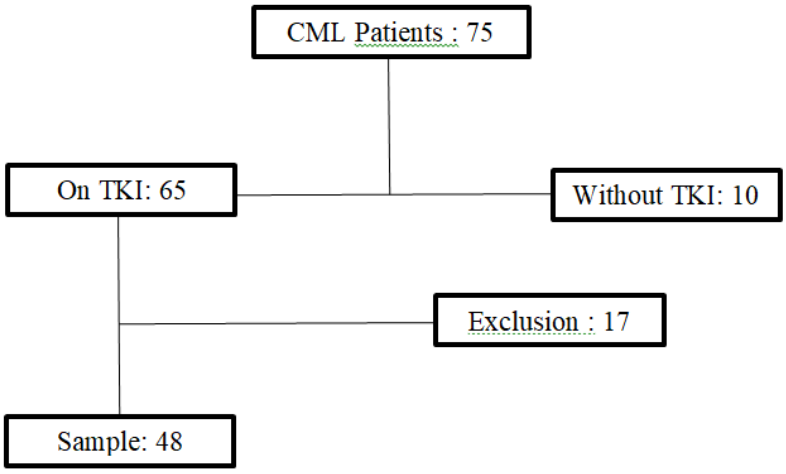

Figure 1. Sampling Flow

Table 1. Characteristics of Study Participants

Characteristics	Imatinib (n=34)	Nilotinib (n=14)	p-value
Age (years), mean ± SD	42.9 ± 14.9	49.1 ± 12.3	0.639
Gender, n (%)			0.623
Male	22 (64.7)	8 (57.1)	
Female	12 (35.3)	6 (42.9)	
Duration of Treatment, n (%)			1.000
>6 months	33 (97.0)	14 (100)	
<6 months	1 (3.0)	0 (0)	
Diabetes Mellitus, n (%)	0 (0)	0 (0)	-
Hypertension, n (%)	0 (0)	0 (0)	-
Heavy Smoker (Brinkman Index >600), n (%)	0 (0)	0 (0)	-
Right ABI, median (min–max)	1.09 (0.8–1.2)	0.91 (0.8–1.2)	0.109
Left ABI, mean ± SD	1.06 ± 0.11	0.91 ± 0.12	0.017

Note: Characteristics of CML patients treated with imatinib (n=34) or nilotinib (n=14) at Adam Malik Hospital, including age, gender, treatment duration, comorbidities, and ABI values. Independent t-tests and chi-square tests were used to assess differences ($p<0.05$). None of the patients had diabetes, hypertension, or heavy smoking (Brinkman Index >600). The left ABI was significantly lower in the nilotinib group ($p=0.017$).

Ankle-Brachial Index (ABI) Findings In the imatinib group, seven patients (20.6%) exhibited abnormal ABI values (<0.9), with a mean left ABI of 1.06 ± 0.11. Conversely, seven patients (50%) in the nilotinib group had abnormal ABI values, with a significantly lower mean left ABI of 0.91 ± 0.12 (p=0.017). The median right ABI values were 1.09 (range: 0.8–1.2) for the imatinib group and 0.91 (range: 0.8–1.2) for the nilotinib group, showing no significant difference (p=0.109).

Statistical analysis confirmed a significant difference in the left ABI values between the imatinib and nilotinib groups (p=0.017), indicating an elevated risk of peripheral arterial disease (PAD) in the nilotinib group. The odds ratio for abnormal ABI values was 3.857 (p=0.042), suggesting that nilotinib is associated with a higher PAD risk than imatinib. These findings highlight the greater propensity for vascular complications in patients treated with nilotinib.

The results demonstrated that CML patients receiving nilotinib exhibited a significantly higher risk of PAD, as indicated by lower left ABI values, compared to those receiving imatinib. The elevated prevalence of abnormal ABI in the nilotinib group underscores the necessity of rigorous cardiovascular monitoring in these patients.

DISCUSSION

Chronic myeloid leukemia (CML) arises from the Philadelphia chromosome, a translocation between chromosomes 9 and 22, resulting in the BCR-ABL1 fusion gene that drives uncontrolled myeloid cell proliferation [12,13]. Tyrosine kinase inhibitors (TKIs), including imatinib, nilotinib, and dasatinib, target this fusion gene and have transformed the management of CML [14]. This study focused on the cardiovascular implications of imatinib and nilotinib, specifically their association with peripheral arterial disease (PAD), assessed through Ankle-Brachial Index (ABI) measurements in 48 CML patients at Adam Malik Hospital, Medan.

Of the 48 patients, 34 received imatinib and 14 received nilotinib, with mean ages of 42.9 ± 14.9 and 49.1 ± 12.3 years, respectively (p=0.639). The sex distribution was comparable (imatinib: 64.7% men; nilotinib: 57.1% men, p=0.623), and the treatment duration showed no significant difference (p=1.000). These findings align with those of Nunes et al., who reported similar sex distributions in TKI-treated CML patients [10]. However, the younger mean age in our study compared to that in Rattanathammethee et al. (54 and 68 years for imatinib and nilotinib groups, respectively) may reflect regional demographic differences [7]. The study revealed a significantly higher prevalence of abnormal ABI values (<0.9) in the nilotinib group (50%) than in the imatinib group (20.6%), with a mean left ABI of 0.91 ± 0.12 versus 1.06 ± 0.11 (p=0.017). The odds ratio for abnormal ABI was 3.857 (p=0.042), indicating a greater risk of PAD with nilotinib. These results corroborate those of Rattanathammethee et al., who reported a PAD prevalence of 30.8 % %in nilotinib-treated patients versus 4.9% in imatinib-treated patients [7]. Similarly, a retrospective study of 3,722 CML patients found higher cardiovascular risks with nilotinib, even after adjusting for baseline risk factors [10].

Mechanistically, nilotinib's higher BCR-ABL1 affinity may enhance its efficacy and cardiovascular toxicity [14]. Nilotinib upregulates pro-atherogenic markers, including thrombin, TNF-α, IL-6, and adhesion molecules (P-selectin, E-selectin, ICAM1, VCAM1), potentially increasing PAD risk [10]. It also elevates blood glucose and LDL cholesterol levels, further promoting atherosclerosis [10]. Imatinib, although less cardiotoxic, inhibits DDR1, PDGF-R, and c-KIT, which may contribute to endothelial damage and atherosclerosis [9]. These mechanisms are likely to underlie the observed ABI differences.

These findings emphasize the need for routine cardiovascular monitoring in CML patients receiving TKIs, particularly nilotinib. Pre-treatment and follow-up assessments, including blood pressure, lipid profiles, fasting glucose, ECG, echocardiography, and ABI, are recommended at baseline, 1-month, 3–6 months, and periodically thereafter [15-17]. Despite its efficacy, nilotinib's cardiovascular risks necessitate careful patient selection, considering factors such as age and comorbidities. Limitations include the small nilotinib group size (n=14), single-center design, and potential unadjusted confounders such as age. Nevertheless, this study highlights the importance of tailored TKI therapy in balancing efficacy and safety. Future research should

explore strategies to mitigate nilotinib's cardiovascular risks and evaluate alternative TKIs for the long-term management of CML.

CONCLUSION

This study revealed a significant association between tyrosine kinase inhibitor therapy and peripheral arterial disease risk in chronic myeloid leukemia patients with CML, with nilotinib linked to a higher prevalence of abnormal Ankle-Brachial Index values (50%) than imatinib (20.6%, p=0.042, odds ratio 3.857). These findings emphasize the need for tailored cardiovascular monitoring, particularly in nilotinib-treated patients, to reduce vascular complications. Optimizing TKI selection based on patient risk profiles is critical for balancing efficacy and safety in CML management.

DECLARATIONS

None

CONSENT FOR PUBLICATION

The Authors agree to be published in the Journal of Society Medicine.

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COMPETING INTERESTS

The authors declare no conflicts of interest in this case report.

AUTHORS' CONTRIBUTIONS

All authors contributed to the work, including data analysis, drafting, and reviewing the article. They approved the final version and were accountable for all aspects.

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