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# IMPACT OF BLOOD PARAMETERS ON BCR/ABL1 P210 TESTING IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA: A PILOT STUDY

## *KRONİK MİYELOİD LÖSEMİ HASTALARINDA KAN PARAMETRELERİNİN BCR/ABL1 P210 TESTİ ÜZERİNE ETKİLERİ: PİLOT ÇALIŞMA*

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**ABSTRACT**

**Objective:** Chronic myeloid leukemia (CML) is one of the most common hematological malignancies derived from the BCR/ABL1 fusion gene. Patients with CML generally manifest leukocytosis with basophilia and neutrophilia. The verification of CML is often based on the detection of BCR/ABL1 fusion. We aimed to investigate the impact of peripheral blood (PB) differential and complete blood count (CBC) on BCR/ABL1 p210 test ordering in patients with suspected CML.

**Methods:** We performed a retrospective assessment of patients tested for the first time for BCR/ABL1 p210 fusion. We obtained clinical and laboratory findings of 235 patients from the database of our clinic. BCR/ABL1 p210 fusion was detected by quantitative real-time polymerase chain reaction (RT-qPCR). We implemented t-tests or Mann–Whitney U tests for the comparison of continuous data. We plotted the receiver operating characteristic (ROC curves) and calculated the area under the ROC curve (AUC) for each parameter.

**Results:** Among 235 patients, 25 (10.6%) received a new diagnosis of CML. CML patients had significantly increased white blood cell count (WBC) with differential. Absolute basophil count showed the highest area under the ROC curve (AUC) value of 0.829, which had a cut-off value of $0.3 \times 10^3$/ µL. 76.00% of CML cases had an absolute basophil count of $\geq 0.3 \times 10^3$/µL, while 95.24% of the non-CML cases had an absolute basophil count of $<0.3 \times 10^3$/µL.

**Conclusion:** Our results indicate that an absolute basophil count of $\geq 0.3 \times 10^3$/µL can help improve BCR/ABL1 p210 test ordering and reduce healthcare costs.

**Keywords:** CML, BCR/ABL1 fusion, RT-qPCR, CBC

**ÖZ**

**Amaç:** Kronik miyeloid lösemi (KML), BCR/ABL1 füzyon geninden kaynaklanan en yaygın hematolojik malignitelerden biridir. KML'li hastalar genellikle bazofili ve nötrofili içeren lökositoz gösterirler. KML'nin doğrulanması genellikle BCR/ABL1 füzyonunun saptanmasına dayanır. KML şüphesi olan hastalarda BCR/ABL1 p210 testi için periferik kan (PK) diferansiyeli ve tam kan sayımının (TKS) etkilerinin araştırılması amaçlandı.

**Yöntem:** BCR/ABL1 p210 füzyonu için ilk kez test edilen hastaların retrospektif bir değerlendirilmesi yapıldı. Kliniğimiz veri tabanından 235 hastanın klinik ve laboratuvar bulgularını elde edildi. BCR/ABL1 p210 füzyonu, kantitatif Gerçek Zamanlı Polimeraz Zincir Reaksiyonu (RT-qPCR) ile tespit edilmiştir. Sürekli verilerin karşılaştırılması için t-testi veya Mann-Whitney U testleri uygulandı. Her parametre için alıcı çalışma karakteristiği (ROC eğrileri) çizildi ve ROC eğrisi altındaki alan (AUC) hesaplandı.

**Bulgular:** 235 hastanın 25'ine (%10.6) yeni KML tanısı kondu. KML hastalarında, diferansiyel ile önemli ölçüde artmış beyaz kan hücresi sayısı (WBC) vardı. Mutlak bazofil sayısı, $0,3 \times 10^3$/µL'lik bir kesme değerine sahip olan 0,829'luk ROC eğrisi (AUC) değerinin altındaki en yüksek alanı gösterdi. KML vakalarının %76,00'ında mutlak bazofil sayısı $\geq 0,3 \times 10^3$/µL iken, KML olmayan vakaların %95,24'ünde mutlak bazofil sayısı $<0,3 \times 10^3$/µL idi.

**Sonuç:** Sonuçlarımız, $\geq 0,3 \times 10^3$/µL mutlak bazofil sayısının BCR/ABL1 p210 test istemini iyileştirmeye ve sağlık hizmeti maliyetlerini düşürmeye yardımcı olabileceğini göstermektedir.

**Anahtar Kelimeler:** KML, BCR/ABL1 füzyonu, RT-qPCR, TKS

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## Introduction

Chronic myeloid leukemia (CML) is a hematological malignancy characterized by abnormal clonal proliferation of myeloid precursor cells. The molecular basis of the CML, BCR/ABL1 fusion gene results from the translocation between the Abelson leukemia kinase (ABL) on chromosome 9 and the breakpoint cluster region (BCR) on chromosome 22.[1] Due to the BCR/ABL1 fusion, many patients with CML produce an oncoprotein called p210 with a molecular weight of 210 kDa which is sufficient for the disease phenotype.[2,3] The proliferation of the immature myeloid lineage in blood, bone marrow, and spleen is governed by tyrosine kinase activity mediated p210.[4] CML is effectively treated with tyrosine kinase inhibitors (TKIs) targeting the oncoprotein.[5] Sensitive detection of BCR/ABL1 fusion transcripts is performed by quantitative real-time polymerase chain reaction (RT-qPCR). Fusion transcripts are monitored by RT-qPCR at certain periods.[6] Patients with CML often have abnormalities of peripheral blood (PB), such as elevated white blood cell (WBC) counts, basophilia, neutrophilia, mildly decreased hemoglobin, relative eosinophilia, and thrombocytosis.[7] We aimed to retrospectively evaluate whether the PB differential and complete blood count (CBC) can effectively be used for BCR/ABL1 p210 test ordering in patients with suspected CML.

## Methods

### Patients

Patients tested for the first time for BCR/ABL1 p210 on PB samples at our hospital between October 2017 and January 2022 were retrospectively analyzed. In total, 242 tests were ordered for the BCR/ABL1 p210 fusion in our institution's database. Of these, 4 were performed for Philadelphia chromosome-positive (Ph+) Acute lymphoblastic leukemia (ALL). Another 3 tests were ordered as part of the routine examinations in the diagnosis of myelodysplastic/myeloproliferative neoplasms (MDS/MPN). These patients were excluded and the remaining 235 patients were enrolled in the study. Clinical and laboratory data were collected from patient records and the database of our clinic. Age, gender, indication, CBC, and PB differential of the patients were examined. The incidence of leukocytosis is defined as WBC $>10 \times 10^3/\mu L$, basophilia as an absolute basophil count $>0.1 \times 10^3/\mu L$, neutrophilia as an absolute neutrophil count $>6 \times 10^3/\mu L$, and eosinophilia as an absolute eosinophil count $>0.4 \times 10^3/\mu L$ at our institution.

### Detection of BCR-ABL fusion transcripts

Total RNA was obtained from WBC. First-strand cDNA was synthesized with fusion-specific primers. After reverse transcription, the determination of b2a2 and b3a2 transcripts was performed by RT-qPCR with primers/probes. Detection of transcripts was made using the Ipsogen BCR-ABL1 Mbcr IS-MMR kit (Qiagen, Germany). Copy numbers of the transcripts, control gene ABL1, and plasmid standards are determined by the threshold cycle (Ct). Ct is directly related to the amount at the beginning of the reaction. A standard curve is generated by plasmid standards, and then the amount of transcripts is detected in the samples. The results of the samples with ABL1 copy number ≥10,000 copies/mL are evaluated. BCR/ABL p210 fusion to ABL1 ratio gives a normalized copy number (NCN). Samples greater than the limit of detection of the assay (LOD) ≥0.0069 NCN are quantified. The normalized copy number on the international scale (IS-NCN%) is calculated using the conversion factor.

### Statistical Analysis

The normality of the data was tested with Anderson-Darling and Kolmogorov-Smirnov test. Parametric data were assessed using the t-test, and Mann–Whitney U test was applied for nonparametric data. P values of <0.05 were considered to indicate statistical significance. The receiver operating characteristic (ROC) curves were plotted and sensitivity, specificity, and area under the ROC curve (AUC) were calculated for each parameter. All statistical analyses were performed with GraphPad Prism version 9 (GraphPad Software, San Diego, CA, USA).

## Results

CBCs and absolute blood cell count in 25 CML cases and 210 non-CML cases were gathered (Table 1). Clinical indications for ordering the test included smear abnormality, cytopenias, thrombocytosis, basophilia, neutrophilia, eosinophilia, splenomegaly, hepatomegaly, and anemia in these patients (Table 2, 3). Of the 235 patients, 34 (%14.4) were detected as BCR/ABL p210 positive. Of these, 25 (%10.6) had equal or higher than ≥ 0.0069 NCN and were diagnosed with CML. The average NCN value of this group was 48.971 (range =0.306-82.309), and the average IS-NCN % value was 42,514% (range =0.427%-102.745%). The majority of CML patients showed leukocytosis (76%), basophilia (76%), neutrophilia (76%), and smear abnormalities. One patient was referred to our clinic for thrombocytopenia with leukocytosis. The patient's PB smear showed an abnormality. Then, the BCR/ABL1 p210 test was ordered. 82.309 (NCN) and 39.825% (IS-NCN %) were obtained. 18 (72%) of 25 patients had immature granulocyte counts. Leukocytosis and basophilia were observed in 12 patients with increased immature granulocyte counts. In the remaining 6 patients, immature granulocyte and WBC counts were within the normal range. The remaining 9 patients (3%) were detected as low-positive (≤0.0069 NCN). The average NCN value of the low-positive group was 0.0016 (range =0.000606-0.003), and the average IS-NCN % value was 0.0015% (range =0.001%-0.003%). This group indicated leukocytosis (44%), neutrophilia (44%), and thrombocytosis (33%). Immature granulocyte counts were within the normal range in this group. One of these

patients had mild basophilia. None of them were defined clinically to have CML 201 patients (85.5%) detected as BCR/ABL p210 negative. These patients showed less leukocytosis (56.6%), basophilia (23.3%), and neutrophilia (16.1%), but they had higher splenomegaly (32.8%) compared with the CML cases. WBC and differential counts of these cases were less than those of the CML cases. WBC and absolute blood cell counts showed statistically significant differences between CML and non-CML cases ($p<0.001$) Ttable 3). The areas under the ROC curve (AUC) were measured by constructing the ROC curve for each PB parameter (table 4). To determine the WBC differential count, a detailed analysis was carried out for each differential. The AUC values of monocytes, basophils, lymphocytes, and neutrophils were 0.737, 0.733, 0.731 and 0.719, respectively. Their cut-off values were 2.5%, 18.9%, 72.9% and 3.6%, respectively. Then, absolute WBC differential counts were applied to the analysis to calculate the AUC values. Basophil count showed the highest AUC value (0.829) among PB parameters at a cut-off value of 0.3 x $10^3$/µL. The AUC values of neutrophils, lymphocytes, immature granulocytes, and eosinophils were 0.795, 0.774, 0.770, and 0.712, respectively. With respect to the CBC parameters, the AUC value of WBC (0.797) was the highest at a cut-off value of 22.2 × $10^3$/µL. In our cohort, WBC of CML cases was observed mostly over 22 × $10^3$/µL, whereas WBC of non-CML cases was observed mostly in the range of 10-22 × $10^3$/µL (Figure). At the upper limit of WBC (10 × $10^3$/µL), sensitivity was 76.00% and specificity was 41.43%. When comparing the cut-off value and upper limit of WBC, sensitivity decreased to 72.00% and specificity increased to 94.29%. The absolute basophil count produced the first high AUC value (0.829). The cut-off values of basophil, the sensitivity and specificity increased to 76.00%, and 95.24%, respectively. When considering the cut-off values of WBC and basophils, the sensitivity was 72.00% and specificity 97.62%. If the cut-off values of either WBC or basophils were selected, the sensitivity increased to 76.00% and specificity decreased to 91.43%. Finally, the absolute neutrophil count yielded the third-highest AUC value of 0.795. When considering the cut-off values of basophils and neutrophils, the sensitivity was 76.00%, but the specificity decreased to 88.57%. If the cut-off values of either basophils or neutrophils were selected, the sensitivity decreased to 72.00% and the specificity increased to 97.61%.

**Table 1.** Recorded clinical indications of p210 positive group

| | **CML** | | **Non-CML** | |
|---|---|---|---|---|
| | **NCN ≥ 0.0069** | | **NCN < 0.0069** | |
| | **WBC = 4-10 × $10^3$/µL** | **WBC >10 × $10^3$/µL** | **WBC = 4-10 × $10^3$/µL** | **WBC >10 × $10^3$/µL** |
| | **n=6** | **n=19** | **n=5** | **n=4** |
| Smear abnormality | 0 | 19 | 2 | 1 |
| Cytopenias | 3 | 9 | 1 | 0 |
| Thrombocytosis | 2 | 9 | 2 | 1 |
| Basophilia | 1 | 19 | 0 | 1 |
| Neutrophilia | 0 | 19 | 3 | 1 |
| Eosinophilia | 0 | 14 | 1 | 1 |
| Splenomegaly | 3 | 4 | 3 | 1 |
| Hepatomegaly | 1 | 4 | 1 | 1 |
| Anemia | 2 | 8 | 1 | 0 |

**Table 2.** Recorded clinical indications of p210 negative group

| | **WBC <4 × $10^3$/µL** | **WBC = 4-10 × $10^3$/µL** | **WBC >10 × $10^3$/µL** |
|---|---|---|---|
| | **n=10** | **n=72** | **n=119** |
| Smear abnormality | 8 | 24 | 62 |
| Cytopenias | 8 | 26 | 26 |
| Thrombocytosis | 0 | 15 | 66 |
| Basophilia | 3 | 2 | 44 |
| Neutrophilia | 0 | 1 | 33 |
| Eosinophilia | 0 | 1 | 11 |
| Splenomegaly | 5 | 43 | 21 |
| Hepatomegaly | 0 | 18 | 11 |
| Anemia | 3 | 12 | 23 |

**Table 3.** Clinical characteristics and CBC parameters of patients.

| | **CML** | | **Non-CML** | | | | |
|---|---|---|---|---|---|---|---|
| | | | **NCN < 0.0069** | | **NCN = 0** | | |
| Number of patients | 25 | | 9 | | 119 | | |
| Sex (M/F) | 12/13 | | 5/4 | | 104/97 | | |
| | Mean ± SD | Range | Mean ± SD | Range | Mean ± SD | Range | p-Value |
| Age (years) | 48.84±17.81 | 42-80 | 45±15.73 | 23-77 | 51.31±16.70 | 18-88 | 0.5351 |
| WBC (× $10^3$/μL) | 60.14±68.26 | 5.01-289.3 | 9.63±3.29 | 5.42-14.06 | 12.03±6.54 | 2.17-38.47 | <0.0001 |
| RBC (× $10^6$/μL) | 4.6±0.85 | 3.4-6.67 | 4.89±0.57 | 4.23-6.1 | 5.06±0.98 | 0.1-7.7 | 0.0142 |
| HGB (g/dL) | 12.95±1.85 | 10.3-16.9 | 14.53±1.65 | 11.5-16.9 | 13.95±2.64 | 6.8-21.4 | 0.0577 |
| HCT (%) | 40.67±5.68 | 32.6-51.8 | 43.56±5.62 | 35.2-54.2 | 43.09±7.56 | 22.1-67.7 | 0.1164 |
| PLT (× $10^3$/μL) | 412.12±347.25 | 17-1358 | 361.78±268 | 119-918 | 391.56±297.68 | 33-1767 | 0.9698 |
| Differentitation (%) | | | | | | | |
| Neutrophils | 74±10.97 | 51.9-87 | 64.84±9.07 | 49.5-75.5 | 63.8±14.02 | 12.3-93 | 0.0002 |
| Lymphocytes | 15.7±10.43 | 4.7-38.7 | 25.18±9.33 | 14.8-42.7 | 24.4±11.27 | 1.8-78.8 | <0.0001 |
| Monocytes | 4.6±2.27 | 1.5-13.5 | 6.89±1.3 | 5.3-8.9 | 7±3.02 | 2.3-34.3 | <0.0001 |
| Basophils | 3.6±3.52 | 0.1-12.4 | 0.66±0.33 | 0.1-0.8 | 0.9±1.22 | 0.1-12.3 | <0.0001 |
| Eosinophils | 2±1.49 | 0.3-6.7 | 2.54±1.68 | 0.6-6 | 4±8.26 | 0-70.9 | 0.1637 |
| Immature granulocytes | 13.4±17.6 | 0.2-33.7 | 0.36±0.1 | 0.1-0.4 | 1.4±3.32 | 0-22.6 | 0.0001 |
| Absolute blood cell count (× $10^3$/μL) | | | | | | | |
| Neutrophils | 48.99±68.26 | 2.62-242 | 6.26±2.46 | 3.79-10.07 | 8.01±5.72 | 0.64-35.49 | <0.0001 |
| Lymphocytes | 5.15±3.56 | 1.53-17.34 | 2.43±1.19 | 1.03-4.35 | 2.64±1.63 | 0.51-14.91 | <0.0001 |
| Monocytes | 2.76±4.69 | 0.27-23 | 0.64±0.20 | 0.42-1.03 | 0.78±0.47 | 0.21-4.41 | 0.0014 |
| Basophils | 2.12±2.95 | 0.01-11.32 | 0.06±0.05 | 0.01-0.16 | 0.10±0.17 | 0.01-1.96 | <0.0001 |
| Eosinophils | 1.04±1.36 | 0.08-5.9 | 0.24±0.15 | 0.05-0.47 | 0.57±1.82 | 0-21.62 | 0.0004 |
| Immature granulocytes | 13.44±17.57 | 0.01-54.56 | 0.03±0.02 | 0.01-0.06 | 0.24±0.75 | 0-19.4 | <0.0001 |

**Table 4.** Area-under-the-curve values and sensitivity and specificity of CBC parameters.

| | **Sensitivity%** | **Specificity%** | **p-value** | **cut-off value** | **AUC** |
|---|---|---|---|---|---|
| Age (years) | NA | NA | 0.5522 | NA | 0.536 |
| WBC (× $10^3$/μL) | 72.00 | 94.29 | <0.0001 | 22.20 | 0.797 |
| RBC (× $10^6$/μL) | 58.82 | 71.9 | 0.002 | 4.615 | 0.639 |
| HGB (g/dL) | 76.00 | 50.95 | 0.0263 | 14.05 | 0.636 |
| HCT (%) | 80.00 | 43.81 | 0.0610 | 44.70 | 0.614 |
| PLT (× $10^3$/μL) | 48.00 | 61.43 | 0.9690 | 260 | 0.502 |
| Differentitation (%) | | | | | |
| Neutrophils | 60.00 | 81.43 | 0.0003 | 72.95 | 0.719 |
| Lymphocytes | 72.00 | 72.38 | 0.0002 | 18.9 | 0.731 |
| Monocytes | 48.00 | 93.33 | 0.0001 | 3.65 | 0.737 |
| Basophils | 52.00 | 97.14 | 0.0001 | 2.55 | 0.733 |
| Eosinophils | 56.00 | 60.29 | 0.1628 | 1.65 | 0.585 |
| Immature granulocytes | 61.11 | 90.86 | 0.0059 | 2.77 | 0.696 |
| Absolute blood cell count (× $10^3$/μL) | | | | | |
| Neutrophils | 72.00 | 91.43 | <0.0001 | 14.51 | 0.795 |
| Lymphocytes | 80.00 | 62.86 | <0.0001 | 2.78 | 0.774 |
| Monocytes | 56.00 | 87.14 | 0.0013 | 1.21 | 0.696 |
| Basophils | 76.00 | 95.24 | <0.0001 | 0.3 | 0.829 |
| Eosinophil | 76.00 | 57.42 | 0.0005 | 0.25 | 0.712 |
| Immature granulocytes | 72.22 | 93.55 | 0.0002 | 0.83 | 0.770 |

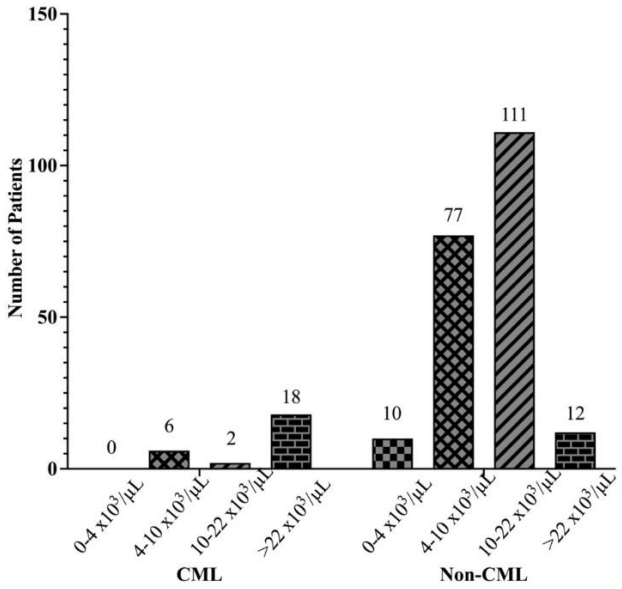


**Figure 1.** Variations of WBC between patients with CML and non-CML

## Discussion

Leukemia is one of the deadliest malignancies worldwide. CML accounts for 15-20% of all leukemias and is caused by the formation of the Philadelphia Chromosome t(9;22), resulting from a fusion between chromosomes 9 and 22 and leads to the expression of the BCR/ABL1 fusion oncogene. Common laboratory findings include leukocytesis, basophilia, neutrophilia, eosinophilia, and anemia.[8,9] Basophilia, a characteristic feature of patients with CML, is seen in many diseases including myeloproliferative neoplasms, cancer, and infections.[10] Our study showed the predictive feature of absolute basophil count at a cut-off value of 0.3 × $10^3$/µL for CML. 76.00% of CML cases had an absolute basophil count of ≥0.3 × $10^3$/µL, while 95.24% of the non-CML cases had an absolute basophil count of <0.3 × $10^3$/µL. Ogunleye et al. defined that the absolute basophil count at a cut-off value of 0.1 × $10^3$/µL was predictive for the BCR/ABL1 PCR test in 99 patients. However, the population of this study was lower than that of our study.[11] Masuda et al. stated that an absolute basophil count higher than 0.5 × $10^3$/µL had a good predictive value for distinguishing CML from non-CML cases.[12] Ogasawara et al. showed that the cut-off value of 0.43 × $10^3$/µL for the absolute basophil count was significantly different between CML and non-CML cases with leukocytosis.[13] In our study, we detected the cut-off value of the absolute basophil count (0.3 × $10^3$/µL), which is lower than those of other studies. At the same time, our study included cases with suspected CML as a control group. We detected absolute neutrophil count at a cut-off value of 14.51 × $10^3$/µL, which was the third highest AUC value. When comparing the absolute neutrophil count of 6 × $10^3$/µL and a cut-off value of 14,51 × $10^3$/µL, the sensitivity decreased to 72.00% and specificity increased to 91.43%. Ogunleye et al. reported that neutrophilia should be present in addition to basophilia for the ordering of PCR tests in patients with suspected CML.[11] When basophils and neutrophils cut-off values were evaluated together, sensitivity decreased to 72.00%, but specificity increased to 97.61%. For the upper limit of WBC, 76.00% of the CML cases had WBC of ≥10 × $10^3$/µL, while 41.43% of the non-CML cases had WBC of <10 × $10^3$/µL. For a cut-off value of WBC, 72.00% of CML cases had WBC of ≥22.20 × $10^3$/µL, while 94.29% of the non-CML cases had WBC of <22.20 × $10^3$/µL. If the cut-off values of WBC and absolute basophil count were selected for the diagnosis of CML, the sensitivity and specificity were 72.00% and 97.62%, respectively. When WBC and absolute basophil count were assessed separately, the sensitivity was increased to 76.00% and specificity decreased to 91.43%. When patients with leukocytosis are evaluated for the BCR/ABL1 p210 test ordering, these values are less effective than the cut-off value of absolute basophil count. In comparison with WBC of ≥10 × $10^3$/µL, the specificity of the absolute basophil count at a cut-off value of ≥0.3 × $10^3$/µL increased from 41.43% to 95.24% with preservation of sensitivity. Our results show that the absolute basophil count (≥0.3 × $10^3$/µL) is a specific marker for cases with suspected CML. If the absolute basophil count of ≥0.3 × $10^3$/µL had been selected for BCR/ABL1 p210 test ordering, 113 fewer PCR tests would have been performed. Healthcare costs are increasing rapidly and will continue to grow. Medical cost increases are one of the most important problems in the health sector. The resources allocated to healthcare services and the expenditures made in their presentation have an important place in the total expenditures for all countries.[14] Hence, the effect of CBC parameters on the BCR/ABL1 p210 test is an undeniable fact. TKIs are successfully used in the standard treatment of patients with chronic phase CML.[15] It has been shown that basophilia is an independent prognostic factor for CML progression before TKI in many studies.[16-18] In recent studies, it has been reported that basophils produce and secrete angiogenic and fibrogenic cytokines that trigger the malignant clone.[19,20] At the same time, basophils express vasoactive amines and enzymes responsible for the transport of leukemic stem cells to extramedullary organs.[21,22] Our results and the characteristics of basophils for malignant progression indicate a relationship with CML. The importance of using basophils with adequate clinical follow-up for easy and cost-effective screening of CML cases in the early period is clear. Our results highlight the potential of an absolute basophil count (≥0.3 × $10^3$/µL) to facilitate the diagnosis of CML and the costs of PCR testing.

In conclusion, the importance of using basophils with adequate clinical follow-up for easy and cost-effective screening of CML cases in the early period is clear. Our results highlight the potential of an absolute basophil count (≥ 0.3 × $10^3$/µL) to facilitate the diagnosis of CML and the costs of PCR testing.

**Compliance with Ethical Standards**
The design of our study was approved by the ethics committee of Afyonkarahisar Health Sciences University (number 2022-14-559).

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None

**Conflict of Interest**
The authors declare that they have no conflict of interest.

**Author contributions**
Study conception and design were performed by C.K. Material preparation, data collection were performed by S.H.Y., M.Ö.E. and F.Y. Analysis was performed by C.K. and H.D. The first draft of the manuscript was written by C.K. and all authors read and approved the final manuscript.

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