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How Does 2016 WHO Criteria for Polycythemia Vera Contribute to Our Daily Practice? A Single-Center Study from Turkey

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ABSTRACT

Background: We evaluated the frequency of subnormal erythropoietin levels, Janus kinase 2 (JAK2) V617F positivity and polycythemia vera (PV) in patients who did not meet World Health Organization (WHO) 2008 criterion for hemoglobin levels but were suggested to be investigated for PV in 2016 revision.

Materials and Methods: We assessed the data of 92 patients who were further evaluated with JAK2V617F mutation and serum erythropoietin (EPO) levels and bone marrow biopsy, if necessary. We also compared this patient group with 20 patients whose Hgb>18.5 g/dL for men and >16.5 g/dL for women.

Results: Nine patients (45%) in the higher hemoglobin group were JAK2V617F positive, while 4 patients (4.3%) in the lower hemoglobin group were JAK2V617F positive ($p<0.001$). The number of patients with serum EPO levels <4.3 mIU/mL was significantly higher in the higher hemoglobin group (n=13, 65%) than the lower hemoglobin group (n=7, 7.6%) ($p<0.001$). Finally, the number of patients who received a diagnosis of PV was significantly higher in the higher hemoglobin group (n=13, 65%) than the lower hemoglobin group (n=9, 9.8%) ($p<0.001$).

Conclusion: We found a substantial increase in patients who were candidates for testing for PV with the introduction of WHO 2016 criteria; these patients were diagnosed with PV with a rate (9.8%) that cannot be underestimated.

Keywords: Polycythemia vera; Janus kinase 2 (JAK2) V617F mutation; Serum erythropoietin; World Health Organization (WHO) 2016 revision

INTRODUCTION

Polycythemia vera (PV) is a clonal stem cell-derived malignancy, which is characterized by erythrocytosis and can lead to leukocytosis, thrombocytosis, splenomegaly, thrombosis, bleeding, microcirculatory symptoms and leukemic or fibrotic transformation. PV is a Philadelphia-negative chronic myeloproliferative malignancy with an incidence of 0.01 to 2.61/100000 [1-3]. Hemoglobin, hematocrit and erythropoietin levels, JAK2V617F/JAK2 exon 12 mutation analysis and bone marrow biopsy are required for the diagnosis of polycythemia vera [4].

In 2016, World Health Organization (WHO) published an update for the classification and diagnostic criteria for myeloproliferative neoplasms, which included important revisions for PV compared to the previous 2008 criteria. Bone marrow biopsy, which was a minor criterion in 2008 diagnostic criteria, has been revised and became a major criterion. Another significant change was in hemoglobin levels. The

hemoglobin threshold, which was >18.5 g/dL for men and >16.5 g/dL for women, is decreased to >16.5 g/dL for men and >16 g/dL for women. A hematocrit threshold was also included in the criteria, which is >49% for men and >48% for women[4-5]. As a result of the decreased hemoglobin threshold with 2016 WHO criteria, we observed a substantial rise in the number of patients tested for PV in our outpatient clinic as well as its high-cost diagnostic tests. In our study, we aimed to investigate the ratio of patients who were diagnosed with PV using the current criteria but would be missed with the old criteria to the total number of patients diagnosed with 2016 criteria. To do so, we evaluated the frequency of subnormal erythropoietin levels, JAK2 positivity and polycythemia vera in patients with hemoglobin levels between 16.5 to 18.5 g/dL for men and 16 to 16.5 g/dL for women and/or hematocrit levels >49% for men and 48% for women, who did not meet WHO 2008 criterion for hemoglobin levels but were suggested to be looked for PV in 2016 update.

MATERIALS AND METHODS

We assessed the data of patients who presented to University of Health Sciences Okmeydanı Training and Research Hospital Hematology Clinic between 1 January 2017 and 1 November 2018 and were found to have hemoglobin (Hgb) 16.5 to 18.5 g/dL and/or hematocrit (Hct) >49% for men and Hgb 16 to 16.5 g/dL and/or Hct>48% for women in a complete blood count performed for any reason (WHO new Hgb). Ninety-two patients, who were found to have no respiratory or cardiac disease that may cause polycythemia, underwent further evaluation with routine biochemistry, including lactate dehydrogenase (LDH), JAK2V617F mutation and serum erythropoietin (EPO) levels. JAK2 exon 12 mutation testing was ordered if JAK2V617F was negative. Bone marrow biopsy was performed on patients with either JAK2V617F or JAK2 exon 12 mutation positivity and/or subnormal EPO levels. The diagnosis of polycythemia vera was made according to WHO 2016 diagnostic criteria[4].

We also compared this patient group with 20 patients who presented to our clinic in the same time period and whose hemoglobin levels were >18.5 g/dL for men and >16.5 g/dL for women (WHO old Hgb). This group of patients received a diagnosis of PV according to WHO 2008 criteria[5]. We assessed whether these two groups had a significant difference in terms of age, sex, total leukocyte count (WBC), serum EPO levels, JAK2V617F positivity and incidence of PV.

The study protocol was approved by the institute's committee on clinical research.

Statistical analysis

Statistical evaluation was made by SPSS 24 program. Data were described as numbers and percentage or median and range, when appropriate. x^2 Fisher's exact test was used for evaluating categorical values and Mann-Whitney U test for continuous values in patient groups. All p-values were 2-sided with statistical significance at 0.05 alpha levels.

RESULTS

Median age of the patients was 47 (range: 18-78). Eighty-six patients (93.5%) were male while 6 (6.5%) were female. Median hemoglobin level was 17.2 g/dL (16.1-18.4), hematocrit 49.9% (46.1-58.8), WBC 8355/µL (3790-24950) and platelet count 218500/µL (82000-602000). Four patients (4.3%) was JAK2V617F positive. JAK2 exon 12 mutation was negative in all 42 patients who were tested for. Serum EPO levels were below 4.3 mIU/mL in 7 (7.6%) patients. Nine patients (9.8%) were diagnosed with PV.

There was no statistically significant difference between the first group with hemoglobin levels 16.5-18.5 g/dL for men and 16-16.5 g/dL for women and the second group with hemoglobin levels >18.5 g/dL for men and >16.5 g/dL for women in terms of age, WBC and platelet count (p=0.410, 0.544 and 0.433, respectively). The frequency of female patients was greater in the higher hemoglobin group (p<0.001). Nine patients (45%) in the higher hemoglobin group were JAK2V617F positive, while 4 patients (4.3%) in the lower hemoglobin group were JAK2V617F positive (p<0.001). The number of patients with serum EPO levels <4.3 mIU/mL was significantly higher in the higher hemoglobin group (n=13, 65%) than the lower hemoglobin group (n=7, 7.6%) (p<0.001). Finally, the number of patients who received a diagnosis of PV was significantly higher in the higher hemoglobin group (n=13, 65%) than the lower hemoglobin group (n=9, 9.8%) (p<0.001) (Table 1).

Table 1: Comparison of patient characteristics between two groups

Patient characteristics	WHO new Hgb (n=92) 16.5-18.5 g/dL for men 16-16.5 g/dL for women	WHO old Hgb (n=20) >18.5 g/dL for men >16.5 g/dL for women	P value
Age, years, median (range)	47 (18-78)	51.5 (22-88)	0.410
Sex, n, (%)			
Female	6 (6.5%)	8 (36.4%)	P<0.001
Male	86 (93.5%)	12 (54.6%)	
Hgb, g/dl, median (range)	17.2 (16.1-18.4)	19.1 (16.7-20.9)	P<0.001
Hct, %, median, (range)	49.9 (46.1-58.8)	55.8 (50.0-67.7)	P=0.139
WBC, /µL, median, (range)	8355 (3790-24950)	10205 (6050-14790)	P=0.544
Platelet, /µL, median, (range)	218500 (82000-602000)	232000 (86000-888000)	P=0.443
JAK2V617F, n, (%)			
Positive	4 (4.3%)	9 (45%)	P<0.001
Negative	88 (95.6%)	11 (55%)	
JAK2 exon 12, n, (%)			
Positive	0	0	P=1
Negative	49 (100%)	7 (100%)	
EPO, mIU/ml, n, (%)			
<4.3	7 (7.6%)	13 (65%)	P<0.001
>4.3	85 (92.4%)	7 (35%)	
Bone Marrow Biopsy, n, (%)			
Positive	9 (100%)	13 (100%)	P=1
Negative	0	0	
Polycythemia Vera, n, (%)			
Yes	9 (9.8%)	13 (65%)	P<0.001
No	83 (90.2%)	7 (35%)	

Hgb: hemoglobin, Hct: hematocrit, WBC: white blood cell, EPO: erythropoietin

DISCUSSION

In 2008, hemoglobin level greater than 18.5 g/dL for men and >16.5 g/dL for women was considered as a major criterion for the diagnosis of polycythemia vera[5]. However, a novel study by Barbui et al. revealed that JAK2-positive patients with hemoglobin levels of 16 to 18.4 g/dL for men and 15 to 16.4 for women had panmyelosis in bone marrow biopsy, low serum erythropoietin levels, more previous arterial thrombosis than the group with higher hemoglobin levels and presented more frequently with platelet counts exceeding the required level of WHO-defined essential thrombocythemia[6]. Therefore, 2016 WHO criteria adopted these results and revised the related criterion to be hemoglobin levels >16.5 g/dL for men and >16.0 g/dL for women or hematocrit >49% for men and >48% for women[4].

JAK2V617F mutation positivity is correlated with age, leukocytosis, low platelet count and elevated hemoglobin levels[7]. Accordingly, we found that patients who received PV diagnosis with lower hemoglobin levels (Hgb 16.5-18.5 g/dL for men and 16-16.5 g/dL for women) had lower JAK2V617F positivity (4 out of 9 patients) than patients with PV diagnosis and higher hemoglobin levels (Hgb >18.5 g/dL for men and >16.5 g/dL for women) (9 out of 13 patients).

Subnormal serum erythropoietin level, a minor diagnostic criterion, lacks high specificity for PV and 20% of patients with PV can have normal or high serum EPO levels [8-10]. In our study, 7 out of 9 patients who received PV diagnosis according to current 2016 criteria and all patients who received PV diagnosis according to 2008 criteria had low serum EPO levels.

Lowered hemoglobin threshold for the diagnosis of polycythemia vera will cause a marked increase in the number of patients investigated for PV, bringing up the concerns that this may give rise to unnecessary and costly tests for healthy individuals[11-13]. Sandes et al. conducted a retrospective study on 248,839 subjects with presumably normal complete blood count results and found that 6.48% of males have Hgb>16.5 g/dL or Hct>49% and 0.28% of females have Hgb>16 g/dL or Hct>48% [11]. In our study, we revealed that the number of patients tested for polycythemia vera increased by 5-fold with WHO 2016 criteria. Out of 112 patients investigated for PV, only 20 patients (17.8%) had hemoglobin levels meeting the old criterion, while the remaining 92 (82.8%) consisted of patients who became eligible for testing with the introduction of new criteria. The majority of patients investigated with new criteria were male (93.5%). 65% of patients who met the 2008 hemoglobin criterion were diagnosed with PV, while this rate was 9.8% for 2016 hemoglobin criterion.

CONCLUSION

In conclusion, while we found a substantial increase in patients who were candidates for testing for PV with the introduction of WHO 2016 criteria, these patients were diagnosed with PV with a rate (9.8%) that cannot be underestimated.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest

Ethical Approval

All procedures performed in studies involving human participants were accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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