Original Article

Tyrosine Kinase Inhibitor Therapies in Chronic Myeloid Leukemia: Effects on Clinical Characteristics and Triglyceride-to-High Density Lipoprotein Cholesterol Ratio

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Abstract

Background and Aim: Tyrosine kinase inhibitors (TKIs) have dramatically improved chronic myeloid leukemia (CML) prognosis. However, TKIs are associated with dyslipidemia and impaired glucosehomeostasis. Triglyceride-to-high-density lipoprotein cholesterol ratio (TG/HDL-C) is proposed to be an indicator of insulin resistance and atherogenic index, but there is no research on TG/HDL-C alterations in patients receiving TKIs for CML. We aimed to evaluate relationships between TKI type/count, clinical characteristics, and laboratory results (particularly TG/HDL-C) in CML patients. **Patients and Methods:** A total of 104 patients with chronic phase CML were enrolled in the study. All patients received initial imatinib therapy at 400 mg daily, the type or dose of TKI was then changed according to treatment response and clinical outcomes. Patients were compared with respect to TG/HDL-C categorization (>2.5 versus <2.5), number of TKIs used, and use of imatinib as the only TKI. **Results:** The median TG/HDL-C was 2.82 (1.03–17.33) and this ratio was higher than 2.5 in 59 (56.7%) patients. Patients with high TG/HDL-C had a significantly higher age than patients with low values ($P < 0.001$). Recipients of more than one TKI had higher EUTOS risk score and white blood cell (WBC) count ($P < 0.05$). Recipients of imatinib as the only TKI had higher age, low EOTUS risk score, low WBC, and low neutrophil count (all, $P < 0.05$). **Conclusion:** TG/HDL-C values were not associated with the number of different TKIs used or the use of imatinib only in chronic-phase patients with CML. Further large-scale prospective studies are needed to determine whether TG/HDL-C can be used for diagnostic or prognostic purposes in TKI recipients.

Keywords: *Chronic myeloid leukemia, CML, TG/HDL-C, TKI, tyrosine kinase inhibitors*

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by the elevated, unregulated and uncontrolled expansion and accumulation of myeloid lineage in the bone marrow and peripheral blood and accounts for about 30% of adult leukemia cases.[1] The global incidence of CML in 2017 was 34,179, with a total of 24,054 CML-related deaths.[2] It is characterized by a chromosomal translocation called the "Philadelphia Chromosome" [t(9;22) (q34;q11.2)] encoding for breakpoint cluster region protein – tyrosine protein kinase ABL1 (BCR-ABL) with elevated tyrosine kinase activity, leading to abnormal proliferation and differentiation of hematopoietic cells.[3] Until 1999, CML management was limited to nonspecific therapeutic agents, such as hydroxyurea, cytosine arabinoside, busulfan, and interferon-α.[4] Advances in tyrosine kinase inhibitors (TKIs) have dramatically improved CML

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prognosis due to their strong influence on the relationship between adenosine triphosphate and the BCR-ABL1 protein, thereby inhibiting the malignant clone.[5] This "targeted" therapy remarkably changed the landscape of CML management, including better cytogenetic response, lower progression rates relative to priortherapies, and higher rate of 10-year survival (from <20% to 80%–90%).[6] Despite these improvements, not all patients achieve a complete cytogenetic response. Imatinib is the primary TKI that is accepted to be the gold standard treatment for CML, but a considerable proportion of patients develop resistance, intolerance, or various adverse effects. Recently, several clinical cases of diabetes mellitus and altered lipid profile among recipients of TKI have been reported.[7] A better understanding of these endocrine consequences and identification of populations at high risk for these outcomes are critical for TKI selection and appropriate long-term management.

Triglyceride-to-high-density lipoprotein cholesterol ratio (TG/HDL-C) has been proposed as a reliable and simple alternative to assess atherogenic index, insulin resistance, and dyslipidemia.[8] Furthermore, positive relationships between the TG/HDL-C ratio and various clinical features of many cancers, such as tumor stage and tumor type, have been reported in previous studies.[9] These findings warrant further studies to explore TG/HDL-C ratio with respect to TKI administration in CML and as a factor associated with side effects, and potentially, to assess its role in prognosis. To our knowledge, there is no study in the literature that has focused on change in TG/HDL-C ratio with the TKI therapy in CML patients.

The aim of the study was to evaluate the relationship between different types of TKIs and various factors, including clinical characteristics and laboratory findings such as TG/HDL-C, in patients with CML.

Patients and Methods

The study was designed as a retrospective cohort study and conducted between December 2002 and August 2022 in the Department of Hematology of University of Health Science Kartal Dr. Lutfi Kirdar City Hospital Istanbul, Turkey. A total of 104 patients with chronic phase CML were enrolled in the study. The diagnosis of CML was performed according to the World Health Organization 2016 classification and confirmed by molecular biology, immunology, bone marrow morphology, and cytogenetics examination.[10] Subjects aged 18 years and older were selected for the study. Participants with a history of pregnancy, severe kidney or liver disease, familial lipid disorders, malignancies other than CML were excluded from the study. Patients who did not have a cytogenetically and/or molecularly confirmed diagnosis of CML at any time of their follow-up were excluded from the study. Those who did not have regular follow-up or whose follow-up was interrupted for more than one year, those who were referred for allogeneic stem cell transplantation, and those who discontinued CML treatment were also excluded from the study. In total, 22 patients were excluded from the study according to the exclusion criteria. All research procedures were evaluated and approved by the Research Ethics Committee of University of Health Science Kartal Dr. Lutfi Kirdar Hospital (date: September 29, 2022: Number: 2022/514/234/17) and were conducted in agreement with the ethical standards specified in the Declaration of Helsinki.

Clinical and demographic characteristics including age, sex, European Treatment and Outcome Study for CML (EUTOS) score risk group, follow-up time, history of medication for CML, current medication of CML at the time of laboratory measurement, dose, type, and the number of TKIs used, other medications, and comorbidities such as diabetes mellitus, hypertension, hypothyroidism, and hyperlipidemia were obtained from patient files. Treatment responses and outcomes were extracted from medical records. The EUTOS CML prognostic scoring system was calculated for each CML patient using the formula EUTOS score = (4 × spleen size) + (7 × basophils) as described in the relevant study, where the spleen was measured in centimeters below the costal margin and basophils were given as percentage ratio in peripheral blood.[11] An EUTOS score of >87 indicated high risk and <87 indicated low risk. All patients received initial TKI therapy of imatinib mesylate at 400 mg daily, type or dose of TKI was then changed according to treatment response and clinical outcomes, when necessary (imatinib, dasatinib, nilotinib, bosutinib, and ponatinib), followed by treatment planning and scheduling of follow-up. It was scheduled to assess patient characteristics according to TG/HDL-C ratio and type of TKI therapy (treatment regimens). All events were meticulously reviewed by the investigators according to strict criteria in order to ensure data reliability.

Biochemical analysis

Blood samples were drawn from antecubital vein after 12-hour fasting on the day of hospital admission and were centrifuged at 1500 × *g* for 5 min to separate the serum. Complete blood count, including white blood cell (WBC) counts, neutrophil counts, hemoglobin values, and platelet counts were determined by a Mindray BC-6800 autoanalyzer (Mindray, Shenzhen, China). All patients included in the analyses had been receiving their planned treatment for CML when complete blood samples were obtained; there were no cases in which treatment

had been altered or discontinued. Serum TG and HDL-C were measured with photometric methods on an Abbott Architect c8000 analyzer with standard kits (Abbott, IL, USA). TG/HDL-C ratio was calculated by simple division of values in mg/dL units. All blood samples were examined within less than one hour after the sampling.

Statistical analysis

All analyses were performed on IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA), with the classical statistical significance threshold ($P < 0.05$). Continuous data were first analyzed to determine distribution characteristics with the Kolmogorov–Smirnov test (Lilliefors correction). According to these results, and given that kurtosis and skewness values were acceptable, data summary and analyses were performed with parametric or nonparametric approaches. Mean ± standard deviation was used for parametric continuous data, median (first quartile–third quartile) was used for nonparametric continuous data, and relative and absolute frequencies were used for categorical data. Normally distributed variables were analyzed with the independent samples *t*-test or the one-way analysis of variances depending on count of groups. Non-normally distributed variables were analyzed with the Mann–Whitney *U* test or the Kruskal–Wallis test depending on count of groups. Categorical variables were analyzed with Chi-square tests or the Fisher's exact or Fisher-Freeman-Halton tests. Pairwise comparisons were adjusted by Bonferroni correction method.

Results

One hundred and four patients diagnosed with CML were included in the study. Baseline demographic, clinical and biochemical characteristics are shown in Table 1. Mean age was 57.74 ± 15.14 (23–95) years, and 59 patients (56.7%) were female. EUTOS risk assessment was low in 87 patients and high in 17 patients. The most common comorbidities of participants were diabetes and hypertension. The mean follow-up period was 78.32 ± 44.21 (1–195) months, and 69 (66.3%) patients were followed for more than five years. All patients received imatinib therapy; 69 of them (66.3%) received only imatinib treatment, 21 (20.2%) patients received two different TKIs, 12 (11.5%) patients received three different TKIs, and four different TKIs were utilized in 2 (1.9%) patients. The drugs used during the biochemical evaluation were imatinib in 70 (67.3%) patients, dasatinib in 12 (11.5%) patients, nilotinib in 14 (13.5%) patients, bosutinib in 7 (6.7%) patients, and ponatinib in 1 (1.0%) patient.

The median TG/HDL-C was 2.82 (1.03–17.33), and this ratio was higher than 2.5 in 59 (56.7%) patients. Study on the population was divided into two groups with respect to this TG/HDL-C threshold. Patients with high (>2.5) TG/HDL-C had a significantly higher age than patients with low values ($P < 0.001$). No significant differences were found between TG/HDL-C groups in terms of sex, EUTOS risk group, the presence of diabetes mellitus, hypertension, hypothyroidism, coronary artery disease, hyperlipidemia or treatment for hyperlipidemia, follow-up time, and TKI use characteristics (all, $P > 0.05$). Similar WBC counts, neutrophil counts, hemoglobin values, and platelet counts were shown in both groups (all, $P > 0.05$).

Since patient counts regarding TKI therapy groups other than imatinib did not allow reliable analyses with separate groups and considering that all patients had received imatinib at initiation, participants were divided into three groups according to the number of different TKIs used ("one," "two," and "three and four") [Table 2]. Patients in the high EUTOS risk score group were using more than one drug ($P < 0.001$). No significant differences were observed between groups in terms of age, sex, the presence of diabetes mellitus, hypertension, hypothyroidism, coronary artery disease, hyperlipidemia or treatment for hyperlipidemia, and follow-up time (all, $P > 0.05$). WBC count was significantly lower in the single TKI group compared to the other groups ($P = 0.008$). Neutrophil count was significantly lower in single TKI recipients compared to those who received two TKIs ($P = 0.046$). Hemoglobin value was found to be significantly higher in the recipients of two drugs compared to those receiving more ($P = 0.004$). Similar platelet count, levels of TG and HDL-C, as well asTG/HDL-C ratio were observed in groups (all, $P > 0.05$).

Clinical and biochemical characteristics of patients according to imatinib use status are summarized in Table 3. Age has been significantly higher in patients using only imatinib compared to other patients ($P = 0.030$). The use of imatinib alone was significantly more frequent in patients in the low EOTUS risk group ($P < 0.001$). No significant differences were observed between groups in terms of sex, the presence of diabetes mellitus, hypertension, hypothyroidism, coronary artery disease, hyperlipidemia or treatment for hyperlipidemia, and follow-up time (all, $P > 0.05$). WBC count and neutrophil count were found to be significantly lower in patients receiving only imatinib compared to the others ($P = 0.002$ and $P = 0.026$, respectively). Similar biochemical results, such as hemoglobin value, platelet count, levels of TG, HDL-C, and TG/HDL-C ratio were observed (all, $P > 0.05$).

Discussion

This study was aimed to assess the effects of TKI

Table 1: Demographic, clinical and biochemical features of patients with regard to triglyceride-to-HDL cholesterol ratio levels

	Total (*n*=104)	Triglyceride-to-HDL cholesterol ratio		*P*
		≤ 2.5(*n*=45)	> 2.5(*n*=59)	
Age, years	57.74±15.14	51.47±16.44	62.53±12.17	<0.001
Sex				
Male	45 (43.3%)	18 (40.0%)	27 (45.8%)	0.698
Female	59 (56.7%)	27 (60.0%)	32 (54.2%)	
EUTOS score risk group				
Low	87 (83.7%)	41 (91.1%)	46 (78.0%)	0.126
High	17 (16.3%)	4 (8.9%)	13 (22.0%)	
Diabetes mellitus	29 (27.9%)	9 (20.0%)	20 (33.9%)	0.179
Hypertension	22 (21.2%)	6 (13.3%)	16 (27.1%)	0.143
Hypothyroidism	8 (7.7%)	2 (4.4%)	6 (10.2%)	0.461
Coronary artery disease	8 (7.7%)	4 (8.9%)	4 (6.8%)	0.724
Hyperlipidemia	3 (2.9%)	0 (0.0%)	3 (5.1%)	0.256
Treatment for hyperlipidemia	2 (1.9%)	0 (0.0%)	2 (3.4%)	0.504
Follow-up time, months	78.32±44.21	76.64±46.17	79.59±43.01	0.738
≤5 years	35 (33.7%)	17 (37.8%)	18 (30.5%)	0.570
>5 years	69 (66.3%)	28 (62.2%)	41 (69.5%)	
TKI regimen				
Imatinib	104 (100.0%)	45 (100.0%)	59 (100.0%)	N/A
Dasatinib	20 (19.2%)	6 (13.3%)	14 (23.7%)	0.279
Nilotinib	21 (20.2%)	9 (20.0%)	12 (20.3%)	1.000
Bosutinib	9 (8.7%)	4 (8.9%)	5 (8.5%)	1.000
Ponatinib	1 (1.0%)	0 (0.0%)	1 (1.7%)	1.000
Number of different TKIs used				
One	69 (66.3%)	29 (64.4%)	40 (67.8%)	0.102
Two	21 (20.2%)	13 (28.9%)	8 (13.6%)	
Three	12 (11.5%)	3 (6.7%)	9 (15.3%)	
Four	2 (1.9%)	0 (0.0%)	2 (3.4%)	
Only imatinib use	69 (66.3%)	29 (64.4%)	40 (67.8%)	0.882
TKI used at the time of sampling				
Imatinib	70 (67.3%)	30 (66.7%)	40 (67.8%)	0.796
Dasatinib	12 (11.5%)	4 (8.9%)	8 (13.6%)	
Nilotinib	14 (13.5%)	7 (15.6%)	7 (11.9%)	
Bosutinib	7 (6.7%)	4 (8.9%)	3 (5.1%)	
Ponatinib	1 (1.0%)	0 (0.0%)	1 (1.7%)	
WBC count ($\times10^3$/mm^3)	6.66 (5.40-8.56)	6.74 (5.47-9.17)	6.55 (5.38-8.12)	0.294
Neutrophil count ($\times10^3$/mm^3)	3.70 (2.74-4.92)	3.88 (2.95-6.31)	3.51 (2.53-4.70)	0.150
Hemoglobin (g/dL)	11.87±2.17	12.22±2.09	11.61±2.21	0.162
Platelet count ($\times10^3$/mm^3)	225 (187-269)	221.5 (189-276.5)	225 (187-264)	0.626
Triglyceride (mg/dL)	138.70±64.96	94.38±13.26	172.51±68.36	<0.001
HDL-C (mg/dL)	42 (36.5-48)	48 (45-52)	38 (32-42)	<0.001
Triglyceride to HDL-C ratio	2.82 (2.07-4.54)	2.04 (1.73-2.19)	4.42 (3.14-5.53)	<0.001

EUTOS: European Treatment and Outcome Study, TKI: Tyrosine kinase inhibitor, WBC: White blood cell, HDL-cholesterol: High density lipoprotein cholesterol. Data are given as mean±standard deviation or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables

Table 2: Demographic, clinical and laboratory characteristics of participants with regard to the number of different tyrosine kinase inhibitors used

	Number of different TKIs used			*P*
	One (*n*=69)	Two (*n*=21)	Three & Four (*n*=14)	
Age, years	60.03±14.59	51.52±14.71	55.79±16.59	0.068
Sex				

Contd...

Table 2: Contd...

	Number of different TKIs used			*P*
	One (*n*=69)	Two (*n*=21)	Three & Four (*n*=14)	
Male	28 (40.6%)	12 (57.1%)	5 (35.7%)	0.337
Female	41 (59.4%)	9 (42.9%)	9 (64.3%)	
EUTOS score risk group				
Low	66 (95.7%)	14 (66.7%)	7 (50.0%)	<0.001
High	3 (4.3%)[a]	7 (33.3%)[b]	7 (50.0%)[b]	
Diabetes mellitus	19 (27.5%)	7 (33.3%)	3 (21.4%)	0.739
Hypertension	16 (23.2%)	3 (14.3%)	3 (21.4%)	0.768
Hypothyroidism	6 (8.7%)	0 (0.0%)	2 (14.3%)	0.223
Coronary artery disease	5 (7.2%)	1 (4.8%)	2 (14.3%)	0.549
Hyperlipidemia	2 (2.9%)	0 (0.0%)	1 (7.1%)	0.442
Treatment for hyperlipidemia	1 (1.4%)	0 (0.0%)	1 (7.1%)	0.291
Follow-up time, months	75.01±44.23	82.29±49.44	88.64±35.96	0.522
≤5 years	25 (36.2%)	8 (38.1%)	2 (14.3%)	0.254
>5 years	44 (63.8%)	13 (61.9%)	12 (85.7%)	
WBC count (×10³/mm³)	6.20 (5.11-7.55)[a]	7.45 (6.62-10.68)[b]	7.75 (5.67-11.20)[b]	0.008
Neutrophil count (×10³/mm³)	3.50 (2.53-4.28)[a]	4.40 (3.27-8.10)[b]	4.24 (2.39-5.30)[ab]	0.046
Hemoglobin value (g/dL)	11.78±1.92[ab]	13.00±1.91[a]	10.56±3.01[b]	0.004
Platelet count (×10³/mm³)	215 (186-268)	242 (200-275)	228 (170-257)	0.506
Triglyceride (mg/dL)	135.64±60.09	143.57±85.95	146.50±55.00	0.792
HDL-C (mg/dL)	42 (36-47)	43 (42-50)	38.5 (32-43)	0.095
Triglyceride to HDL-C ratio	2.88 (2.12-4.42)	2.38 (2.00-5.30)	3.59 (2.63-5.53)	0.226
≤2.5	29 (42.0%)	13 (61.9%)	3 (21.4%)	0.068
>2.5	40 (58.0%)	8 (38.1%)	11 (78.6%)	

EUTOS: European Treatment and Outcome Study, TKI: Tyrosine kinase inhibitor, WBC: White blood cell, HDL-C: High density lipoprotein cholesterol. Data are given as mean±standard deviation or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. Same letters denote the lack of statistically significant differences between groups

Table 3: Patient characteristics and laboratory measurements according to use of imatinib only

	Only imatinib use		*P*
	No (*n*=35)	Yes (*n*=69)	
Age, years	53.23±15.39	60.03±14.59	0.030
Sex			
Male	17 (48.6%)	28 (40.6%)	0.570
Female	18 (51.4%)	41 (59.4%)	
EUTOS score risk group			
Low	21 (60.0%)	66 (95.7%)	<0.001
High	14 (40.0%)	3 (4.3%)	
Diabetes mellitus	10 (28.6%)	19 (27.5%)	1.000
Hypertension	6 (17.1%)	16 (23.2%)	0.646
Hypothyroidism	2 (5.7%)	6 (8.7%)	0.714
Coronary artery disease	3 (8.6%)	5 (7.2%)	1.000
Hyperlipidemia	1 (2.9%)	2 (2.9%)	1.000
Treatment for hyperlipidemia	1 (2.9%)	1 (1.4%)	1.000
Follow-up time, months	84.83±44.07	75.01±44.23	0.287
≤5 years	10 (28.6%)	25 (36.2%)	0.574
>5 years	25 (71.4%)	44 (63.8%)	
WBC count (×10³/mm³)	7.60 (6.20-11.20)	6.20 (5.11-7.55)	0.002
Neutrophil count (×10³/mm³)	4.32 (3.02-8.10)	3.50 (2.53-4.28)	0.026
Hemoglobin value (g/dL)	12.06±2.64	11.78±1.92	0.528
Platelet count (×10³/mm³)	232.5 (198-272)	215 (186-268)	0.420
Triglyceride (mg/dL)	144.74±74.19	135.64±60.09	0.502

Contd...

Table 3: Contd...

	Only imatinib use		*P*
	No (*n*=35)	Yes (*n*=69)	
HDL-C (mg/dL)	42 (38-48)	42 (36-47)	0.801
Triglyceride to HDL-C ratio	2.67 (2.04-5.46)	2.88 (2.12-4.42)	0.781
≤2.5	16 (45.7%)	29 (42.0%)	0.882
>2.5	19 (54.3%)	40 (58.0%)	

EUTOS: European Treatment and Outcome Study, TKI: Tyrosine kinase inhibitor, WBC: White blood cell, HDL-C: High density lipoprotein cholesterol. Data are given as mean±standard deviation or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables

therapies on clinical features and TG/HDL-C in patients diagnosed with chronic-phase CML. The TG/HDL-C ratio in CML patients were found to be relatively higher when compared with the results of previous studies. When patients were dichotomized according to TG/HDL-C value, the groups demonstrated similar characteristics except for age. We found an association between high TG/HDL-C and advanced age in our patient group. We revealed that using more than one TKI medication was associated with a high EUTOS risk score and a high WBC. No correlations were observed between the number of TKIs and other clinical features or TG/HDL-C. Use of imatinib alone was associated with advanced age, low EOTUS risk score, low WBC, and low neutrophil count. No difference was found in terms of other clinical and biochemical features, including TG/HDL-C, according to imatinib use status.

CML is a clonal hematological neoplastic condition that leads to uncontrolled and excessive proliferation and differentiation of myeloid cells in patients. It appears more commonly in older people with a median age at diagnosis of 57–60 years in Western countries.[12] Consistently, the mean age of our study population was 57 years. The life expectancy of patients with CML has approached that of the general population with the advent of TKIs. After the introduction of TKIs, the EUTOS risk score was established in 2011 as a tool to estimate the chance of achieving complete cytogenetic response and the success of therapy and survival.[11] We observed better clinical results in patients with low EUTOS score or low WBC value, consistent with previous studies, providing further evidence that these parameters can be used as prognostic indicators in CML patients.

Lipid homeostasis is known to have an impact on tumor development and progression, as well as adaptive immune functions.[13] Actively proliferating tumor cells require a sustained delivery of lipids for membrane construction.[14] It has been shown that lipid metabolism is reprogrammed in cancers through fatty acid oxidation and lipolysis, as well as other forms of control including lipophagy, tuning of extracellular lipid uptake, cholesterol formation, and activation of de novo lipogenesis.[15] TG is a primary lipid member of the serum, the great majority of which are carried by serum proteins. TGs are known to exert proliferative effects on cancer cells,[16] and many studies have reported increased serum TG levels in various types of cancer.[17] Ni *et al*. demonstrated in a meta-analysis that TG levels were significantly associated with an increased risk of breast cancer mortality.[18] HDL-C, which is another primary member of serum lipids, has been described to have anti-cancer effects in multiple *in vitro* and experimental studies, an effect which has been linked with its immunomodulatory, anti-inflammatory, anti-oxidant, anti-angiogenesis, and anti-apoptosis activities.[19,20] HDL-C can induce cholesterol removal from cancer cells, thus changing their homeostasis. Decreased levels of HDL-C have been associated with poor prognosis in many cancers.[20] HDL-C can interact with the ATP binding cassette (ABC) transporters, ABCA1 and ABCG1, to inhibit the stem cell proliferations.[21] In addition, accumulating evidence suggests that upregulated TG and downregulated HDL-C have a carcinogenic effect due to their close involvement in oxidative stress and chronic inflammation.[16,22] Although TG/HDL-C was initially suggested as an indicator for atherogenic index, recent studies have found that it can be used in a variety of clinical settings such as insulin resistance and as an indicator of cancer prognosis.[8] Sun *et al*. showed that TG/HDL-C ratio had higher sensitivity to predict five-year overall survival in gastric cancer when compared with any single lipid parameter.[23] Luo *et al*. demonstrated in 167 postmenopausal women with endometrial cancer and 464 controls that TG/HDL-C was positively correlated with the clinical characteristics of endometrial cancer, including tumor stage and pathogenetic type.[24] Kong *et al*. revealed in 284 patients with non-small cell lung cancer (NSCLC) that TG/HDL-C had a relationship with the survival and prognosis of NSCLC patients, suggesting that preoperative values may be effective independent prognostic factors in predicting NSCLC patients.[25] We found the median TG/HDL-C levels in our study group to be 2.82, which was similar to the results of the studies

mentioned above. This increased value indicates that altered lipid homeostasis may be a crucial factor in the causation or consequences of carcinogenesis and cancer progression. The observed abnormalities in serum lipids and lipoproteins are strongly associated with cancer progression and development, suggesting their potential role in tumorigenesis and providing an innovative theoretical basis for anticancer therapy. It should be examined whether the increased TG/HDL-C values observed in CML patients can be used to serve as an independent prognostic indicator in larger studies.

Different TKIs interfere with glucose and lipid metabolism in various ways. Although the precise mechanisms of adverse/beneficial effects are still unclear, improvement or worsening of dyslipidemia or glycemic control is associated with the type of TKI. Surprisingly, however, even in studies for this particular molecule, contrasting effects have been reported according to their age, sex, comorbidities, and the presence of additional traditional and non-traditional cardiovascular risk factors. Iurlo *et al*. demonstrated in 168 chronic-phase CML patients (without history of diabetes mellitus, impaired fasting glucose, or metabolic syndrome at baseline) that type of TKI medication was not associated with the prevalence of diabetes mellitus, glucose intolerance, and metabolic syndrome.[4] However, notably, the nilotinib group had significantly higher levels of insulin, insulin resistance, fasting glucose, C-peptide, as well as LDL-C and total cholesterol compared to the imatinib and dasatinib groups. They reported findings associated with impaired fasting glucose in 25% of patients treated with imatinib and dasatinib and in 33% of those receiving nilotinib. The 10-year follow-up results of the ENEST and study demonstrated an elevation in the incidence of grade 3 and 4 hyperglycemia, among recipients of nilotinib 300 mg twice per day (7.2%) and nilotinib 400 mg twice per day (6.9%) compared to imatinib recipients (0.4%).[26] In contrast, Franklin *et al*. showed in a large-scale retrospective study of 1,272 patients that the mean time to onset of diabetes mellitus was shorter under dasatinib therapy (3 months) compared to nilotinib (10.4 months).[27] Agostino *et al*. reported a decrease in blood glucose levels in a retrospective study of diabetic (17) and non-diabetic (61) patients treated with dasatinib (8), imatinib (39), sorafenib (23), and sunitinib.[28] In addition, they reported that glycemic findings improved in 8 (47%) patients with the reduction or termination of antidiabetic therapy. Gottardi *et al*. showed improved total cholesterol levels in 8 out of 9 CML patients, and normalized serum TGlevels in 3 of the 4 patients within one month after imatinib treatment at a dose of 400 mg per day, which persisted for months.[29] In contrast, Song *et al*. found hyperlipidemia in 85 of their 155 patients (54.9%) under TKI therapy (pazotinib, sunitinib, famitinib, sorafenib).[30] We found no relationship with number of TKI types received and TG/HDL-C in patients diagnosed with CML. This may be due to the small number of patients treated with TKI therapy other than imatinib. This may also be due to the diversity of TKIs in our study. Further large-scale studies with different types of TKIs are needed to evaluate the hypo-/hyper-glycemic effect or lipid aggravating/improving effects of TKIs. Nonetheless, clinicians should be aware about potential effects of TKIs, particularly in patients with advanced age, uncontrolled dyslipidemia or diabetes mellitus, and those deemed to have high-risk for cardiovascular adverse effects, when initiating therapy to ensure maximum benefit with TKI treatment.

The primary limitation of the present study lies in its retrospective design with a relatively limited sample size, and also, considering the single centeredness of data and exclusion criteria, we believe the effect of selection bias cannot be ignored. Second, we found relatively higher TG/HDL-C ratios when compared with previous studies, and since there was no control group in our study, this difference may be associated with lifestyle characteristics of our population. Third, our findings may be representative of only patients in the chronic phase of CML. Lastly, due to the small number of patients receiving different types of TKI therapy, we could not compare the effect of different TKI drug types on lipid metabolism. Large-scale prospective studies are required to determine whether cut-off values for TG/HDL-C ratio can be used to predict prognosis in TKI recipients with CML. Furthermore, we also believe there would be value in conducting studies to understand whether TKI use and/or CML is impactful on lipid profile, especially TG and HDL-C.

In conclusion, we found that TG/HDL-C values in our group of chronic-phase CML patients was relatively higher in comparison to the literature; however, neither the number of TKIs nor the use of imatinib only were found to be associated with TG/HDL-C values. We also provided additional evidence that lower EUTOS score and WBC levels are associated with better prognosis in patients with CML. Further large-scale prospective studies are needed to determine whether TG/HDL-C can serve as a diagnostic or prognostic tool in patients with CML.

Ethics committee approval

Ethical approval for study conduct was obtanined from Clinical Research Ethics Committee of Kartal Dr. Lutfi Kirdar City Hospital (Date: September 29th 2022- Number: 2022/514/234/17), All experiments or tests performed involving human subjects were conducted according to institutional ethical standards and the Declaration of Helsinki.

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Conflicts of interest

There are no conflicts of interest.

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