Original article

Clinical characteristics and outcomes of patients with polycythemia vera in Thailand: a single center study

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Abstract:

Introduction: *The JAK2V617F mutation is the most common mutation among patients with polycythemia vera (PV). This study aimed to determine the clinicopathological profiles and outcomes of Thai patients with PV.* ***Methods:*** *A retrospective analysis was performed of all PV cases diagnosed at our single institute between January 2010 and December 2019. Their age, sex, clinical presentations, laboratory investigations, treatments, and follow-up durations were analyzed. Appropriate statistics were used to analyze the data.* ***Results:*** *Sixty patients received a diagnosis of PV during the study. At diagnosis, median age was 58 (range, 26-85) years (21.7% female). The most common initial clinical findings were erythrocytosis from check-up (43.3%), dizziness (23.3%) and arterial thrombosis (21.7%). Of the 73.3% patients positive for the JAK2V617F mutation, their mean hemoglobin level was 18.28 g/dL (SD 3.08), and hematocrit level was 58.25% (SD 8.95). The median follow-up time was 27.6 months. Sixty percent (n = 35) of the entire patient cohort was treated with phlebotomy, hydroxyurea, and aspirin, either alone or combined. None of the patients transformed to myelofibrosis or myelodysplasia during the follow-up period. We found no association between leukemic transformation and hydroxyurea use.* ***Conclusion:*** *Although the JAK2V617F mutation remains the most common mutation among Thai patients with PV, its prevalence in this study was remarkably lower than those in related reports. Moreover, bleeding was an uncommon initial clinical manifestation among this study cohort.*

Keywords : ● *Polycythemia vera* ● *Myeloproliferative neoplasm* ● *Clinicopathological features* ● *JAK2V617F mutation*

J Hematol Transfus Med. 2021;31:57-64.

Received 9 July 2020 Corrected 15 July 2020 Accepted 18 December 2020

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นิพนธ์ต้นฉบับ

ลักษณะทางคลินิกและผลการรักษาผู้ป่วยโรคเลือดข้นในประเทศไทย: การศึกษาจากหนึ่งสถาบัน

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บทคัดย่อ

บทนำ *การกลายพันธุ์ของผู้ป่วยโรคเลือดข้น (polycythemia vera) ที่พบบ่อยที่สุด คือ การกลายพันธุ์แบบ JAK2V617F* ***วัตถุประสงค์*** *เพื่อศึกษาอาการและอาการแสดงทางคลินิก ลักษณะทางพยาธิวิทยา การรักษาในผู้ป่วยที่ได้รับการวินิจฉัยโรคเลือดข้นระหว่างเดือนมกราคม พ.ศ.2553 ถึง เดือนธันวาคม พ.ศ.2562* ***ผลการศึกษา*** *มีผู้ป่วยที่ได้รับการวินิจฉัย 60 ราย ค่ามัธยฐานของอายุ 58 ปี (พิสัย 85-26) เป็นผู้หญิงร้อยละ 21.7 ลักษณะทางคลินิกที่พบบ่อยที่สุด ได้แก่ การตรวจพบระดับฮีโมโกลบินสูงโดยบังเอิญจากการตรวจเลือด (ร้อยละ 43.3) รองลงมาคือ อาการมึนศีรษะ (ร้อยละ23.3) และภาวะหลอดเลือดแดงอุดตัน (ร้อยละ 21.7) ในผู้ป่วยที่มีการกลายพันธุ์ของยีน JAK2V617F (ร้อยละ 73.3) ค่าเฉลี่ยระดับฮีโมโกลบิน 18.28 กรัม/ดล. ค่าเฉลี่ยระดับฮีมาโทคริตร้อยละ 58.25 ระยะเวลาในการติดตามผู้ป่วยอยู่ที่ 27.6 เดือน มีผู้ป่วยร้อยละ 60 ได้รับการรักษาด้วยการทำ phlebotomy, การให้ยาแอสไพรินและ/หรือยา hydroxyurea ในระหว่างการศึกษาไม่พบผู้ป่วยมีการดำเนินโรคกลายเป็น myelofibrosis และ myelodysplastic syndrome การให้ยา hydroxyurea ไม่พบว่าทำให้ผู้ป่วยมีการดำเนินโรคกลายเป็น acute leukemia* ***สรุป*** *การกลายพันธุ์ที่พบมากที่สุดในผู้ป่วยโรคเลือดข้นคือ JAK2V617F โดยความชุกของรายงานการศึกษานี้พบน้อยกว่าที่ผ่านมา นอกจากนี้พบว่าภาวะเลือดออก เป็นลักษณะทางคลินิกที่พบได้น้อย*

คำสำคัญ : ● *โรคเลือดข้น* ● *กลุ่มโรคไขกระดูกผลิตเม็ดเลือดมากผิดปกติ* ● *ลักษณะทางคลินิกและพยาธิวิทยา* ● *การกลายพันธุ์แบบ JAK2V617F*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2564;31:57-64.

Introduction

Myeloproliferative neoplasms (MPNs) are clonal disorders of hematopoietic stem cells characterized by an overproduction of one or more myeloid cell lineages. According to the World Health Organization[1,2] classifications, MPNs comprise chronic myeloid leukemia, polycythemia vera (PV), essential thrombocythemia, primary myelofibrosis, chronic neutrophilic leukemia, chronic eosinophilic leukemia-not otherwise specified, and unclassifiable myeloproliferative neoplasms. Patients with PV attend the hospital either because of erythrocytosis during an annual health checkup; or MPNs-related symptoms, such as pruritus, dizziness, headaches, erythromelalgia, thrombosis or hemorrhage. The *JAK2*V617F mutation, the most common mutation found among patients with PV, accounts for 95% of all mutations[3, 4]. In general, *JAK2*V617F is correlated with patients of an older age, higher hemoglobin (Hb) levels, leukocytosis and lower platelet counts; as well, the 3 health conditions tend to have an aggressive nature[5]. Patients with the *JAK2*V617F mutation are not similar to patients with *JAK2* exon 12 mutated PV who predominantly present with erythroid myelopoiesis and are at a younger age at diagnosis[6]. The transformation of PV to acute myeloid leukemia, myelodysplastic syndrome or myelofibrosis is a major cause of death[7]. The median survival in cases of treated PV is 14 years[8,9]. The treatment goal is to relieve symptoms and prevent thrombosis without increasing the risk of bleeding. The therapeutic modalities are based on risk stratification and include phlebotomy, low dose aspirin, hydroxyurea and interferon-alpha; all have been described and are well-documented.[10–16] This study aimed to compile and analyze PV clinicopathological profiles and patient outcomes in southern Thailand.

Materials and methods

This retrospective analysis was performed at the Hematology Unit, Vachira Phuket Hospital. The study was approved by the Institutional Ethics Committee. All patients with newly diagnosed PV between January 2010 and December 2019 were enrolled. The hospital's electronic medical records were searched for patients with PV using the ICD1-10 code, and cases not fit for diagnosis were excluded. Overall, 64 patients came to the hospital during the 10-year study period. Four were excluded for being incompatible with the latest PV diagnostic criteria, used the 2008, 2016 WHO classification and diagnostic criteria for PV leaving 60 cases for analysis. PV has 2 risk categories: high risk (age > 60 years or a history of thrombosis) and low-risk (the absence of both risk factors). Their clinical details (age, sex, clinical presentations, laboratory investigations, treatment and follow-up duration) were compiled and analyzed. IBM SPSS Statistics for Windows, Version 19.0 (IBM Corp., Armonk, NY, USA) was used to analyze data. Continuous variables were expressed as mean ± standard deviation or median (minimum, maximum). To compare the continuous variables, Student's t-test or the Mann–Whitney U test were utilized. Categorical variables were represented as frequency and percentage, and Fisher's exact or the Chi-squared test was used to compare the results. The overall survival rate was assessed using a Kaplan-Meier curve. All results were considered statistically significant when the *p*-value was < 0.05.

Results

A total of 60 patients with a diagnosis of PV were enrolled in this study. At diagnosis, their median age was 58 years (range, 26-85 years), and 21.7% were female. The age and sex distribution of the study population are detailed in Table 1. The common initial clinical findings included erythrocytosis discovered during a recent annual health checkup (43.3%), dizziness (23.3%) and arterial thrombosis (21.7%). Other disease features included fatigue, vasomotor symptoms, palpable splenomegaly, and much less frequently, major hemorrhage at diagnosis. Arterial thrombosis consisted of acute ischemic stroke (13.3%), acute myocardial infarction

Table 1 Sex-stratified outline of baseline characteristics of PV patients

	All patients (n = 60)	Male (n = 47)	Female (n = 13)	*p*-value[#]
Median ages (minimum, maximum)	58 (26, 85)	57 (26, 85)	61 (30, 83)	0.572
Initial clinical presentation				
Checkup-found erythrocytosis	26 (43.3%)	21 (44.7%)	5 (38.5%)	0.760
Dizziness	14 (23.3%)	12 (25.5%)	2 (15.4%)	0.713
Fatigue	2 (3.3%)	1 (2.1%)	1 (7.7%)	0.389
Vasomotor symptom	3 (5.0%)	2 (4.3%)	1 (7.7%)	0.526
Palpable spleen	2 (3.3%)	1 (2.1%)	1 (7.7%)	0.389
Arterial thrombosis before/at diagnosis	13 (21.7%)	11 (23.4%)	2 (15.4%)	0.713
Venous thrombosis before/at diagnosis	1 (1.7%)	1 (2.1%)	0 (0.0%)	1.000
Major hemorrhage before/at diagnosis	1 (1.7%)	1 (2.1%)	0 (0.0%)	1.000
Site of arterial thrombosis before/at diagnosis				0.835
No	47 (78.3%)	36 (76.6%)	11 (84.6%)	
Acute ischemic stroke	8 (13.3%)	6 (12.8%)	2 (15.4%)	
Transient ischemic attack	1 (1.7%)	1 (2.1%)	0 (0.0%)	
Acute myocardial infarction	3 (5.0%)	3 (6.4%)	0 (0.0%)	
Other site	1 (1.7%)	1 (2.1%)	0 (0.0%)	
Site of venous thrombosis before/at diagnosis				1.000
No	59 (98.3%)	46 (97.9%)	13 (100.0%)	
Deep vein thrombosis	1 (1.7%)	1 (2.1%)	0 (0.0%)	
site of major hemorrhage				N/A
No	60 (100.0%)	46 (100.0%)	13 (100.0%)	
History of tobacco use	9 (15.0%)	9 (19.1%)	0 (0.0%)	0.184
History of diabetes mellitus	7 (11.7%)	4 (8.5%)	3 (23.1%)	0.166
History of dyslipidemia	18 (30.0%)	13 (27.7%)	5 (38.5%)	0.504
History of coronary artery disease	2 (3.3%)	2 (4.3%)	0 (0.0%)	1.000
History of chronic kidney disease	4 (6.7%)	3 (6.4%)	1 (7.7%)	1.000
History of chronic obstructive pulmonary disease	2 (3.3%)	2 (4.3%)	0 (0.0%)	1.000
History of cerebrovascular disease	6 (10.0%)	6 (12.8%)	0 (0.0%)	0.324
History of gout	2 (3.3%)	2 (4.3%)	0 (0.0%)	1.000

Data are presented as n (%); [#]Fisher's exact or chi-squared test; N/A = not applicable

(5%) and transient ischemic attack (1.7%). Venous thrombosis was uncommon. In this study, only 1 patient (1.7%) was found to have deep vein thrombosis. The hematological parameters of the study population are presented in Table 2. A higher Hb level was more frequent among men than women (19.0 g/dL vs.16.4 g/dL; $p < 0.01$). In contrast, thrombocytosis was significantly higher among women than the men (380 x10^9/L vs. 750 x10^9/L; $p < 0.01$).

In all, 73.3% of patients were found to be positive for the *JAK2*V617F mutation, having a median Hb level of 18.3 g/dL. A higher leukocyte count level (17.18 x 10^9/L. vs. 10.00 x10^9/L; $p < 0.01$) and a higher platelet count (537 x10^9/L vs. 234 x10^9/L; $p < 0.01$) were significantly found among the *JAK2*V617F mutation-positive patients than the *JAK2*V617F mutation-negative patients.

Of the 40 patients with PV, classified as the high risk group, thirteen (21.7%) experienced arterial thrombosis comprising 1 (1.7%) venous thrombosis and 1 (1.7%) major hemorrhage. Their median follow-up period was 27.6 months. Thirty-seven of 58 patients (64%) continued their follow-up at the hospital's Hematology Clinic; 60% (n = 35) of patients were treated with phlebotomy, hydroxyurea, and aspirin either alone or combined. None of the

Table 2 Hematological parameters of the study population

Hematological parameter	All patients (n = 60)	Male (n = 47)	Female (n = 13)	*p*-value[#]
Hemoglobin (g/dL)	18.44 (3.00)	19.01 (2.70)	16.35 (3.20)	0.004*
Hematocrit (%)	58.10 (8.91)	59.64 (7.73)	52.56 (10.89)	0.044*
Mean cell volume (fl)	80.65 (9.97)	82.22 (9.68)	74.96 (9.22)	0.019*
Leukocyte count (x10^9/L)	15.36 (14.17)	15.58 (15.63)	14.55 (7.06)	0.819
Leukocytosis (> 10.5 x10^9/L)				1.000
● No	23 (38.3%)	18 (38.3%)	5 (38.5%)	
● Yes	37 (61.7%)	29 (61.7%)	8 (61.5%)	
Platelet count (x10^9/L)	450 (80, 1807)	380 (80, 1728)	750 (308, 1807)	0.006*
Thrombocytosis (> 450 x 10^9/L)				
● No	31 (51.7%)	27 (57.4%)	4 (30.8%)	
● Yes	29 (48.3%)	20 (42.6%)	9 (69.2%)	
Extreme thrombocytosis (> 1,000 x10^9/L)				0.059
● No	52 (86.7%)	43 (91.5%)	9 (69.2%)	
● Yes	8 (13.3%)	4 (8.5%)	4 (30.8%)	

Data are presented as mean (SD), median (minimum, maximum), or n (%); # Independent t-test or Mann–Whitney U test was used for continuous data and Fisher's exact or chi-squared test for categorical data.

Table 3 Clinical features and hematological parameters of patients with and without the *JAK2*V617F mutation

	***JAK2*V617F mutation-positive PV (n = 44)**	***JAK2*V617F mutation-negative PV (n = 16)**	***p*-value[#]**
Initial clinical presentation			
Checkup-found erythrocytosis	19 (43.2%)	7 (43.8%)	1.000
Dizziness	10 (22.7%)	4 (25%)	1.000
Fatigue	2 (4.5%)	0 (%)	1.000
Vasomotor symptom	3 (6.8%)	0 (%)	0.558
Palpable spleen	2 (4.5%)	0 (%)	1.000
Arterial thrombosis before/at diagnosis	10 (22.7%)	3 (18.8%)	1.000
Venous thrombosis before/at diagnosis	0 (%)	1 (6.3%)	0.267
Major hemorrhage before/at diagnosis	1 (2.3%)	0 (%)	1.000
Hematologic parameter			
Hemoglobin (g/dL)	18.28 (3.08)	18.88 (2.82)	0.498
Hematocrit (%)	58.25 (8.95)	57.69 (9.06)	1.000
Mean cell volume (fl)	77.80 (8.34)	88.47 (10.12)	0.832
Leukocyte count (x10^9/L)	17.18 (15.83)	10.00 (5.87)	< 0.001*
Leukocytosis (> 10.5 x10^9/L)			0.098
● No	12 (27.3%)	11 (68.7%)	0.006*
● Yes	32 (72.7%)	5 (31.3%)	
Platelet count (x10^9/L)	537 (111, 1807)	234 (80, 802)	0.001*
Thrombocytosis (> 450 x10^9/L)			0.008*
● No	18 (40.9%)	13 (81.3%)	
● Yes	26 (59.1%)	3 (18.7%)	
Extreme thrombocytosis (> 1,000 x10^9/L)			0.095
● No	36 (81.8%)	16 (100%)	
● Yes	8 (18.2%)	0 (%)	

Data are presented as mean (SD), median (minimum, maximum), or n (%); [#]Independent t-test or Mann–Whitney U test was used for continuous data and Fisher's exact or chi-squared test for categorical data

Table 4 Treatment details and follow-up of patients continuing their treatment in our study

Treatment	Polycythemia vera, N (%)
Aspirin	60 (100.0%)
Hydroxyurea	46 (76.7%)
Anagrelide	2 (3.3%)

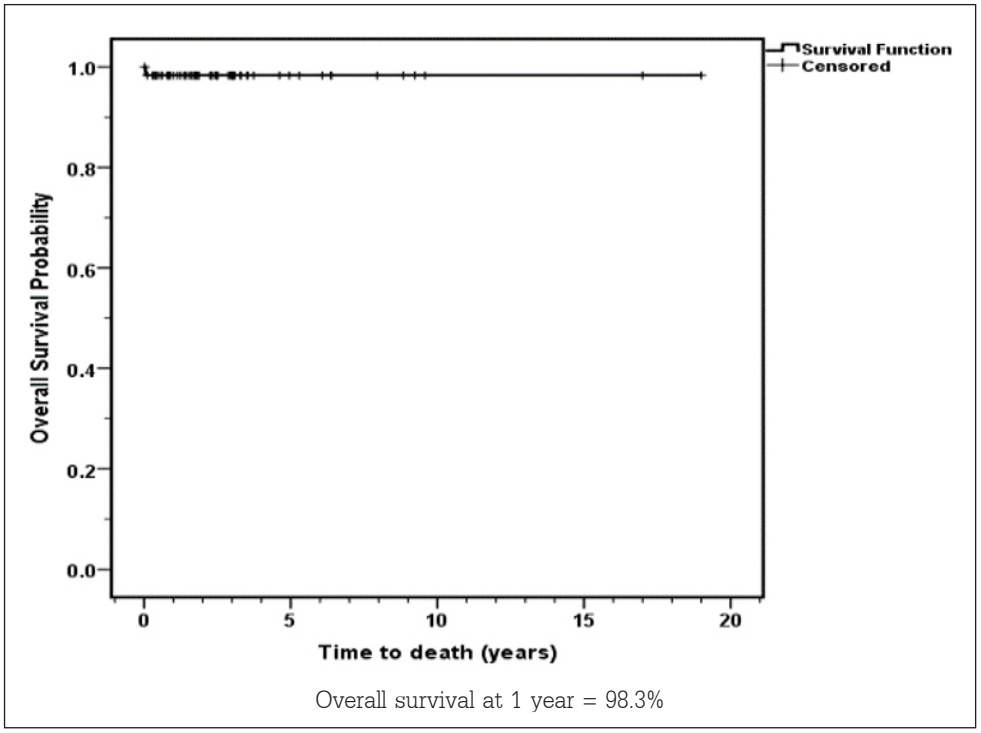

Figure 1 Kaplan–Meier curve of overall survival

patients transformed to myelofibrosis or myelodysplasia during the follow-up period. No association was found between leukemic transformation and hydroxyurea use. The 1-year overall survival rate was 98.3% (Figure 1).

Discussion

Our study analyzed the clinical features and laboratory findings of Thai patients with PV, and revealed several important characteristics. Firstly, while the median age at presentation of the patients with PV in our study was comparable to related results[9], the sex distribution differed markedly from international data.[9] Specifically, although a female-to-male ratio of 1:1 has been reported in a large internationalstudy[9], men were considerably more common in our study, with a male:female ratio of 4:1. Almost half of the patients were asymptomatic and received a new diagnosis in our study as a result of erythrocytosis being discovered during a health check-up. Palpable splenomegaly, pruritus and vasomotor symptoms occurred among only 5% of patients, whereas the prevalence of these conditions has been reported to be as high as one third of related reports.[9] Arterial thrombosis was present in 21.7% (13/60) of patients with PV, comparable with published international data.[9] Venous thrombosis was uncommon in this study, but an international study found that the condition occurred significantly more often in males than females (9.3% vs. 5.4%; $p < 0.01$).[9] On the other hand, thrombocytosis was more frequent among the women in the present study, which was consistent with the findings of an international study.[9]

Unexpectedly, only 73.3% of patients in this study were found to be positive for the *JAK2*V617F mutation. This proportion was much lower than that reported by several other studies, in which the prevalence of that mutation was reported to account for as much as 95% of

all mutations among patients PV[4]. Those patients, not presenting the *JAK2*V617F mutation, were compatible with PV diagnosis including high hemoglobin level, panmyelosis in bone marrow biopsy and low to normal serum erythropoietin. Unfortunately for these patients, we didn't work up due to financial considerations and limitation of the Universal Health Insurance rights and social security rights. In the current research, patients with the *JAK2*V617F mutation had high leukocyte counts and low platelet counts. This somewhat differed from the general situation, in which *JAK2*V617F has been found to cluster with older ages, a higher Hb level, leukocytosis and a lower platelet count. The mutation is also often said to be associated with the more aggressive nature of these conditions.[5]

For the patients with PV in the low risk group who continued their follow-up at our hospital, aspirin and phlebotomy were the most common treatment modalities. As to the patients with PV in the high risk group, aspirin and hydroxyurea were typically prescribed. In the case of those patients requiring phlebotomy, the follow-up period was 22.8 months (range, 0.0-226.9).

No patient transformed to myelofibrosis or myelodysplasia during the follow-up period; however, this might have been the result of the follow-period being relatively short. In large international studies, leukemic transformation was associated with treatment exposure to pipobroman or P32/chlorambucil.[9] The present work; however, found no association between leukemic transformation and hydroxyurea use. The next study should increase the time for follow-up.

Conclusion

While the *JAK2*V617F mutation remains the most common mutation among Thai patients with PV, its prevalence was remarkably lower than the levels noted by related reports. Moreover, thrombosis and bleeding were uncommon initial clinical manifestations among this study cohort.

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