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Association of Chemotherapy Hydroxyurea and Imbalance of Thyroid Hormones among Sudanese Patients with Chronic Myeloid Leukemia

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Abstract: ***Background: BCR-ABL1-positive chronic myelogenous or myeloid leukemia (CML) is identified as a myeloproliferative tumor that is primarily made up of proliferating granulocytes and has the Philadelphia chromosome/translocation t (9;22). Bone marrow and peripheral blood are both impacted by CML. Survivors of the atomic bomb have a higher incidence of CML.Some patients presented with Ph-negative, so they took another type of anti-CML drug; it has been observed that thyroid function tests always deviated from normality among oncology patients, so this study aimed to assess the levels of TFT among both groups to highlight the effect of anti-carcinogenic drugs. The data were analyzed using the Statistical Package of Social Science (SPSS) Version 20.***

Objective of the study: To evaluate the thyroid function tests in patients diagnosed with Chronic Myeloid Leukemia treated with tyrosine kinase inhibitors- Shendi.

Method: This cross-sectional study was conducted on patients with CML to assess thyroid function tests (TFT). The study involved CML patients treated with tyrosine kinase inhibitors (ph+ve) and others diagnosed as ph-ve treated with other drugs.

Result:Comparing TFT among ph +ve with results of ph-ve showed that a significant difference was obtained by FT3 only (p-value <0.05), and other hormones, FT4 and TSH, did not show differences (p-value> 0.05) for each. Pearson's correlation for age and duration of disease with TFT among all CML patients showed that all TFT parameters had negative correlations with age and positive correlations with duration; no significant differences were observed (p-value > 0.05) for each.

Conclusion: This study concluded that FT3 hormone is the only affected TFT parameter in Ph+ve patients compared with Ph-ve patients.

Keywords: chronic myeloid leukemia, thyroid function tests, tyrosine kinase inhibitor

I. INTRODUCTION

Leukemia is a class of malignancies that mostly affect the blood and bone marrow, leading to an excess of aberrant white blood cells[1]. The body's capacity to make healthy blood cells is hampered by these cancerous cells, which can result in a number of problems include anemia, bleeding disorders, and a compromised immune system[2-3]. The prevalence of leukemia varies by age, sex, and geographic location, making it one of the most prevalent cancers in both adults and children.Although the precise etiology of leukemia is still unknown, some chemicals, infections, radiation exposure, and genetic changes have all been linked to the disease's development [1-3]. Understanding the molecular biology of leukemia has advanced significantly in recent decades, allowing for the creation of more focused and potent treatments [2].

A. Chronic myeloid leukemia

Chronic myeloid leukemia or chronic myelogenous leukemia (CML) is a hematopoietic stem cell (HSC) disorder, as are all leukemias. In CML, the disorder is characterized by translocation t(9;22) (q34;q11), resulting in the fusion of BCR and ABL1 genes into the pathogenic BCR-ABL1 oncogene, with many subsequent effects on downstream pathways.

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The main pathway effect of this fused oncogene is to activate tyrosine kinase pathway constitutively, resulting in a proliferative advantage of the mutant HSCs compared to normal HSCs, and the gradual displacement of normal HSCs[4]. CML symptoms range from asymptomatic to overt leukocytosis, depending on the stage of CML; leukocytosis often occurs in the blast phase. Meanwhile, hyper leukocytosis is the most common symptom, and is often present in all phases (chronic phase, accelerated phase, and blast phase) [5].

B. The Philadelphia chromosome

The BCR:ABL1 fusion gene was subsequently discovered as the primary pathophysiological driver of CML, and the Philadelphia (Ph)-chromosome, or translocation t (9,22), was found to be the cytogenetic signature of the disease. In leukemic cells, the constitutively active tyrosine kinase activity of the 210 KDa chimeric protein produced by BCR:ABL1 stimulates several downstream signaling cascades [6]. In particular, this oncoprotein's expression modifies cell adherence to extracellular matrix and stromal components, improving survival and preventing apoptosis[7].

C. Ph –ve CML

This example illustrates an uncommon form of CML known as Ph-negative CML, which has a normal karyotype but is positive for BCR::ABL1. According to published research, complicated chromosomal abnormalities, such as three-way or multi-way translocations involving chromosomes 9, 22, and other chromosomes, may be the cause of those occurrences[8]. Although these patients lack a Ph chromosome, some of them exhibit a rearrangement inside the major breakpoint cluster region (M-BCR), depending on the selection criteria. The existence of an entity known as atypical chronic myeloid leukemia (aCML) that would include patients lacking a Ph chromosome and a rearrangement within M-BCR, as well as whether this disorder should be regarded as distinct from CML and chronic myelomonocytic leukemia (CMML), have been the subject of numerous debates using various criteria (clinical, morphologic, or molecular) [9]. Patients typically have hyperleukocytosis and organomegaly. 50% to 75% of patients have been documented to have splenomegaly, whilst 49% of patients in one case series have been observed to have hepatomegaly. Several case series have shown that the median white blood cell (WBC) count at presentation might vary from 23x109/L to 97x109/L. Approximately two thirds of the patients are transfusion dependent, and they are often moderately to severely anemic (median hemoglobin (Hb) level, 8.6 g/dL to 11.7 g/dL). In certain instances, the platelet count may be elevated, reduced, or normal. Peripheral blood smears typically contain 10% to 20% of immature myeloid precursors (promyelocytes, myelocytes, and metamyelocytes), while peripheral blasts are either nonexistent or very low. Monocyte and basophile counts are typically within normal limits. In most cases, the neutrophils are extremely dysplastic, exhibiting classic pseudo-Pelger-Huet alterations and cytoplasmic hypogranularity; dyserythropoiesis and dysmegakaryopoiesis may also be present. Marrow fibrosis may be present, and the bone marrow is hypercellular with an elevated myeloid-to-erythroid ratio (often up to 10:1). Blood or bone marrow blasts are, by definition, less than 20%[10].

D. Pathophysiology of CML Progression

The chronic phase, accelerated phase, and explosion phase are the three stages of CML. LSCs are limited to hematopoietic tissues during the chronic phase. But during the blast phase, the LSCs acquire the potential to invade other organs, including the spleen, which causes splenomegaly. Additionally, during the blast phase, immature blast cells now predominate. Amplification of the BCR-ABL1 protein, enhanced activation of the downstream tyrosine kinase pathway, and the appearance of extra chromosomal abnormalities (ACAs) are assumed to be the causes of the transition from chronic CML to the accelerated phase or blast phase [11--13]. Impaired DNA repair and oxidative stress have also been linked. Granulocyte immaturity has also been linked to mutations such as lack of CCAAT protein expression and deletion of the IKZF1 gene. Patients in the blast phase frequently have many gene alterations [4].

E. Diagnosis of CML

A regular physical examination or blood tests are frequently used to diagnose CML. The three phases of CML are blast phase (BP), accelerated phase (AP), and chronic phase (CP). The majority of patients (90%–95%) have CML-CP. Anemia and splenomegaly are common signs and symptoms of CML-CP. Fatigue, weight loss, malaise, easy satiety, and soreness or fullness in the left upper quadrant are some of these. Rare symptoms include retinal hemorrhages, upper gastrointestinal ulceration and bleeding (from elevated histamine levels due to basophilia), thrombosis (associated with thrombocytosis and/or marked leukocytosis), gouty arthritis (from elevated uric acid levels), priapism (usually with marked leukocytosis or thrombocytosis),

and bleeding (associated with a low platelet count and/or platelet dysfunction). Despite white blood cell (WBC) levels reaching 100 × 109/L, leukostatic symptoms (dyspnea, sleepiness, lack of coordination, and disorientation) caused by leukemic cells sludging in the pulmonary or cerebral arteries are rare in CP. The most common physical symptom found in 20% to 40% of individuals is splenomegaly. Less than 5% to 10% of people have hepatomegaly. Skin or other tissue involvement and lymphadenopathy are uncommon. When they are present, they prefer AP or BP of CML or Ph-negative CML. With CML transformation, headaches, bone pain, arthralgias, splenic infarction pain, and fever are more common [14].

The normal karyotype by conventional cytogenetics combined with the FISH pattern suggests the possibility of a cryptic insertion between chromosomes 9 and 22, where a partial ABL1 segment from chromosome 9 may have inserted into the BCR locus on chromosome 22, impeding detection by conventional cytogenetics. Because instances with a normal karyotype may nevertheless have complicated chromosomal abnormalities that are only identifiable by FISH and PCR testing, this emphasizes the significance of combining molecular cytogenetics and molecular biology techniques with traditional cytogenetics for thorough CML diagnosis[8].

F. Treatment of CML and TFT

Small compounds known as tyrosine kinase inhibitors (TKIs) either specifically block a particular kinase that is encoded by a cancer driver oncogene or, less selectively, a group of overexpressed kinases that contribute to the development of cancer. The majority of multi-target TKIs are angiogenesis inhibitors that bind to many receptor families, including platelet-derived growth factors and vascular endothelial growth factors. TKIs can result in a variety of treatment-related side effects since their targets are involved in numerous physiological systems [15].

TKIs target intracellular kinases and/or receptor tyrosine kinase signaling pathways that control tumor angiogenesis and cellular proliferation. The potency, mechanism of action, selectivity, and safety profile of different TKIs are all influenced by how selectively they bind to their targets. The majority of TKIs block several kinases (~10–100), increasing the potential of toxicities, while only a small number of TKIs show selectivity to particular protein kinases. For example, earlier research found that approximately 5% of patients stopped using imatinib or other multi-kinase inhibitors (MKIs) because of side effects. Both on-target consequences from excessive inhibition of the desired TK activity and off-target effects from the simultaneous inhibition of several other kinases due to low selectivity might be linked to toxicity [16].

G. Thyroid function tests

Thyroid hormone abnormalities are common during treatment with TKIs, typically manifesting as an increased serum thyroid-stimulating hormone (TSH) concentration and a reduced tri-iodothyronine (T3) to thyroxine (T4) ratio, both in patients with an intact thyroid gland and those with hypothyroidism who are receiving thyroid hormone treatment. Studies have highlighted the effect of TKIs on peripheral thyroid hormone metabolism, particularly through interference with the activity of deiodinases in healthy tissues [17].

Several observational studies have even suggested clinical improvement in patients who develop hypothyroidism while on TKIs. In a retrospective study of 65 patients with renal cell carcinoma (RCC), hypothyroidism occurred in 25% of patients treated with TKI, which was associated with significantly longer progression-free survival (PFS) and overall survival (OS) [18].

Several other small studies in patients with RCC treated with sunitinib or sorafenib similarly demonstrated that hypothyroidism was correlated with a greater treatment response rate and longer PFS and OS. Whether these results are generalizable to other cancer types or to other TKIs is unclear. Most existing data come from clinical trials of cancer therapy, which frequently include patients with preexisting thyroid disease and evaluate treatment with only a single TKIs [19].

II. MATERIAL AND METHOD

This cross-sectional study was conducted among 180 patients diagnosed with Chronic Myeloid Leukemia (CML) who were receiving Tyrosine Kinase Inhibitor (TKI) therapy. Patients with other types of leukemia or those treated with medications other than TKIs were excluded. They were 90 Ph –ve and Ph+ve karyotype. Data were collected using a structured questionnaire that included demographic and clinical information such as age, disease duration, and type of Philadelphia chromosome detected.For laboratory analysis, 3 mL of whole blood was collected in heparinized containers, centrifuged to separate plasma, and used for thyroid function testing (TFT). TFT levels were measured using the enzyme-linked immunosorbent assay (ELISA) technique based on the sandwich principle. Ethical approval was obtained from the Nepta College Medical Laboratory Science Program, and informed consent was secured from all participants, who were informed of their right to withdraw at any time. Data were analyzed using SPSS version 20.

III. RESULT

This descriptive cross sectional study involved 90 CML patients with Ph+ve and 90CML with Ph-ve karyotyping. The mean age of patients was comparable between the groups,with Ph+ CML patients having a mean age of 36.5 ± 14.6 years and Ph– CML patients having a mean age of 38.7 ± 14.5 years. The average duration of disease was also similar, at 2.5 ± 2.2 years for the Ph+ group and 2.2 ± 1.2 years for the Ph– group. The average duration of disease was also similar, at 2.5 ± 2.2 years for the Ph+ group and 2.2 ± 1.2 years for the Ph– group as in table 1.

Table 1: descriptive statistics of CML patients

	Mini to Max	Mean ±SD	Mini to Max	Mean ±SD
	Ph+ CML		Ph– CML	
Age (Years)	11 - 78	36.5 ± 14.6	11 - 77	38.7±14.5
Duration of CML/Y	0.1 - 14.0	2.5 ± 2.2	0.1 - 6.0	2.2 ± 1.2
Total	90		90	

The gender distribution of CML patients according to Philadelphia chromosome status. Among the Ph-positive (Ph+) CML group, females constituted the majority, accounting for 61.1% (55 patients), while males represented 38.9% (35 patients). In contrast, the Ph-negative (Ph–) CML group showed a more balanced distribution, with 52.2% (47 patients) being female and 47.8% (43 patients) being male as in table 2 and figure 1.

Table 2: gender distribution according to Philadelphia chromosome status:

Gender	Ph +ve CML		Ph –ve CML	
	Frequency	Percent	Frequency	Percent
Male	35	38.9 %	43	47.8 %
Female	55	61.1 %	47	52.2 %
Total	90	100.0 %	90	100.0 %

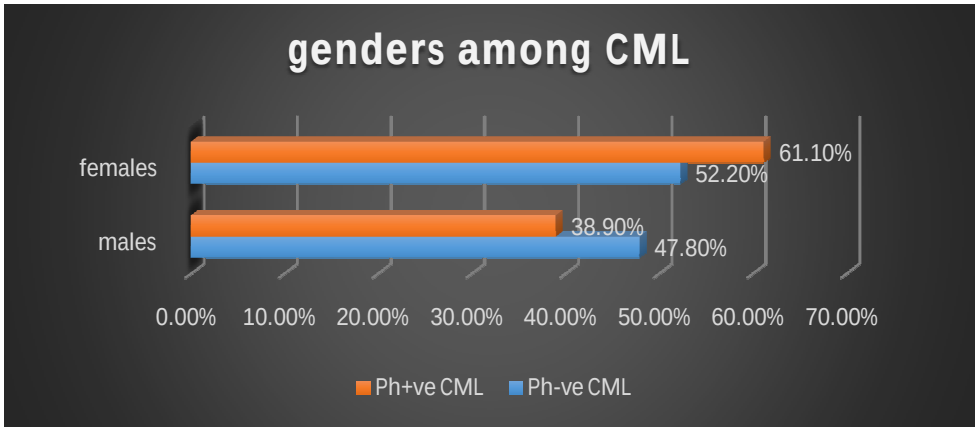


Figure 1: genders among CML patients

Regarding thyroid function tests, FT3 levels were higher in the Ph+ group (6.8 ± 4.2 pg/mL) compared to the Ph– group (4.8 ± 1.2 pg/mL). Similarly, FT4 levels were elevated in Ph+ patients (20.9 ± 15.7 ng/dL) relative to Ph– patients (18.3 ± 5.6 ng/dL). The mean TSH level was also markedly higher among Ph+ patients (7.3 ± 19.7 mIU/L) than among Ph– patients (2.8 ± 1.8 mIU/L) as in table 3.

Table 3: TFTs among both Ph –ve and +ve CML patients

Parameters	Mini to Max	Mean ± SD	Mini to Max	Mean ± SD
	Ph+ CML		Ph– CML	
FT3 (pg/mL)	.03 - 30.5	6.8 ±4.2	1.50 - 7.21	4.8 ±1.2
FT4 (ng/dL)	0.95 - 100.0	20.9 ±15.7	10.03 - 33.80	18.3 ±5.6
TSH (mIU/L)	0.01 - 100.1	7.3 ±19.7	.02 - 7.44	2.8 ±1.8

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Checking the results with Shapiro–Wilk test of normality for thyroid function parameters (FT3, FT4, and TSH). The test revealed that all variables significantly deviated from a normal distribution, with FT3 (W = 0.555, p < 0.001), FT4 (W = 0.666, p < 0.001), and TSH (W = 0.279, p < 0.001). Since the p-values for all parameters were less than 0.05, the null hypothesis of normality was rejected, indicating that the data were not normally distributed and that non-parametric statistical tests may be more appropriate for further analysis as in table 4.

Table 4: shows Tests of Normality:

Parameters	Shapiro-Wilk	P. value
FT3	.555	<0.001*
FT4	.666	<0.001*
TSH	.279	<0.001*

Comparing the thyroid function test (TFT) parameters between Philadelphia chromosome-positive (Ph+) and Philadelphia chromosome-negative (Ph–) CML patients. A statistically significant difference was observed in FT3 levels, with Ph+ patients showing a higher median value and mean rank compared to Ph– patients (p < 0.001).In contrast, FT4 and TSH brought no significant differences as p value for each was >0.05 as in table 5.

Table 5: Comparison of TFT Between Ph +ve and –ve CML Patients:

Parameter	group	Median	Mean Rank	P. value
FT3 (pg/mL)	Ph+ CML	6.1	114.92	<0.001
	Ph– CML	5.1	66.08	
FT4 (ng/dL)	Ph+ CML	16.2	88.18	0.551
	Ph– CML	16.8	92.82	
TSH (mIU/L)	Ph+ CML	1.7	83.59	0.075
	Ph– CML	2.7	97.41	

Compares thyroid function test (TFT) parameters between male and female participants in the study. There was no significant different for each parameter among genders as in table 6.

Table 6: Comparison of TFT by Gender Among All Study Participants:

Parameter	Gender	N	Mean Rank	Median	P. value
FT3 (pg/mL)	Male	78	90.63	5.59	0.977
	Female	102	90.40	5.59	
FT4 (ng/dL)	Male	78	93.04	16.85	0.567
	Female	102	88.55	16.31	
TSH (mIU/L)	Male	78	95.08	2.39	0.303
	Female	102	87.00	2.03	

Considering gender, comparing TFTs among males and females among CML Ph+ve and Ph-ve showed no significant differences as table 7.

Table 7: Gender-Based Comparison of TFTs according to Ph chromosome status:

Parameter	Gender	Ph+ve CML			Ph–ve CML		
		Mean Rank	Median	P. value	Mean Rank	Median	P. value
FT3	Male	51.11	6.3	0.104	42.37	4.9	0.277
	Female	41.93	5.9		48.36	5.1	
FT4	Male	44.31	15.9	0.731	48.78	18.6	0.255
	Female	46.25	16.2		42.50	16.4	
TSH	Male	45.71	2.2	0.950	49.08	3.0	0.213
	Female	45.36	1.7		42.22	2.6	

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Pearson's correlation of measured hormones of TFTs with age and duration of the disease showed, negative correlations of age with all TFT without significant differences as p value for each was more than 0.05 and correlation of duration with all TFTs were positive correlations without significant difference as well, as in table 8.

Table 8: Pearson's Correlation of TFT with Age and Duration of CML patients: (N = 180)

Parameter	Age		Duration of disease	
	Regression value	P-value	Regression value	P-value
FT3	-0.101	0.177	0.032	0.671
FT4	-0.068	0.364	0.009	0.901
TSH	-0.004	0.962	0.065	0.386

IV. DISCUSSION

Tyrosine kinase inhibitors (TKIs) have made chronic myeloid leukemia (CML) less deadly and more treatable. TKIs have been linked to endocrine-related side effects, most notably thyroid dysfunction, despite their therapeutic advantages. The side effects, which might manifest as hypothyroidism, hyperthyroidism, or thyroiditis, can have a substantial impact on patients' quality of life and pose clinical difficulties throughout the course of long-term treatment. Furthermore, research indicating that some adverse effects, including hypertension, hypothyroidism, and hand-foot syndrome, may serve as possible predictive biomarkers of therapy success have increased interest in TKI-induced hypothyroidism [20].

A partial agreement was obtained with the study involving a patient with (Ph+ve) CML. The mean duration of disease among patients was 2.5 ± 2.2 years (range: 0.1–14 years), whereas the (Ph−ve) group showed a slightly shorter duration with a mean of 2.2 ± 1.2 years (range: 0.1–6 years)[21].

In 2019, at Rajavithi Hospital, a cross-sectional study aimed to explore the prevalence and associated factors of thyroid dysfunction among cancer patients treated with tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs). There were 144 patients on TKIs with a mean age of 56.0 years. Thyroid dysfunction was found in 14.6% of patients, and most had subclinical hypothyroidism among 11.1%. Imatinib among 11, 10.8%. Thyroid dysfunction was associated with male sex [22].

A cross-sectional study was conducted on CML patients using a hydroxyl urea treatment protocol from March to August 2019 at Khartoum Nuclear and Radiology Hospital. A total of 100 participants, 53% female and 47% male, aged 11 to 70 years, were assessed for thyroid function parameters, including thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4). Results: The study revealed that thyroid hormone levels were elevated among CML patients compared with reference values. In addition, there was a strong correlation between duration of drug usage and thyroid hormones levels. However, there was no statistically significant difference between hormones levels and gender [23].

A study conducted in Khartoum, Sudan, from September to December 2019, aimed to assess thyroid hormone levels in CML patients. 87 serum samples, obtained from 42 cases (who were diagnosed using the BCR-ABL mutation discovered by polymerase chain reaction molecular analysis and assessment of bone marrow and peripheral blood morphology) and 45 controls, were tested for thyroid hormone levels by using the enzyme-linked immunosorbent assay (ELISA) technique. Compared to the control group, CML patients had a significant increase in TSH (P value = 0.00) and no significant changes in T3 and T4 levels (P value > 0.05). When comparing the duration of disease across study cases, significant differences with a weak negative correlation for T3 (P value = 0.037) and T4 (P value = 0.007), but insignificant differences with a negative correlation for TSH (P value = 0.228) were observed [24].

The (Ph+ve) group showed a higher mean TSH level with large variability, as means+Standard devotion (7.3 ±19.7), indicating that some patients had markedly elevated TSH suggestive of subclinical or overt hypothyroidism, while the (Ph−ve) group had TSH levels closer to normal (2.8 ±1.8). This supports evidence that CML treatment, particularly tyrosine kinase inhibitors, may contribute to thyroid dysfunction, commonly presenting as subclinical hypothyroidism [25].

A study in the general population has reported a slightly higher prevalence of thyroid dysfunction among females, largely due to autoimmune thyroid disorders. The lack of such differences in the present study may be explained by the dominant effect of leukemia-related physiological changes, which could mask subtle gender-related variations[26].

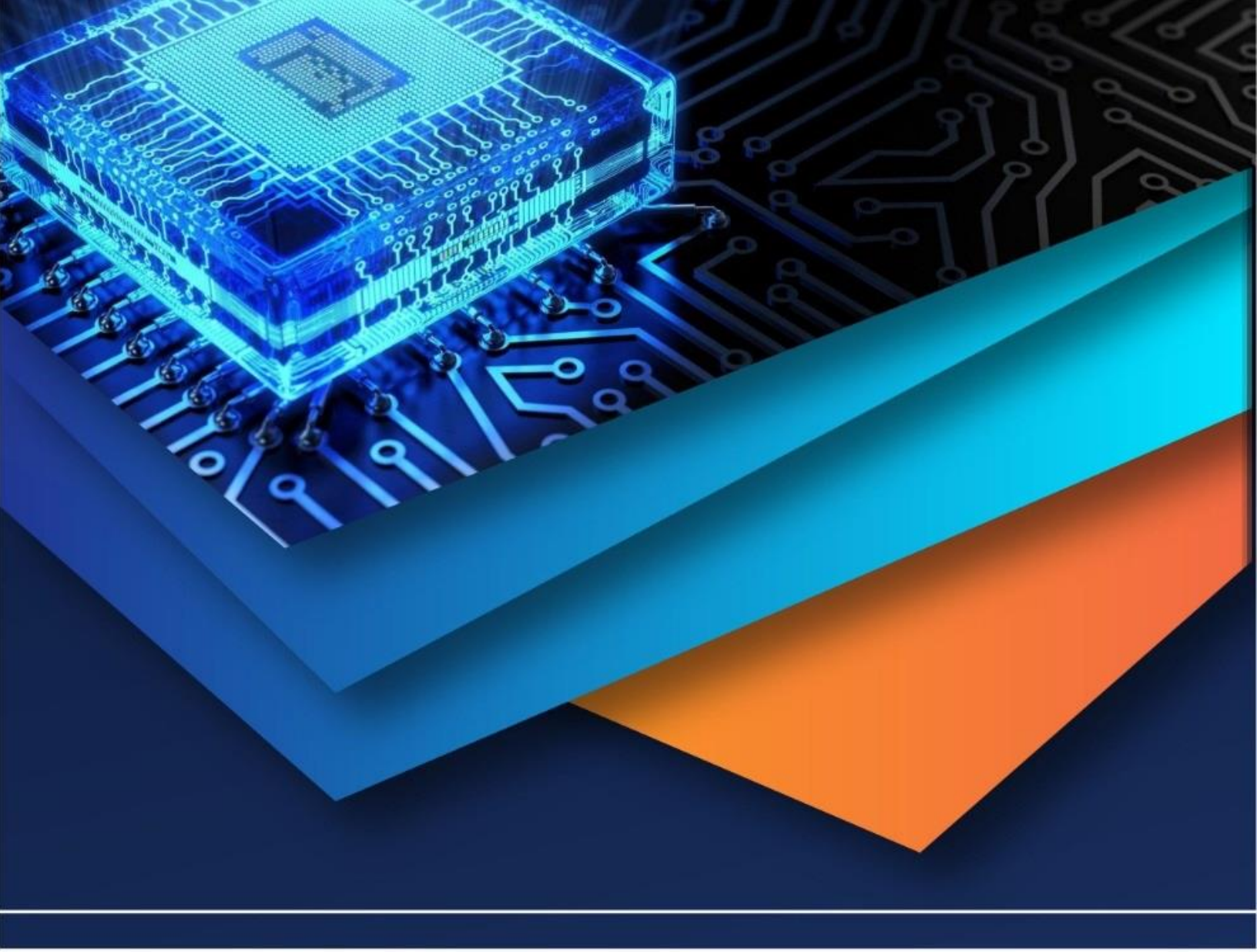
Comparing with other studies evaluating CML patients receiving imatinib (TKI) therapy reported normal FT3, FT4, and TSH levels with no correlation to cytogenetic status, suggesting that the BCR-ABL mutation does not directly affect thyroid hormone regulation[27]. Other clinical investigations found that thyroid dysfunction occurs mainly as a treatment-related effect, particularly in patients treated with certain TKIs, while baseline thyroid function between different CML subtypes remained similar [28].

V. CONCLUSION

This study concluded among CML patients with different karyotypes, TFTs among Ph +ve were affected more than Ph –ve patients. Gender has no effect on levels of TFTs among CML patients administrated TKIs.
FT3 hormone is the only affected TFT parameter in Ph+ve patients compared with Ph-ve patients.

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