นิพนธ์ต้นฉบับ

อุบัติการณ์และปัจจัยเสี่ยงต่อการเกิดลิ่มเลือดอุดตันเมื่อเริ่มวินิจฉัยโรค Polycythemia vera (PV)

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ความเป็นมา

ภาวะลิ่มเลือดอุดตันในโรค Polycythemia vera (PV) ส่งผลกระทบต่อการเจ็บป่วยและอัตราการเสียชีวิต ที่ปัจจัยเสี่ยงต่อการเกิดลิ่มเลือดอุดตันยังคงมีความหลากหลาย

วัตถุประสงค์

เพื่อศึกษาอุบัติการณ์ของภาวะลิ่มเลือดอุดตันในผู้ป่วย PV รวมถึงปัจจัยเสี่ยงและผลลัพธ์ทางคลินิก รวมทั้งการรอดชีวิตโดยปราศจากภาวะลิ่มเลือดอุดตัน และอัตราการรอดชีวิตโดยรวม (Overall survival; OS)

วิธีการศึกษา

ทำการเก็บข้อมูลย้อนหลังตั้งแต่ มกราคม พ.ศ.2543 ถึง พฤศจิกายน พ.ศ. 2566 ในโรงพยาบาลพระมงกุฎเกล้า ผู้ป่วยที่ได้รับการวินิจฉัยเป็น PV (ตามเกณฑ์ WHO 2022) จะถูกรวบรวมเข้าสู่งานวิจัย โดยเก็บข้อมูลพื้นฐาน ความเสี่ยงต่อหัวใจและหลอดเลือด ปัจจัยเสี่ยงต่อการเกิดภาวะลิ่มเลือดอุดตัน และค่าทางห้องปฏิบัติการ

ผลการศึกษา

รวบรวมข้อมูลผู้ป่วยจำนวน 190 ราย ถูกรวบรวมเข้าสู่งานวิจัย (เพศชายร้อยละ 73.68) อายุเฉลี่ย 60.94±13.83 ปี ค่ามัธยฐานของการติดตามผู้ป่วยอยู่ที่ 3.13 ปี ผู้ป่วยร้อยละ 65.79 จัดเป็นผู้ป่วยความเสี่ยงสูงตาม ELN โดยพบภาวะลิ่มเลือดอุดตัน 67 ราย (ร้อยละ 35.26) ที่เกิดก่อนหรือขณะวินิจฉัย PV ส่วนใหญ่เป็นหลอดเลือดแดงอุดตัน พบปัจจัยเสี่ยงต่อหัวใจและหลอดเลือด ได้แก่ ความดันโลหิตสูง (ร้อยละ 75.79) ไขมันโลหิตสูง (ร้อยละ 56.84) เบาหวาน (ร้อยละ 50) สูบบุหรี่ (ร้อยละ 34.74) ผู้ป่วยร้อยละ 73.16 พบการกลายพันธ์ของยีน *JAK2*^{V617F} ระดับฮีโมโกลบินเฉลี่ย 18.08±1.84 ก./ดล. ค่ามัธยฐานของเม็ดเลือดขาวและเกล็ดเลือดอยู่ที่ 11,270/ลบ.มม. (IQR: 8,200-16,600) และ 387,000/ลบ.มม. (IQR: 245,000-611,000) การวิเคราะห์พหุตัวแปรพบว่า อายุ ≥60 ปี (aOR 2.30; 95% CI: 1.21-4.38) เพศหญิง (aOR 1.60; 95% CI: 0.80-3.19) และเม็ดเลือดขาว >11,000/ลบ.มม. (aOR 1.81; 95% CI: 0.96-3.41) เป็นปัจจัยเสี่ยงที่สัมพันธ์ต่อการเกิดภาวะลิ่มเลือดอุดตันก่อนหรือขณะวินิจฉัย PV พบการเกิดภาวะลิ่มเลือดอุดตันภายหลังการวินิจฉัย PV อยู่ที่ร้อยละ 8.95 โดยมีอุบัติการณ์สะสมที่ 10 ปี อยู่ที่ร้อยละ 19.53 การรอดชีวิตโดยปราศจากภาวะลิ่มเลือดอุดตันและ OS ที่ 10 ปี จะต่ำลงในผู้ป่วยที่มีภาวะลิ่มเลือดอุดตันก่อนหรือขณะวินิจฉัย PV โดยอยู่ที่ร้อยละ 59.65 กับ 76.71 (p=0.2037) และ ร้อยละ 67.06 กับ 87.54 (p=0.027) ตามลำดับ

บทสรุป

อุบัติการณ์การเกิดลิ่มเลือดอุดตันที่เกิดก่อนหรือขณะวินิจฉัย PV ใกล้เคียงกับการศึกษาก่อนหน้า โดยจากปัจจัยเสี่ยงที่วิเคราะห์พบว่า อายุ ≥60 ปี เป็นปัจจัยเสี่ยงสำคัญเพียงชนิดเดียวที่มีนัยสำคัญทางสถิติ

คำสำคัญ: ● *Polycythemia vera* ● *ภาวะลิ่มเลือดอุดตัน* ● *ปัจจัยเสี่ยง* ● *การรอดชีวิต*

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Original article

Incidence and Risk Factors Associated with Thrombosis at Presentation of Polycythemia Vera (PV)

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Background

Polycythemia vera (PV) thromboembolism has a significant impact on morbidity and mortality, with a variety of risk factors.

Aims

To evaluate the incidence of thrombosis in PV patients, identify associated risk factors, and assess clinical outcomes, including thrombosis-free survival and overall survival (OS).

Methods

Data from Phramongkutklao Hospital (January 2000 to November 2023) were retrospectively analyzed. Patients diagnosed with PV (WHO 2022 criteria) were included, and demographic information, cardiovascular risk factors, thrombotic events, and laboratory data were collected.

Results

We enrolled 190 patients (73.68% male) with a mean age of 60.94±13.83 years and a median follow-up period of 3.13 years. Of these, 65.79% were classified as ELN high-risk. Thrombosis occurred in 67 patients (35.26%) either before or at PV diagnosis, with predominantly arterial. Key cardiovascular risk factors included hypertension (75.79%), dyslipidemia (56.84%), diabetes mellitus (50%), and smoking (34.74%). The *JAK2*^{V617F} mutation was present in 73.16%. Mean hemoglobin was 18.08±1.84 g/dL; median WBC and platelet counts were 11,270/mm³ (IQR: 8,200-16,600) and 387,000/mm³ (IQR: 245,000-611,000), respectively. Multivariable analysis identified age ≥60 years (aOR 2.30; 95% CI: 1.21-4.38), female (aOR 1.60; 95% CI: 0.80-3.19), and WBC >11,000/mm³ (aOR 1.81; 95% CI: 0.96-3.41) as factors associated with thrombosis either before or at PV diagnosis. Post-diagnosis thrombosis occurred in 8.95%, with a 10-year cumulative incidence of 19.53%. Thrombosis-free survival and overall survival (OS) at 10 years were lower in the thrombosis group either before or at diagnosis group, at 59.65% vs. 76.71% (p=0.2037) and 67.06% vs. 87.54% (p=0.027), respectively.

Conclusions

The incidence of thrombosis occurring either before or at the time of PV diagnosis is consistent with findings from previous studies. Among the factors analyzed, age ≥60 years is the only statistically significant risk factor.

Keywords: ● *Polycythemia vera* ● *thrombosis* ● *risk factors* ● *survival*

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Introduction

Polycythemia vera (PV) is a myeloproliferative neoplasm (MPN) characterized by the abnormal proliferation of red blood cells due to dysregulation in bone marrow function. This condition is associated with mutations in the JAK2 gene (97% JAK2 V617F; 3% JAK2 exon12), leading to uncontrolled production of blood cells. Clinically, patients with PV usually present with a variable degree of disease-related symptoms including fatigue, pruritus, and night sweats, as well as a range of symptoms driven by high red blood cell mass, such as headachesand difficulties with concentration.[1,2] Other significant concerns of PV are the risk of thromboembolic events, both arterial and venous, and the risk of progression to acute myeloid leukemia (AML).[3,4]

Thrombotic complications in PV are more prevalent compared to other MPNs[5,6] and are a major cause of morbidity and mortality with a reported incidence of 12% to 39%.[7] Advancing age, along with a history of previous thrombosis, are major risk factors for thrombosis and contribute to the risk classification of PV into low risk (no history of thrombosis and age <60 years) and high risk (history of thrombosis or age ≥60 years) by the European LeukemiaNet (ELN).[8,9] Additional risk factors for thrombosis include the presence of cardiovascular risk factors; high-risk mutations such as ASXL1, DNMT3A, TET2 and/or BCOR/BCORL1, a high JAK2 allele burden, leukocytosis, uncontrolled hematocrit, and a diagnosis within the first 3 months.[2] However, conflicting results regarding thrombosis risk factors have been reported in PV studies.

A previous study in Thailand reported the incidence of thrombosis either before or at PV diagnosis to be 23.3%, mostly involving arterial thrombosis.[10] However, it did not include an analysis of risk factors associated with thrombosis in PV patients. Another study reported an incidence of thrombosis in PV at 24.3%, but without details of the timing of the thrombosis.[11] In this study, our aims were to explore the incidence and risk factors associated with thrombosis, particularly either before or at the time of PV diagnosis. Additionally, we sought to evaluate the long-term clinical outcomes in PV patients to provide a comprehensive understanding of Thai PV patients.

This study aimed to evaluate the incidence of thrombosis in PV patients before, at, and after PV diagnosis, and to assess the risk factors associated with thrombosis occurring either before or at PV diagnosis. Additionally, we analyzed the rates of transformation to myelofibrosis and acute leukemia. Thrombosis-free survival and overall survival (OS) were examined.

The primary outcome of this study was the incidence of thrombosis either before or at the time of PV diagnosis. Secondary outcomes included the cumulative incidence of thrombosis after PV diagnosis, transformation to myelofibrosis and AML, thrombosis-free survival, and OS.

Materials and methods

Study participants

All patients diagnosed with PV according to the 5th edition of WHO criteria[1] at Phramongkutklao Hospital between 1 January 2010 and 30 November 2023 were included in the study.

Study design

This was a retrospective descriptive study approved by the Institutional Review Board of the Royal Thai Army Medical Department (approval number IRBRTA 1581/2566). The study was conducted in accordance with the Declaration of Helsinki and followed the International Conference on Harmonization Guidelines for Good Clinical Practice.

Sample size calculation

A study from Italy on PV patients with a 20-year follow-up reported that the incidence of thrombosis either before or at the time of PV diagnosis was 34%,[12] while a report from Thailand reported a lower incidence of 23.3%.[10] Therefore, a total sample of 145 patients was needed to detect a change in proportion difference of 10.7% with 80% power using a 5% level two-sided test.

Methods

We searched the ICD-10 codes, including polycythemia vera (D45), secondary polycythemia (D751), and erythrocytosis (D75), in electronic medical records at Phramongkutklao Hospital, Bangkok, Thailand, between January 2010 and November 2023. Only patients who met the diagnostic criteria for PV[1] were enrolled in the study. Cases that did not meet the criteria for PV were excluded.

Demographic data, cardiovascular risk factors, driver mutation status, treatments, complications encompassing both thrombosis and bleeding, and laboratory results at diagnosis and post-treatment were collected. The incidences of hydroxyurea or hydroxycarbamide (HU) intolerance/resistance, transformation to myelofibrosis, development of AML, and mortality were also gathered.

Statistical analysis

Categorical variables were expressed as frequencies and percentages. Continuous variable data were presented as mean ± standard deviation (SD) or as median and interquartile range (IQR). Categorical data were compared using the Chi-square test or Fisher's exact test, while continuous data were assessed using the independent T-test or Mann-Whitney U test.

Survival analysis was conducted using Kaplan-Meier curves, and the log-rank test was employed to compare survival curves. The cumulative incidence of thrombosis after PV diagnosis and the transformation to myelofibrosis or acute leukemia were estimated using the Kaplan-Meier method. Patients who died or were lost to follow-up were censored at the time of death or their last follow-up.

To investigate factors associated with thrombosis, logistic regression models were utilized. Variables with a p-value <0.2 in univariable analysis were selected for multivariable analysis.

All statistical analyses were performed using STATA software, Version 17.0 (Stata Corp.,

College Station, TX, USA). All p-values were two-sided; a p-value of less than 0.05 was considered statistically significant.

Results

Clinical characteristics (Table 1)

We identified 420 patients from electronic medical records, but only 190 individuals were diagnosed with PV and included in this study, with a median follow-up time of 3.13 years (IQR: 0.88-6.61). Sixty-seven patients (35.26%; 95% confidence interval [CI]: 28.49-42.51) were found to have thrombosis either before or at PV diagnosis, with 32 patients (16.84%) having thrombosis prior to PV diagnosis. One hundred and twenty-five patients (65.79%) were classified as the high-risk group by ELN. At diagnosis, the mean age of all patients was 60.94 ± 13.83 years, with 54.74% being aged ≥60 years. The proportion of patients aged ≥60 years was higher in the thrombosis-before-or-at-PV-diagnosis group than the no-thrombosis group (68.66% vs. 47.15%; p-value = 0.006). Males (73.68%) were more predominant than females (26.32%) in PV patients. However, the proportion of females in the thrombosis-before-or-at-PV-diagnosis group was higher than in the no-thrombosis group (35.82% vs. 21.14%; p-value = 0.038). Cardiovascular risk factors that were commonly found in the PV patients were hypertension (75.79%), dyslipidemia (56.84%), diabetes mellitus (50%), and smoking (34.74%), with no significant difference between the thrombosis-before-or-at-PV-diagnosis group and the no-thrombosis group (Table 1).

Table 1. Baseline characteristics of the patients

Characteristic	All	Thrombosis either before/ or at PV diagnosis	No thrombosis either before/ or at PV diagnosis	P-value
	N = 190 (100%)	N = 67 (35.26%)	N = 123 (64.74%)	
Age				
Mean ± SD -- yr	60.94 ± 13.83	64.46 ± 13.95	59.02 ± 13.44	0.009
Age ≥60 yr -- no. (%)	104 (54.74)	46 (68.66)	58 (47.15)	0.006
Sex				0.038
Male -- no. (%)	140 (73.68)	43 (64.18)	97 (78.86)	
Female -- no. (%)	50 (26.32)	24 (35.82)	26 (21.14)	
Median follow-up time (IQR) -- yr	3.13 (0.88-6.61)	2.52 (0.55-6.57)	3.39 (1.08-6.63)	0.375
Underlying disease -- no. (%)				
Dyslipidemia	108 (56.84)	42 (62.69)	66 (53.66)	0.283

Characteristic	All	Thrombosis either before/ or at PV diagnosis	No thrombosis either before/ or at PV diagnosis	P-value
	N = 190 (100%)	N = 67 (35.26%)	N = 123 (64.74%)	
Hypertension	144 (75.79)	54 (80.60)	90 (73.17)	0.291
Diabetes mellitus	95 (50.00)	34 (50.75)	61 (49.59)	1.000
Smoking -- no. (%)	66 (34.74)	22 (32.84)	44 (35.77)	0.751
Presence of cardiovascular risk factors* -- no. (%)	175 (92.11)	62 (92.54)	113 (91.87)	1.000
Diving mutation -- no. (%)				0.632
JAK2 V617F	139 (73.16)	52 (77.61)	87 (70.73)	
No *JAK2* V617F	37 (19.47)	11 (16.42)	26 (21.14)	
No data	14 (7.37)	4 (5.97)	10 (8.13)	
Hepatomegaly -- no. (%)	7 (4.43, n = 158)	3 (5.08, n = 59)	4 (4.04, n = 99)	1.000
Splenomegaly -- no. (%)	21 (13.29, n = 158)	5 (8.47, n = 59)	16 (16.16, n = 99)	0.227
Prior thrombosis before PV diagnosis -- no. (%)	32 (16.84)	32 (47.76)	0 (0.00)	<0.001
Prior anticoagulation -- no. (%)	7 (3.68)	7 (10.45)	0 (0.00)	0.001
Prior antiplatelet -- no. (%)	38 (20.00)	28 (41.79)	10 (8.13)	<0.001
ELN risk -- no. (%)				<0.001
Low	65 (34.21)	0 (0.00)	65 (52.85)	
High	125 (65.79)	67 (100.00)	58 (47.15)	
Hemoglobin -- g/dL	18.08 ± 1.84	17.76 ± 1.52	18.25 ± 1.98	0.059
White blood cell count				
Median (IQR) -- per mm^3	11,270 (8,200-16,600)	12,700 (9,000-17,300)	10,000 (8,000-15,700)	0.058

Characteristic	All	Thrombosis either before/ or at PV diagnosis	No thrombosis either before/ or at PV diagnosis	P-value
	N = 190 (100%)	N = 67 (35.26%)	N = 123 (64.74%)	
WBC >11,000 /mm^3 -- no. (%)	96 (50.53)	41 (61.19)	55 (44.72)	0.034
Median absolute monocyte count (IQR) –- per mm^3	500.35 (338-694.2)	519 (366-848)	489 (324.8-655.2)	0.258
Median platelet count (IQR) – per mm^3	387,000 (245,000-611,000)	450,000 (261,000-652,000)	370,000 (242,000-568,000)	0.113
Platelet ≥450,000 /mm^3 -- no. (%)	83 (43.68)	34 (50.75)	49 (39.84)	0.169
Platelet ≥600,000 /mm^3 -- no. (%)	48 (25.26)	23 (34.33)	25 (20.33)	0.038
Thrombosis after diagnosis of PV -- no. (%)	17 (8.95)	7 (10.45)	10 (8.13)	1.000
Transformation -- no. (%)				
Acute leukemia	4 (2.11)	1 (1.49)	3 (2.44)	1.000
Secondary myelofibrosis	20 (10.53)	6 (8.96)	14 (11.38)	0.805
Death -- no. (%)	17 (8.95)	10 (14.93)	7 (5.69)	0.059
Treatment -- no. (%)				
Phlebotomy	156 (82.11)	52 (77.61)	104 (84.55)	0.241
Aspirin	183 (96.32)	65 (97.01)	118 (95.93)	1.000
Hydroxyurea/ hydroxycarbamide	149 (78.42)	59 (88.06)	90 (73.17)	0.017
Bleeding complication -- no. (%)				0.103
Clinically relevant non-major bleeding	12 (6.32)	3 (4.48)	9 (7.32)	
Major bleeding	5 (2.63)	4 (5.97)	1 (0.81)	

* Presence of one or more of the following risk factors: dyslipidemia, hypertension, diabetes mellitus, or smoking.

JAK2 V617F mutation was detected in 73.16% of patients. *JAK2* V617F-negative PV was found in 19.47% of patients, while data regarding the type of mutation was not available for 7.37%. The prevalence of *JAK2* V617F-positive PV in the thrombosis-before-or-at-PV-diagnosis group (77.61%) was higher than in the no-thrombosis group (70.73%), but this difference was not statistically significant (p-value = 0.632).

Laboratory data showed that the mean hemoglobin (Hb) level was 18.08 ± 1.84 g/dL. The mean Hb was not statistically significantly different between the thrombosis-before-or-at-PV-diagnosis group and the no-thrombosis group (17.76 ± 1.52 g/dL vs. 18.25 ± 1.98 g/dL; p-value = 0.059). The median white blood cell (WBC) count was 11,270 /mm³ (IQR: 8,200-16,600), with about half of the patients (50.53%) having WBC counts >11,000 /mm³. The proportion of patients with WBC counts >11,000 /mm³ was higher in the thrombosis-before-or-at-PV-diagnosis group compared to the no-thrombosis group (61.19% vs. 44.72%; p-value = 0.034). The median platelet count was 387,000 /mm³ (IQR: 245,000-611,000). In the thrombosis-before-or-at-PV-diagnosis group, the proportion of patients with platelet counts ≥600,000 /mm³ was higher compared to the no-thrombosis group (34.33% vs. 20.33%; p-value = 0.038).

PV patients were treated with aspirin (96.32%), phlebotomy (82.11%), and hydroxyurea (78.42%), respectively. Treatment with hydroxyurea was more common in the thrombosis-before-or-at-PV-diagnosis group (88.06% vs. 73.17%; p-value = 0.017). Among 149 patients receiving hydroxyurea treatment, 12 patients (8.05%) developed hydroxyurea resistance or intolerance. Three-fourths (8 patients) met the criteria for hydroxyurea intolerance (5 hematologic side effects and 3 non-hematological toxicities), while one-fourth (4 patients) had hydroxyurea resistance due to leukocytosis and thrombocytosis according to ELN hydroxyurea resistance/intolerance definitions.[13]

Bleeding complications after treatment were found in 2.63% as major bleeding and 6.32% for clinically relevant non-major bleeding, without statistically significant difference in the thrombosis-before-or-at-PV-diagnosis group and the no-thrombosis group (p-value = 0.103).

Vascular events

Thrombosis was detected before the diagnosis of PV in 32 patients (16.84%; 95% CI: 11.81-22.94%): 19 with ischemic stroke, 12 with myocardial infarction, and 1 with portal vein thrombosis. Seven patients (3.68%) had received prior treatment with anticoagulants, and 38 patients (20.00%) had received prior treatment with antiplatelets. Thrombosis was diagnosed at the time of PV diagnosis in 42 patients (22.11%; 95% CI: 16.42-28.68%): 39 with ischemic stroke, 1 with myocardial infarction, and venous thromboembolism in 2 patients. Additionally, 7 patients experienced recurrent thrombosis before the diagnosis and treatment of PV.

Factors associated with thrombosis either prior to or at presentation of PV in multivariable analysis were age ≥60 years (odds ratio [OR] 2.30; 95% CI: 1.21-4.38), female gender (OR 1.60; 95% CI: 0.80-3.19), and WBC >11,000 /mm^3 (OR 1.81; 95% CI: 0.96-3.41) (Table 2).

Table 2. Univariable and multivariable analysis of factors associated with thrombosis at prior to or at presentation of PV

Variables	Univariable analysis			Multivariable analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age ≥60 yr	2.45	1.31-4.59	0.005	2.30	1.21-4.38	0.011
Female	2.08	1.075-4.03	0.030	1.60	0.80-3.19	0.185
Smoking	0.88	0.47-1.65	0.685			
Dyslipidemia	1.45	0.08-2.67	0.231			
Hypertension	1.52	0.74-3.14	0.255			
Diabetes mellitus	1.05	0.58-1.90	0.879			
JAK2 V617F mutation	1.41	0.64-3.09	0.388			
Hb (per 1 g/dL)	0.86	0.73-1.02	0.082			
WBC >11,000 /mm^3	1.95	1.06-3.58	0.031	1.81	0.96-3.41	0.066
Platelet ≥600,000 /mm^3	2.05	1.05-4.00	0.035			

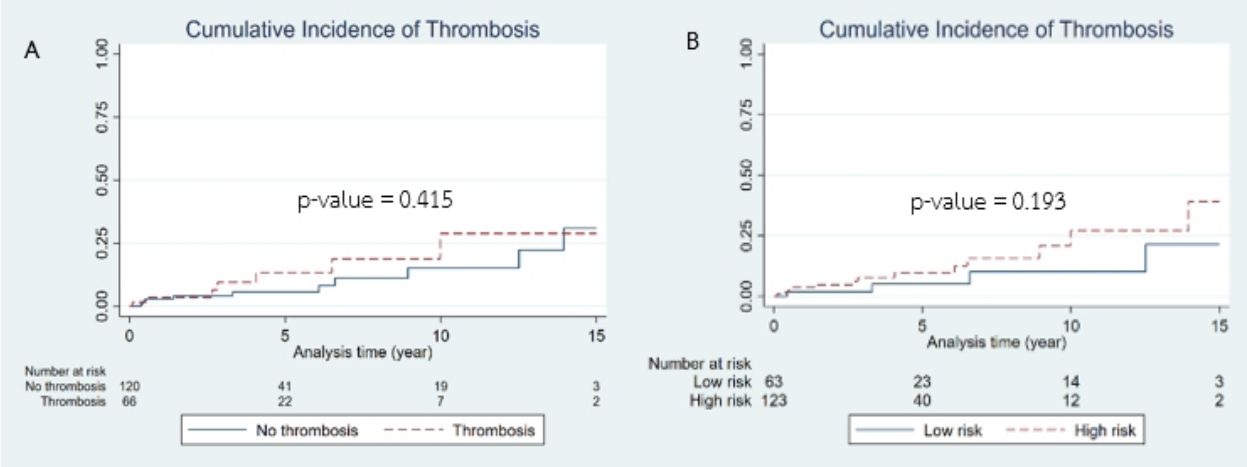
Cumulative incidence of thrombosis and thrombosis-free survival

Thrombosis after PV diagnosis was found in 17 patients (8.95%; 95% CI: 5.30-13.94%): 1 with transient ischemic attack, 9 with ischemic stroke, 6 with myocardial infarction, and 1 with pulmonary embolism. The incidence of thrombosis after PV diagnosis did not differ significantly between the thrombosis-before-or-at-PV-diagnosis group and the no-thrombosis group (10.45% vs. 8.13%; p-value = 1.000). However, when examining the ELN high-risk and low-risk groups, thrombosis incidence after PV diagnosis was higher in the high-risk group than in the low-risk group, though it lacked statistical significance (10.40% vs. 6.15%; p-value = 0.427). With a follow-up time of 835.98 patient-years, the incidence rate of thrombosis after PV diagnosis was 2.03 events/100 patient-years (95% CI: 1.26-3.27). As classified by ELN risk group, the incidence rate of thrombosis after PV diagnosis was higher in the ELN high-risk group (2.51 events/100 patient-year) compared to the ELN low-risk group (1.26 events/100 patient-year).

The cumulative incidence of thrombosis in PV patients at 5, 10, and 15 years was 8.12% (95% CI: 4.34-14.93), 19.53% (95% CI: 11.15-32.91), and 30.57% (95% CI: 16.95-51.16), respectively. In the no-thrombosis group, the cumulative incidence at 5 and 10 years was 5.61% and 15.16%, respectively. In the thrombosis-before-or-at-PV-diagnosis group, the cumulative incidence at 5 and 10 years was 13.27% and 28.86%, respectively (Figure 1).

Figure 1. Cumulative Incidence of Thrombosis

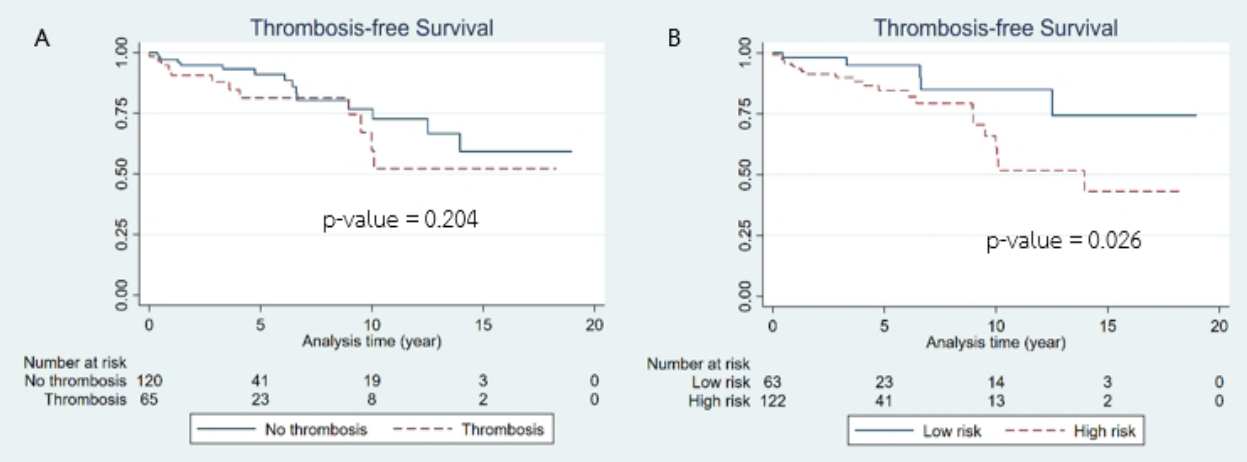
Cumulative incidence of thrombosis stratified by **(**A**)** thrombosis either before**/**or at PV diagnosis **(**B**)** ELN risk**.**



Thrombosis-free survival, defined as the time from PV diagnosis to the date of the first major thrombosis or death from any cause, was lower in the thrombosis-before-or-at-PV-diagnosis group compared to the no-thrombosis group. The 10-year thrombosis-free survival was 59.65% and 76.71%, respectively, although this difference was not statistically significant (p-value = 0.204). However, when stratifying PV patients by ELN risk stratification, the high-risk group had statistically significantly lower thrombosis-free survival than the low-risk group. The 10-year thrombosis-free survival was 61.09% and 84.92%, respectively (p-value = 0.026) (Figure 2).

Figure 2. Thrombosis-free Survival

Thrombosis-free survival stratified by **(**A**)** thrombosis before**/**or at PV diagnosis **(**B**)** ELN risk**.**



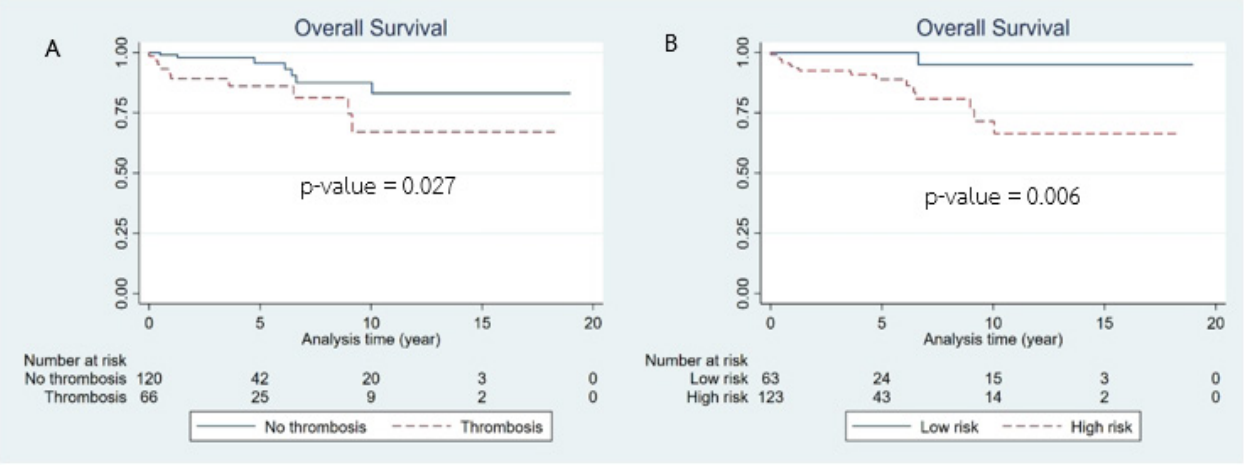
Overall survival (OS)

The OS, defined as the time from PV diagnosis to the date of death from any cause, was favorable in PV patients, with 5- and 10-year OS of 92.45% and 80.55%, respectively. PV patients with prior thrombosis or thrombosis at diagnosis experienced significantly inferior OS compared to

those without thrombosis, with 10-year OS of 67.06% and 87.54%, respectively (p-value = 0.027). When classified by ELN risk, the 10-year OS in the ELN high-risk group was 71.51%, while in the ELN low-risk group, it was 95.00%, which was statistically significantly higher (p-value = 0.006) (Figure 3).

Figure 3. Overall Survival (OS)

OS stratified by **(**A**)** thrombosis before**/**or at PV diagnosis **(**B**)** ELN risk**.**

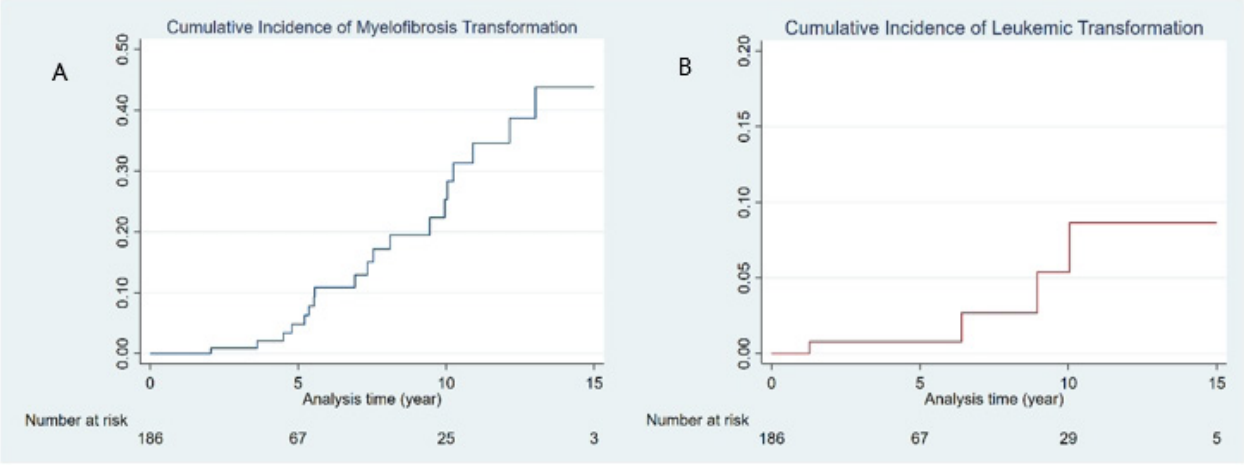


Myelofibrosis and leukemic transformation

The incidence rate of myelofibrosis transformation was 2.41 events/100 patient-years (95% CI: 1.55-3.73), with a cumulative incidence at 10 years of 25.33% (95% CI: 15.26-40.28). The incidence rate of leukemic transformation was 0.46 events/100 patient-years (95% CI: 0.17-1.23), with a cumulative incidence at 10 years of 5.39% (95% CI: 1.59-17.45) (Figure 4).

Figure 4. Cumulative Incidence of Transformation

Cumulative incidence of transformation to (A) myelofibrosis (B) acute leukemia.



Discussion

This study investigated the incidence of thrombosis in PV patients, a significant contributor to morbidity and mortality in this population. Among 190 PV patients, 67 (35.26%) experienced thrombosis. Of these, 16.84% had a prior history of thrombosis, and 22.11% presented with thrombosis as their initial manifestation. Additionally, 3.68% of these patients experienced recurrent thrombosis before the diagnosis of PV. These findings align with previous studies reporting thrombotic events in 20% to 39% of PV patients. For instance, the ECLAP study, involving 1,638 PV patients, found that 39% had a prior thrombotic history.[14] Another study from Italy, with a 20-year follow-up of 1,213 PV patients, reported that 14% had thrombosis before diagnosis, and 20% at the time of diagnosis, closely matching our results.[12]

In contrast, some studies reported lower thrombosis incidences. The CYTO-PV study found a 28.8% incidence of prior thrombotic events among 365 patients.[15] A single-center study of 587 patients reported that 25% presented with thrombosis either before or at diagnosis.[4] Similarly, a study in Thailand involving 60 PV patients reported a thrombosis incidence of 23.4% either before or at diagnosis.[10] Other reports from Thailand, involving 140 and 116 patients, indicated thrombosis incidences of 24.3% and 20.7%, respectively.[11,16] However, the timing of thrombosis in these studies was unclear. To our knowledge, this study represents the largest cohort of PV patients in Thailand, suggesting a high incidence of thrombosis comparable to European data.[7,14,17]

In our cohort, arterial thrombosis was more common than venous thrombosis, primarily manifesting as ischemic stroke and myocardial infarction. These findings are consistent with reports indicating that arterial sites are predominantly affected in PV patients. Our study found arterial thrombosis occurred in 33.7% of patients either before or at diagnosis, compared to just 1.6% for venous thrombosis. The ECLAP and CYTO-PV studies reported arterial thrombosis in 27% and 17% of patients and venous thrombosis in 11% and 12%, respectively.[14,15] In contrast, a Thai study reported a venous thrombosis incidence of just 1.7% either before or at PV diagnosis, corroborating our finding of low venous thrombosis in Thai PV patients.[10]

In our study, the mean age at PV diagnosis was 60.94 ± 13.83 years, consistent with previous reports indicating an average age around 60 years.[3,14,18] Patients aged ≥60 years comprised 54.74% of the cases. We observed a higher male predominance (73.68% vs. 26.32%) compared to previous studies where males were only slightly more predominant.[14,19] PV patients with thrombosis either before or at diagnosis were significantly older, and the proportion of females in this group was higher than in those without thrombosis. Prior research suggests sex differences in JAK2 V617F allele burden, with women having significantly lower burdens than men.[20] The ECLAP study found that women had higher rates of venous thrombosis, while men had more arterial events.[21] In our study, age ≥60 years was the only statistically significant risk factor for thrombosis either prior to or at PV diagnosis, aligning with other studies that also identify older age as a significant thrombosis risk factor.[4,8,14,22,23]

In this study, a WBC exceeding 11,000 /mm³ was observed to be associated with thrombosis either prior to or at the diagnosis of PV. However, in multivariable analysis, this association did not reach statistical significance. The relationship between leukocytosis and thrombosis in PV patients remains inconclusive, with varying results across studies. Thresholds of WBC >11,000/mm³ or >15,000/mm³ are often utilized as indicators of increased thrombosis risk.[2] Data from the ECALP study indicated that a WBC exceeding 15,000 /mm³, compared to those with a WBC below 10,000 /mm³, exhibited a significant increase in thrombosis risk, with a HR of 1.71 (95% CI: 1.10-2.65), primarily driven by a heightened risk of myocardial infarction (HR 2.84; 95% CI: 1.25-6.46).[24] Meta-analyses have shown a strong association between leukocytosis and arterial thrombosis.[25] Additionally, a recent large prospective observational study involving 2,510 patients found that acute and sustained elevation of WBC count was significantly correlated with an increased risk of thrombotic events, even when hematocrit levels were ≤45%.[26]

There is no previously published data in Thailand regarding the rate of thrombosis after PV diagnosis. In our study, thrombosis following PV diagnosis was found to occur at a rate of 8.95%, lower than a range of 18% to 22% as reported in previous studies. Arterial thrombosis remained the predominant type of thrombosis post-diagnosis, with ischemic stroke and myocardial infarction being the most common types of thrombosis. Our study's findings are consistent with other studies indicating that arterial thrombosis is usually associated with PV.[4,12,27]

Patients with thrombosis either before or at PV diagnosis had lower thrombosis-free survival, although this difference was not statistically significant. However, ELN risk stratification remains a valuable predictive tool for post-diagnosis thrombosis. High-risk PV patients had significantly lower thrombosis-free survival compared to low-risk patients. Due to the low incidence of post-diagnosis thrombosis, we did not analyze risk factors for thrombosis occurring after diagnosis.

The hematocrit level after PV diagnosis is another factor that may influence the outcomes of PV. Data from the CYTO-PV study showed that strict hematocrit control (goal ≤45%) resulted in a nearly four-fold reduction in the risk of cardiovascular death and major thrombosis.[15,28] Due to its retrospective nature, we were unable to find information about the hematocrit level for every patient. Data on hematocrit levels at 6, 12, 18, and 24 months were available for 130, 111, 95, and 86 patients, respectively. At 6 months after PV diagnosis, the mean hematocrit was 42.74 ± 6.32%, which appeared to align with the recommended treatment for hematocrit control.[29]

The prevalence of JAK2 V617F-positive PV was 73.16%, closely aligning with a previous study conducted in Thailand, which reported a positivity rate for the JAK2 V617F mutation of 73.3%.[10] However, this proportion of JAK2 V617F mutations remained lower than that reported in several studies, which have shown positive rates of up to 97%.[30,3]1 The disparity in proportions could be attributed to a lack of precision in molecular diagnostic studies in the past.[30,32]

The incidence rates of myelofibrosis and leukemic transformation in PV were low, with rates of 2.41 events/100 patient-years and 0.46 events/100 patient-years, respectively. In our study, the 10-year cumulative incidence of leukemic transformation was 5.39%, consistent with previous

reports, which cite cumulative incidences ranging from 2.3% to 14.4% over a 10-year period.[3,33] Furthermore, the OS in PV was favorable, exceeding 80% at 10 years. However, PV patients who had prior thrombosis or thrombosis at PV diagnosis had statistically significantly lower OS compared to those without. Among risk factors associated with OS in previous studies, some found that previous thrombosis was associated with inferior thrombosis-free survival or OS.[3,4]

Our study had several limitations. Firstly, as a retrospective study, some data were missing, and the short follow-up time (median: 3.13 years, IQR: 0.88-6.61) may have led to underestimations of thrombosis, myelofibrosis transformation, and leukemia rates. Since data were extracted from electronic medical records, the incidence of thrombosis was based on documented cases, typically symptomatic or incidentally discovered through imaging, excluding asymptomatic thrombosis.

We also lacked information on JAK2 V617F allele burden and high-risk mutations, which are important prognostic indicators in myeloid neoplasms. While a JAK2 V617F variant allele frequency (VAF) >50% is linked to a higher risk of venous thrombosis, it is not associated with arterial thrombosis.[34,35] Mutations in ASXL1, DNMT3A, TET2, and BCOR/BCORL1 have been associated with thrombosis risk,[27,36] and mutations in SRSF2, IDH2, RUNX1, TP53, ASXL1, and IDH1/IDH2 have been correlated with leukemic transformation.[37,38] Future research should integrate molecular mutations into the assessment of thrombosis risk, myelofibrosis transformation, and leukemia development, as these factors significantly influence outcomes, particularly thrombosis-free survival and OS.

Conclusions

The incidence of thrombosis either before or at PV diagnosis in Thai PV patients was consistent with findings from previous studies. Age ≥60 years was the sole risk factor associated with thrombosis either before or at PV diagnosis in multivariable analysis. PV patients with thrombosis either before or at diagnosis had inferior thrombosis-free survival, which was not statistically significant, and significantly lower OS.

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