Research Article / Araştırma Makalesi

Comparison of Polystemia Vera Patients Diagnosed Before and After the Updated Diagnostic Criteria

Güncellenen Tanı Kriterleri Öncesi ve Sonrası Tanı Alan Polistemia Vera Hastalarının Karşılaştırılması

Şevket Katılmış, Eren Gündüz

Eskisehir Osmangazi University Faculty of Medicine, Department of Internal Medicine, Division of Haematology, Eskişehir, Türkiye

Özet: Polisitemia vera, eritroid serilerde artışla birlikte lökositoz, trombositoz ve splenomegali ile karakterize kronik, klonal ve ilerleyici bir miyeloproliferatif hastalıktır. Bu çalışmada, 2008 ve 2016 DSÖ tanı kriterlerine göre PV tanısı alan hastaların klinik ve laboratuvar özellikleri ile takip sırasında gelişen komplikasyonları karşılaştırmayı ve tanı kriterlerindeki değişikliğin gerçek hayata etkisini retrospektif olarak değerlendirmeyi amaçladık. Çalışmaya 2011-2015 yılları arasında 50 ve 2016-2020 yılları arasında 50 olmak üzere JAK2-V617F mutasyonu pozitif olan toplam 100 polisitemia vera hastası dahil edilmiştir. İki grup tanı anındaki laboratuvar değerleri açısından karşılaştırıldığında, hemoglobin, hematokrit ve kırmızı kan hücresi sayısı 2016'dan önce tanı alan grupta anlamlı olarak daha yüksekti (p=0,036). Hastalar son takipte tromboz, kanama, miyelofibrozise ilerleme, lösemik dönüşüm ve miyelodisplastik sendroma dönüşüm komplikasyonları açısından değerlendirildiğinde, 2016 öncesi grupta 19 (%38) hastada, 2016 sonrası grupta ise 5 (%10) hastada komplikasyon geliştiği tespit edilmiştir (p=0,002). Miyelofibrozis komplikasyonu gelişen hasta sayısı 2016 öncesi grupta anlamlı olarak daha yüksekti (p=0,006). Tromboz gelişen hasta sayısı 2016 öncesi grupta daha yüksekti, ancak fark istatistiksel olarak anlamlı düzeye ulaşmadı (p=0,055). Diğer komplikasyonlar açısından iki grup arasında fark bulunmamıştır (p > 0,05). Özet olarak, çalışmamızda sadece miyelofibrozis komplikasyonu görülen hasta sayısında anlamlı bir fark bulunmuştur. Tanı kriterlerinde 2016'da yapılan değişikliğin diğer komplikasyonlar üzerindeki etkisini belirlemek için daha fazla hasta ile daha ileri çalışmalara ihtiyaç duyulacaktır.
Anahtar Kelimeler: Polistemia vera, Tanı, Tedavi, Komplikasyon

Abstract: Polycythemia vera is a chronic, clonal and progressive myeloproliferative disease characterized by leukocytosis, thrombocytosis and splenomegaly with increased erythroid series. In this study, we aimed to compare the clinical and laboratory features of patients diagnosed with PV according to the 2008 and 2016 WHO diagnostic criteria and the complications that developed during follow-up, and to retrospectively evaluate the impact of the change in diagnostic criteria on real life. A total of 100 polycythemia vera patients with positive JAK2-V617F mutation were enrolled in the study, 50 between 2011-2015 and 50 between 2016-2020. When the two groups were compared in terms of laboratory values at the time of diagnosis, hemoglobin, hematocrit and red blood cell count were significantly higher in the group diagnosed before 2016 (p=0.036). When patients were evaluated for complications of thrombosis, hemorrhage, progression to myelofibrosis, leukemic transformation, and transformation of myelodysplastic syndrome at last follow-up, it was found that 19 (38%) patients in the pre-2016 group and 5 (10%) patients in the post-2016 group developed complications (p=0.002). The number of patients who developed a myelofibrosis complication was significantly higher in the pre-2016 group (p=0.006). The number of patients who developed thrombosis was higher in the pre-2016 group, but the difference did not reach a statistically significant level (p=0.055). About other complications, there was no difference between the two groups (p > 0.05). In summary, our study found a significant difference only in the number of patients with myelofibrosis complications. Further studies with more patients will be needed to determine the impact of the 2016 change in diagnostic criteria on other complications.
Keywords: Polycythemia vera, Diagnosis, Treatment, Complications

ORCID ID of the authors: ŞK. 0009-0005-1132-7716, EG. 0000-0001-7455-2949

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Correspondence: Şevket KATILMIŞ – Eskisehir Osmangazi University Faculty of Medicine, Department of Internal Medicine, Division of Haematology, Eskişehir, Türkiye

e-mail : sevketktlms@gmail.com

1. Introduction

Polycythemia vera (PV) is a chronic, clonal and progressive myeloproliferative disorder characterized by leukocytosis, thrombocytosis and splenomegaly with increased erythroid series. The incidence was reported as 2.3-2.8 per 100,000 persons/year, the median age at diagnosis as 60 years and the male/female ratio as 1.2/1(1).

With the updated World Health Organization (WHO) diagnostic criteria for the diagnosis of PV published in 2016, the hemoglobin (Hgb) threshold was lowered to 16.5 g/dL for men and 16 g/dL for women, and the hematocrit (Hct) was lowered to 49% for men and 48% for women. These changes were made based on retrospective studies showing that patients with JAK2-V617F mutation-positive myeloproliferative neoplasia and hemoglobin levels below 18.5 g/dL in men and 16.5 g/dL in women had an increased risk of thrombotic complications and a poorer prognosis during follow-up. These patients were mostly diagnosed as essential thrombocythemia (ET) but had bone marrow characteristics compatible with PV (2-6). Such patients are defined as "masked" or "prodromal" PV. According to the current WHO diagnostic criteria, these patients are categorized as having PV (7). However, the new Hgb and Hct cut-offs, when used to define individuals to be screened for potential PV, lead to a significant increase in diagnostic testing, particularly in men.

The second important change introduced with the 2016 WHO criteria is the inclusion of histopathological features as important diagnostic criteria. The morphology of the bone marrow in PV is characterized by age-related hypercellularity and panmyelosis. Approximately 20% of patients with PV have grade 1 reticular fibrosis in the bone marrow at the time of diagnosis, which is associated with a higher risk of developing myelofibrosis (8).

The third important diagnostic criterion is the characterization of the mutation. JAK2 mutations that lead to activation of the JAK-STAT signaling pathway are present in the majority of patients. The V617F mutation is found in 95% to 97% of patients, while exon 12 mutations are found in most of the remaining patients (9-12). New diagnostic criteria allow the diagnosis of JAK2 mutation-negative PV, which is extremely rare (11).

A reduced serum erythropoietin (EPO) level is the only minor diagnostic criterion retained in the 2016 WHO criteria. However, a significant proportion of patients with PV (7%-40%) have normal serum EPO levels, indicating a low negative predictive value for this test (13).

Endogenous erythroid colony formation is no longer considered an insignificant diagnostic criterion. Although it is highly specific for erythropoietin-independent erythroid progenitor cells with JAK2V617F mutation, it is technically demanding and expensive and only available in a limited number of research laboratories. The 2008 and 2016 WHO diagnostic criteria for polycythemia vera are listed in Table 1.

Survival of patients with PV treated with current therapies usually lasts decades, but symptoms (e.g., pruritus, erythromelalgia, splenomegaly), complications (e.g., venous or arterial thrombotic events), and hematologic changes (e.g., myelofibrosis, acute myeloid leukemia, myelodysplastic syndromes) cause significant morbidity and limit life expectancy. Bleeding is common in PV, but major bleeding is relatively rare.

Progression to myelofibrosis (MF) is one of the most common complications of PV. The treatment of patients who develop MF after PV is similar to that of patients with primary MF. PV patients have a 10% risk of myelofibrotic transformation at 10-year follow-up and a 25% risk at 25-year follow-up.

The prognosis of patients who develop secondary myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) after PV is generally poor. The rates of conversion to leukemia were 2%, 5% and 10% with a follow-up of 10, 15 and 20 years, respectively. Advanced age, splenomegaly, leukocytosis and abnormal karyotype have been reported as

risk factors for leukemic transformation (14, 15).

The median survival of untreated symptomatic patients with PV is estimated at 18 months (16). In treated patients, however, survival is at least 13 years (17). Age, leukocytosis, history of venous thrombosis and abnormal karyotype have been defined as independent risk factors for survival (18).

2. Materials and Methods

The study included 100 patients aged 18 years and older with positive JAK2V617F mutation who were diagnosed with PV in Eskişehir Osmangazi University Faculty of Medicine, Department of Haematology. Patients diagnosed with PV before and after 2016 were analysed in 2 separate groups because the diagnostic criteria had changed in that year. January 2011-December 2015 (n=50) and January 2016-December 2020 (n=50) were chosen as diagnosis dates to compare the change in the number of diagnosed patients and to ensure a follow-up period of at least 1 year for both groups. Data were obtained from the hospital's automation system and patient records.The study was evaluated by the Eskişehir Osmangazi University Non-Interventional Clinical Studies Ethics Committee and approved with decision number 15 on 13.07.2021.

The IBM SPSS Statistics Version 25 package program was used for all analyses. The conformity of the continuous variables with the normal distribution by the group was assessed using the Shapiro-Wilk normality test. The Mann-Whitney U test was used for comparison between groups for continuous variables and chi-square analysis for comparison between groups for categorical variables. In the descriptive statistics, number and percentage (%) were used for categorical variables. Pearson, Yates, Fisher's Exact Test and exact test methods determined using Monte Carlo simulation were used for the chi-square analyses. P <0.05 was set as the significance level.

2. Findings

Some clinical characteristics of patients that may be related to the risk of complications are listed in Table 2.

Table 1. World Health Organisation Diagnostic Criteria for PV

	Diagnostic criteria for PV (2008)	**Diagnostic criteria for PV (2016)**
Major Criteria	1. Hemoglobin level >18.5 g/dl in men and >16.5 g/dl in women or other signs of increased erythrocyte mass 2. Presence of functionally similar mutation such as JAK2 V617F or JAK2 Exon 12	1. Hemoglobin >16.5 g/dl for men and >16 g/dl for women or hematocrit >49% for men and >48% for women or increased erythrocyte mass 2. Bone marrow characterized by myeloproliferative (panmyelosis) of three series with mature megakaryocytes, hypercellular and pleomorphic for age 3. Presence of JAK2V617F or JAK2 exon12 mutation
Minor Criteria	1. Panmyelosis characterized by age-appropriate hypercellular bone marrow biopsy, marked erythroid, granulocytic and megakaryocytic proliferation 2. Low serum erythropoietin level	1. Subnormal serum erythropoietin level

	3. In vitro endogenous erythroid colony formation	
For diagnosis necessary criteria	The presence of 2 major criteria and 1 minor criterion or 1 major criterion and 2 minor criteria is required for the diagnosis.	All 3 major criteria or the presence of the first 2 major criteria and minor criteria are required for the diagnosis.

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Table 2. Clinical Features

Parameters	Before 2016 (n=50)	After 2016 (n=50)	p-value
Male/Female ratio	30/20	32/18	0.837
Age at diagnosis (mean±sd)(years)	58.5±12.25	62±13.8	0.960
High risk group (n, %)	28 (%56)	33 (%66)	0.412
Follow-up period(mean±sd)(months)	95.5±36.4	29±19.3	**0.000**
Smoking	28 (%56)	26 (%52)	0.840

sd: standard deviation

Eleven (11%) patients were asymptomatic and were diagnosed during routine examinations. In the evaluation of symptomatic patients, itching (36%) was the most common symptom. Other symptoms included headache/dizziness (23%), thrombosis (11%), fatigue (6%), paresthesia (4%), tinnitus (3%), erythromelalgia (2%), dyspnea (2%), abdominal pain (1%) and sweating (1%). The occurring complaints were similar in the groups before and after 2016 (p=0.121). The comorbidities of the patients are listed in Table 3.

Table 3. Concomitant Comorbidities

Comorbidity	Before 2016 (n=50)	After 2016 (n=50)	p value
DM	18 (%36)	11 (%22)	0.18
HT	29 (%58)	23 (%46)	0.31
CAD	20 (%40)	13 (%26)	0.20
CVE	7 (%14)	5 (%10)	0.75
PAD	6 (%12)	4 (%8)	0.73
COPD	8 (%16)	7 (%14)	1.00

DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery disease, CVE: Cerebrovascular event, PAD: Peripheral artery disease, COPD: Chronic obstructive pulmonary disease

Thrombosis was observed in 5 (10%) patients in the pre-2016 group and 6 (12%) patients in the post-2016 group (p=1). Of the thromboses, 9 (81.8%) were venous and 2 (18.2%) arterial thromboses. Venous thromboses included 5 (55.5%) deep vein thromboses, 3 (27.3%) portal vein thromboses and 1 (9.1%) hepatic vein thrombosis; arterial thromboses included 1 (9.1%) thrombosis of the digital artery of the hand and 1 (9.1%) celiac boot thrombosis. In both groups, no patients had bleeding symptoms and signs at the time of diagnosis.

Hepatomegaly was detected in 23 (46%) patients in the pre-2016 group and 16 (32%) patients in the post-2016 group; splenomegaly was detected in 28 (56%) patients before 2016 and in 19 (38%) patients after 2016 (p=0.219 and p=0.109, respectively).

The complete blood count parameters of the patients at the time of diagnosis are summarised in Table 4. No significant difference was found between the 2 groups for uric acid, LDH, CRP and D-dimer, which could be related to complications (p> 0.05).

Table 4. Complete Blood Count Parameters at Diagnosis

Parameters	Before 2016 (n=50)	After 2016 (n=50)	p value
Hgb (gr/dl) (mean±sd)	18.6±1.03	17.1±1.16	0.000
Hct (%) (mean±sd)	58.1±4.1	52.2±4.2	0.000
Erythrocytes /µl (median)	7.262.800	6.433.200	0.000
Leukocytes /µl (median)	16.990	11.424	0.056
Platelets/µl (median)	489.520	442.580	0.340
MCV (fl) (median)	94.3	83.3	0.340

sd: standard deviation, Hgb: Hemoglobın, Hct: Hematocrıt, MCV: Mean Corpuscular Volüme

Diagnostic bone marrow biopsy was performed in 36 (72%) patients in the pre-2016 group and 40 (80%) patients in the post-2016 group. The results of the classical cytogenetic examination and fluorescence in situ hybridization (FISH) of the bone marrow of 34 (68%) patients in the group before 2016 and 38 (76%) patients in the group after 2016 were available. Conventional cytogenetic testing revealed genetic mutations in 1 (2.9%) patient in the pre-2016 group and 1 (2.6%) patient after 2016 (22q12 deletion or trisomy 9).

Bone marrow biopsy showed hypercellularity in 32 (88.9%) patients in the pre-2016 group and 35 (87.5%) patients in the post-2016 group (p=1). Panmyelosis was present in 30 (83.3%) in the pre-2016 group and 26 (65%) in the post-2016 group; pleomorphic mature megakaryocytes were present in 26 (74.3%) in the pre-2016 group and 28 (70%) in the post-2016 group; fibrosis was present in 5 (13.9%) in the pre-2016 group and 9 (22.5) patients (p=0.12, p=0.87 and)p=0.5, respectively). Regarding the degree of fibrosis in the bone marrow, 2 patients in the pre-2016 group had grade 1 fibrosis and 3 patients had grade 2 fibrosis; 4 patients had grade 1 fibrosis and 5 patients had grade 2 fibrosis in the post-2016 group.

The phlebotomies were performed in 98 (98%) patients during follow-up. In 2 (2%) patients in whom cytoreductive treatment had been started since diagnosis and hematocrit control had been achieved, phlebotomy was not performed due to advanced age and CHD. In the pre-2016 group, phlebotomy was performed on average 4±2.8 times in the first year and 7.5±9.7 times in the follow-up period until the last visit; in the post-2016 group, phlebotomy was performed on average 3±2.2 times in the first year and 4±5.7 times in the follow-up period until the last visit. The total number of phlebotomies performed in the first year after diagnosis and up to the last visit was higher in the pre-2016 group (p=0.013 and p <lock><</lock> 0.001, respectively).

46 (92%) patients in the pre-2016 group and 38 (76%) patients in the post-2016 group received cytoreductive treatment. Table 5 shows the distribution of treatment among patients.

Table 5. Treatments for PV

Treatment	Before 2016 (n=50)	After 2016 (n=50)
Phlebotomy+HU	39	34
Phlebotomy+HÜ+Anagrelide	7	-
Phlebotomy+HÜ+Interferon	-	2
Phlebotomy	4	12
HU	-	1
HU+Anagrelide	-	1

Hu: Hıdroksıure

46 (92%) patients in the pre-2016 group and 47 (94%) patients in the post-2016 group received antiaggregant therapy (p=1). ASA was the most commonly used agent in antiaggregant treatment. In the pre-2016 group, 3 patients received ASA+clopidogrel, 1 patient received clopidogrel only and in the post-2016 group 6 patients received ASA+clopidogrel. When analyzing the two groups about anticoagulant treatment, 9 (18%)

patients in the pre-2016 group and 4 (8%) patients in the post-2016 group received anticoagulant treatment (p=0.23). In the pre-2016 group, 6 patients received warfarin, 1 patient rivaroxaban, 1 patient apixaban, 1 patient edoxaban; in the post-2016 group, 2 patients received warfarin and 2 patients rivaroxaban.

The patients were examined for complications (thrombosis, bleeding, conversion to MF, AML, MDS) at the end of the first year and the last visit. At the end of the first year, complications occurred in 3 (6%) patients in the pre-2016 group and 2 (4%) patients in the post-2016 group (p=1). At the last visit, complications occurred in 19 (38%) patients in the pre-2016 group and 5 (10%) patients in the post-2016 group (p=0.002).

At the end of the first year, thrombosis was detected in 2 (4%) patients in the pre-2016 group, while no thrombosis was observed in the post-2016 group (p=0.495). At the last visit, thrombosis was detected in 9 (18%) patients in the pre-2016 group and 2 (4%) patients in the post-2016 group (p=0.055). The duration of thrombosis development since diagnosis was calculated as 50.7±33.8 months in the pre-2016 group and 27±4.2 months in the post-2016 group.

When analyzing the thrombosis sites, it was found that 5 venous thromboses (deep vein of the lower extremities, sigmoid sinus, hepatic vein) and 4 arterial thromboses (coronary, iliac, superior mesenteric artery) developed in the pre-2016 group and 2 deep vein thromboses of the lower extremities developed in the post-2016 group. When comparing the 2 groups with thrombotic complications, only Hgb, Hct and erythrocyte count (p=0.036) were significantly higher in the pre-2016 group (p=0.036 for all), and the other parameters were similar between the 2 groups.

At the end of the first year, only 1 (2%) patient in the post-2016 group experienced bleeding complications. At the last visit, bleeding occurred in 6 (12%) patients in the pre-2016 group and 1 (2%) patient in the post-2016 group (p=0.11). The duration of bleeding complications was 81.5±24.4 months in the pre-2016 group and 12 months in the post-2016 group. Bleeding sites were subcutaneous (n=1), nasal (n=1) and gastrointestinal bleeding (n=4) in the pre-2016 group and gastrointestinal bleeding in the post-2016 group. No significant difference was found between the two groups in terms of factors that may influence bleeding (p> 0.05).

At the end of the first year, MF was detected in 2 (4%) patients in the pre-2016 group and 1 (2%) patient in the post-2016 group (p=1). At the last visit, 11 (22%) patients in the pre-2016 group and 1 (2%) patient in the post-2016 group developed MF (p=0.006). The duration of MF development was 85.5±31.2 months in the pre-2016 group and 10 months in the post-2016 group. There was no significant difference between the two groups in terms of factors that may influence the development of MF (p>0.05). Splenomegaly was present in all patients who developed MF.

During follow-up, transformation to AML was observed in a total of 2 patients, 1 (2%) in the pre-2016 group and 1 (2%) in the post-2016 group. None of the patients developed MDS.

During the data analysis phase, 7 (14%) patients in the pre-2016 group and 4 (8%) patients in the post-2016 group died. However, the cause of death data could not be accessed.

4. Discussion

PV is the most common myeloproliferative neoplasm. Since 1892, when the disease was defined, both the diagnostic criteria and the treatment methods have changed. The most recent diagnostic criteria were updated by the WHO in 2016 (18). In our study, we aimed to compare our patients diagnosed in the five years before and after 2016 in terms of clinical and laboratory features and complications that developed during follow-up and to evaluate the impact of the change in diagnostic criteria on real life.

It has been reported that PV is more common in men(19, 20). In a study conducted in our country, the M/F ratio was found to be 1.5(21). In our study, PV was more common in men, similar to the literature, and the M/F

ratio was 1.5 in the pre-2016 group and 1.7 in the post-2016 group.

Most patients with PV are diagnosed in the fifth and sixth decades(22-24). In our study, the average age at diagnosis was also 58.5 years in the pre-2016 group and 62 years in the post-2016 group.

In a study of 141 patients conducted by Anger et al. (25), neurological symptoms were observed in 46% of the patients, pruritus in 18%, thrombosis in 18%, and hemorrhage in 8%. Sadia Sultan et al. (20) reported a symptomatic patient rate of 69.3%, with 30.8% experiencing headache, 23.1% experiencing abdominal pain, 11.5% experiencing pruritus, and 11.5% experiencing thrombosis. In our study, the rate of symptomatic patients was higher at 89%, with the most common symptoms being pruritus (36%), headache/dizziness (23%), and thrombosis (11%). The higher rate of symptomatic patients compared to the literature may be related to the consideration of non-specific symptoms such as sweating, fatigue, dyspnea, etc.

Tefferi et al(18) observed 46% HT, 18.3% hyperlipidemia and 8.4% DM in their study of 1545 patients. In the ECLAP study, HT was found in 39%, CHF in 8%, DM in 7% and hyperlipidemia in 4%(26). In a study of 195 patients from our country, HT was found in 51.8%, CHF in 23.1%, DM type 2 in 21% and LVO in 8.2% (27). In our study, DM was present in 29%, HT in 52%, CHD in 33%, LVO in 12%, PAH in 10% and COPD in 15%. Although the rates of comorbidity were similar to the study in our country, they were higher compared to other literature studies. It has been suggested that this may be related to differences in the general population structure.

Previous studies have observed that leukocytosis and thrombocytosis are associated in about half of PV patients (18, 28). In our study, leukocytosis was also observed in 51% and thrombocytosis in 47% of patients. While no significant difference was found in leukocytosis and thrombocytosis between the pre-and post-2016 groups (p=0.42), hemoglobin, hematocrit and erythrocyte count were higher in the pre-2016 group, reflecting the change in diagnostic criteria ($p<0.001$).

In the study by Muhammed Shariq Shaikh et al.(29), the thrombosis rate at diagnosis was approximately 14%. Tefferi et al.(18) found arterial thrombosis in 16% and venous thrombosis in 7.4% of patients before or at diagnosis. In the largest study completed in 2003 and conducted to date on PV, the pre-diagnosis major thrombosis rate was 38%, the pre-diagnosis major hemorrhage rate was 8%, the follow-up major thrombosis rate was 11.5%, death with thrombosis was 41%, and death with hemorrhage was 4.3% (30, 31). In our study, the number of patients with thrombosis at the time of diagnosis was 5 (10%) in the pre-2016 group and 6 (12%) in the post-2016 group; no patient with major bleeding symptoms and signs at presentation was observed. The rates were thought to be lower due to the small number of patients and differences in patient characteristics.

The most mortal complication in PV is thrombosis, and it has been observed that patients with thrombosis have 1.6 times higher mortality compared to the general population (32). In a study of 1213 patients conducted by the Italian Polycythemia Vera Study Group, thrombosis was observed in 19%, and arterial thrombosis rates of 62.5% and venous thrombosis rates of 37.5% were reported (33). In the follow-up of our study, thrombosis was found in 9 (18%) patients in the pre-2016 group and 2 (4%) patients in the post-2016 group. Although the number of patients with thrombosis was higher in the pre-2016 group, it did not reach statistical significance ($p = 0.055$). It was thought that the increase in the number of patients might change this result.

In the ECLAP study, being older than 65 years and having a history of thrombosis were reported as the 2 parameters that increased the possibility of thromboembolic events the most (34). In our study, the median age at diagnosis of PV in patients who developed thrombosis was 61 years in the pre-2016 group and 71.5 years in the post-2016 group. While our findings supported the ECLAP study in terms of age, our patients who developed thrombosis complications did not have a

history of thrombosis at the time of diagnosis. The higher rate of thrombosis complications in the pre-2016 group may be explained by the hyperviscosity caused by the high number of Hgb, Htc and erythrocytes at diagnosis and the longer follow-up period in the pre-2016 group.

Hemorrhagic complications are less common in PV patients compared to thrombotic complications and have been reported at a rate of 2–20% (35–37). In our study, hemorrhage was found in 6 (12%) patients in the pre-2016 group and 1 (2%) patient in the post-2016 group, which was compatible with the literature. Although not statistically significant, it was higher in the pre-2016 group. Among the pre-2016 patients who developed bleeding, 1 patient was on warfarin+ASA for superior mesenteric artery thrombosis, 2 patients were on ASA for CAD, 1 patient was on ASA for PAH, 1 patient was on rivaroxaban+ASA for pulmonary embolism detected at the time of PV diagnosis, and 1 post-2016 patient was on ASA for CVO. Only 1 patient who developed bleeding before 2016 had no history of antiaggregant or anticoagulant treatment. Considering the data of patients who developed bleeding, it can be explained that patients with comorbidities (such as CAD, PAH, or LVO) or patients who developed one complication may be more likely to develop another complication, but it can also be concluded that bleeding is more common in this group due to the use of more aggressive antiaggregant and anticoagulant therapy in patients with a history of thrombosis. When these results are evaluated together, it should be kept in mind that PV patients with a history of thrombosis and those under anticoagulant therapy should be monitored more closely for bleeding. In the ECLAP study, being older than 65 years and having a history of thrombosis were reported as the two parameters that increased the possibility of thromboembolic events the most (34). In our study, the median age at diagnosis of PV in patients who developed thrombosis was 61 years in the pre-2016 group and 71.5 years in the post-2016 group. While our findings supported the ECLAP study in terms of age, our patients who developed thrombosis complications did not have a history of thrombosis at the time of diagnosis. The higher rate of thrombosis complications in the pre-2016 group may be explained by the hyperviscosity caused by the high number of Hgb, Htc, and erythrocytes at diagnosis and the longer follow-up period in the pre-2016 group.

It is known that the risk of transformation to leukemia and/or MF in the course of PV patients is higher than in the normal population. However, a parameter that can determine the risk of transformation has not been defined. MF transformation in PV patients has been reported to be in the range of 11–20%, and the time until MF transformation has been reported to be 7–10 years (38–40). Our study is compatible with the literature in terms of the number of patients who developed MF (22% before 2016 and 2% after 2016, $p = 0.006$). The duration of MF development was 85.5±31.2 months in the pre-2016 group and 10 months in the post-2016 group. In our study, AML transformation was detected in 1 (2%) patient in the pre-2016 group and 1 (2%) patient in the post-2016 group, while no patient was found to have MDS transformation. Before and after 2016, there was no significant difference between the two groups when patients with MF progression were compared in terms of age at diagnosis, gender, comorbidities, splenomegaly, laboratory values at diagnosis, bone marrow pathology findings, and treatments given.

In a study published in China including 272 PV patients, the development of MF was found to be associated with splenomegaly and leucocytosis (38). Passomonti et al. (41) concluded that leucocytosis may be effective in progression. In the same study, JAK2 positivity was observed in 91–100% of the patients, and it was mentioned that 96% of the patients who progressed received myelosuppressive treatment. In our study, splenomegaly was present in all patients with MF, consistent with the literature. Since all patients were selected from JAK2-positive patients, its effect could not be evaluated. The mean leukocyte count of the patients was 34055/µl in the pre-2016 group and 9600/µl in

the post-2016 group, and all patients were receiving cytoreductive treatment.

Since it was thought that there might be a change in the frequency of complications due to differences in the follow-up period, the frequency of complications at the end of the first year was also evaluated for both groups. The fact that no significant difference was found between the two groups in this evaluation was thought to be due to the insufficient number of patients in the two groups.

There were certain limitations in our study. Firstly, our study was designed retrospectively. Therefore, there were data losses and patients lost to follow-up. This led to the exclusion of patients whose predetermined data could not be accessed and a decrease in the number of patients.

In conclusion, although the number of patients who developed complications in PV was higher in the pre-2016 group, a statistically significant difference was found only in the development of MF. It was thought that the higher number of patients with complications in the pre-2016 group may be related to the higher hemoglobin, hematocrit, and erythrocyte counts at the time of diagnosis and the longer follow-up period. It was concluded that the change in the diagnostic criteria had a positive effect in terms of follow-up of complications, and with larger studies, a significant difference in terms of other complications may occur in real life.

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Ethics

Ethics Committee Approval: The study was approved by Eskişehir Osmangazi University Noninterventional Clinical Research Ethical Committee (Decision no: 15, Date: 13.07.2021).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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