

Thrombotic Complications, Disease Progression, and Survivals in *BCR::ABL1*-Negative Myeloproliferative Neoplasms: A 12-Year Retrospective Study at a Single Center in Thailand

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Objective: To assess the incidence of thrombotic events among patients with *BCR::ABL1*-negative myeloproliferative neoplasm (MPN) within a single center in Thailand.

Materials and Methods: Conducted as a retrospective cohort study between 2008 and 2019, the present research focused on patients diagnosed with *BCR::ABL1*-negative MPN. Diagnoses were reviewed and reclassified based on the WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues (2017). Data collected encompassed demographic details, comorbidities, investigation results, treatments, and outcomes. The primary focus was on thrombosis rates in arterial and venous sites. Secondary outcomes included the incidence of major bleeding, thrombosis-free survival (TFS), and overall survival (OS).

Results: One hundred seventy-five patients participated in the present study and comprised of 46 patients (26.3%) with polycythemia vera (PV), 123 (70.3%) patients with essential thrombocythemia (ET), and six patients (3.4%) with primary myelofibrosis (PMF). Most patients were over 60 years old. The rate of overall thrombosis rate was 28.0%, with 43.5% in PV and 23.6% in ET. Common sites of thrombotic events included the cerebral artery at 16.6%, coronary artery at 6.3%, peripheral artery at 4.0% and venous thromboembolism at 3.4%. The overall bleeding event rate was 13.7%, with 70.8% classified as major bleeding. The all-cause mortality rate within the present cohort was 30.9%. TFS and OS stood 72.0% and 69.1%, respectively.

Conclusion: Thrombosis emerged as a significant complication in patients with *BCR::ABL1*-negative MPN, affecting 28.0% of individuals in the present cohort. Arterial thromboses, particularly ischemic stroke and cardiovascular events, were the predominant occurrences.

Keywords: Myeloproliferative neoplasm; Polycythemia vera; Essential thrombocythemia; Thrombosis; Bleeding

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The World Health Organization (WHO) classification defines Myeloproliferative neoplasms (MPNs) as clonal hematopoiesis featuring increased cellular proliferation. Polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) are *BCR::ABL1*-negative MPNs

driven by mutations in *JAK2 V617F*, calreticulin (*CALR*), or thrombopoietin receptor (*MPL*)^(1,2). These mutations trigger heightened activity in hematopoietic cell receptors, leading to increased erythrocytosis, thrombocytosis, leukocytosis, marrow hypercellularity, and expanded precursor compartments in the bone marrow^(3,4). The reported annual incidences of classic MPNs is approximately two cases per 100,000⁽⁵⁾.

Thrombosis represents a major complication of MPNs, potentially causing disability, morbidity, or mortality⁽⁶⁾. The overall reported prevalence of thrombosis in MPNs stands at 20.0%⁽⁷⁾. Risk factors of thrombosis in MPNs include age older than 60 years, previous arterial or venous thrombosis, atherosclerotic risk, and *JAK2* mutation status^(8,9). Arterial thrombosis is more common than venous thrombosis, with ischemic stroke being a prevalent manifestation^(7,10).

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The elevation of cellular components, particularly all three blood cell series, significantly contributes to thrombotic risk. Current guidelines recommend risk stratification and appropriate treatment, especially cytoreductive agents, for high-risk MPN patients, although such studies have mostly focused on high-risk populations^(10,11). Limited data exists on the Thai MPN population, and previous research suggested lower thrombotic events in Thai individuals compared to Western populations^(7,12-14).

The present study aimed to report the thrombosis rates in Thai MPN patients and describe their characteristics, treatments, complications, and survival outcomes in a single center study.

Materials and Methods

Study design and patients

The retrospective study was conducted at the Division of Hematology, Department of Medicine, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand. Patients diagnosed with PV, ET, and PMF between January 1, 2008, and December 31, 2019, were included, confirmed, and reclassified based on the WHO Classification 2017^(1,2). Patients with incomplete data or not meeting inclusion criteria were excluded. PV and ET patients were evaluated according to European LeukemiaNet (ELN) recommendations, while PMF patients were assessed using the international prognostic scoring system (IPSS)⁽¹⁵⁻¹⁷⁾. The present study was conducted in compliance with the Declaration of Helsinki and the International Harmonization Project on Good Clinical Practice. Informed consent was waived due to the retrospective nature of the study, and not more than minimal risk of subjects involved. The study protocol was approved by the Institutional Review Board of Faculty of Medicine Vajira Hospital, Navamindradhiraj University, number 197/63 (COA002/2564).

The primary objective was to determine the cumulative thrombotic event rates, including arterial and venous events. Secondary objectives included rates of major bleeding, thrombosis-free survival (TFS), and overall survival (OS). Major bleeding was defined according to the International Society on Thrombosis and Hemostasis (ISTH) criteria, and OS was measured from MPN diagnosis to all-cause death. TFS was time from MPN diagnosis to thrombosis or death.

Statistical analysis

Descriptive statistics were utilized for demo-

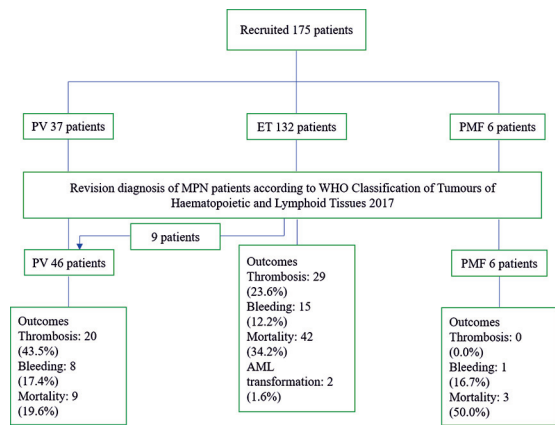


Figure 1. Diagram showed patients of each MPN subtypes and outcomes.

AML=acute myeloid leukemia; ET=essential thrombocythemia; MPN=myeloproliferative neoplasm; PMF=primary myelofibrosis; PV=polycythemia vera

graphic and clinical characteristics, presenting variables as median and interquartile range (IQR) for continuous data and as frequency and percentages for categorical data. Group comparisons (PV, ET, and PMF) employed the chi-square test or Fisher's exact test for categorical variables, while the Kruskal-Wallis test analyzed continuous variables. OS was assessed using the Kaplan-Meier method. Differences in survival among groups were evaluated via the log-rank test. The Cox proportional hazards regression model identified factors associated with survival. Variables with p-value less than 0.2 in univariate analysis underwent multivariate analysis to ascertain independent factors. The cumulative incidence of thrombosis was calculated using the Fine-Gray method, considering death as competing events. Statistical analyses were conducted using Stata, version 13 (StataCorp LP, College Station, TX, USA). A p-value of less than 0.05 denoted statistical significance.

Results

Demographics and baseline characteristics

One hundred seventy-five patients were recruited according to the inclusion criteria. ET was the most common MPN subtype followed by PV and PMF, respectively. According to diagnostic criteria from WHO Classification 2017, nine of ET patients were reclassified as PV (Figure 1). The median age at diagnosis was 65 years (IQR 52 to 77), of which 61.1% were older than 60 years. Male gender was predominant. Demographic data are shown in Table 1.

PV had the highest prevalence of *JAK2 V617F*

Table 1. Demographic data, baseline characteristics, investigation, and treatment of MPN patients

Variables	All patients (n=175)	PV (n=46)	ET (n=123)	PMF (n=6)	p-value
Age (years); median (IQR)	65 (52 to 77)	64 (53 to 72)	66 (51 to 74)	68 (52 to 77)	0.796
Age 60 years or more; n (%)	107 (61.1)	28 (60.9)	75 (61.0)	4 (66.7)	0.961
Female; n (%)	72 (42.4)	25 (56.8)	42 (35.0)	5 (83.3)	0.004
Diabetes mellitus; n (%)	41 (23.4)	7 (15.2)	33 (26.8)	1 (16.7)	0.305
Dyslipidemia; n (%)	62 (35.4)	19 (41.3)	42 (34.2)	1 (16.7)	0.457
Hypertension; n (%)	105 (60.0)	33 (71.7)	70 (56.9)	2 (33.3)	0.086
Coronary artery disease; n (%)	19 (10.9)	7 (15.2)	12 (9.8)	0 (0.0)	0.484
High risk group; n (%)	131 (74.9)	38 (82.6)	88 (71.5)	5 (83.3)	0.351
Splenomegaly by any source; n (%)	35 (20.0)	14 (30.3)	18 (14.6)	3 (50.0)	0.009
Laboratory investigation					
Hemoglobin (g/L); median (IQR)	132 (111 to 159)	171 (162 to 188)	124 (108 to 139)	80 (77 to 83)	<0.001
WBC ($\times 10^9/L$); median (IQR)	11.5 (8.3 to 16.3)	15.2 (10.5 to 19.2)	10.9 (8.2 to 14.9)	6.2 (4.5 to 13.5)	0.001
Platelet ($\times 10^9/L$); median (IQR)	815 (600 to 1,108)	733 (440 to 996)	857 (689 to 1,186)	211 (119 to 300)	<0.001
<i>JAK2</i> mutation; n (%)	104 (76.5)	35 (94.6)	68 (72.3)	1 (20.0)	<0.001
Treatment; n (%)					
Phlebotomy	25 (14.3)	25 (54.4)	-	-	N/A
Hydroxyurea	151 (86.3)	43 (93.5)	106 (86.2)	2 (33.3)	0.002
Anagrelide	10 (5.7)	1 (2.2)	9 (7.3)	0 (0.0)	0.503
Antiplatelet given	163 (93.1)	42 (91.3)	117 (95.1)	4 (66.7)	<0.001
Warfarin given	12 (6.9)	4 (8.7)	6 (4.9)	2 (33.3)	0.041

ET=essential thrombocythemia; IQR=interquartile range; PMF=primary myelofibrosis; PV=polycythemia vera; WBC=white blood cell

mutation at 94.6%, in contrast to 72.3% and 20.0% for ET and PMF, respectively. There was no patient with *JAK2* exon 12 mutation among the PV patients in the present study. Data of *CALR*, *MPL* and triple-negative mutation were unavailable because of inaccessibility of investigation. In terms of risk classification, the majority of patients were in the high-risk group. Antiplatelets were prescribed in most of the patients at 93.1% followed by hydroxyurea at 86.3%. Phlebotomy was utilized in more than half of PV patients (Table 1).

Outcomes

Thrombotic events occurred in 49 patients (28.0%). Twelve patients (6.9%) had thrombosis at the diagnosis of MPNs with five from the PV group, seven from the ET group, and none from the PMF group. The rate of arterial thrombosis was much higher than venous thrombosis at 24.6% versus 3.4%. A quarter of the patients had experienced more than one thrombotic event after the diagnosis of MPNs. Almost half of the patients with PV experienced thrombotic events at 43.5%, while only 23.6% of the ET patients had thrombosis. Patients with PMF had no occurrence of thrombotic event. Ischemic stroke was the most common site of arterial thrombosis and had the highest prevalence in PV. On the other hand,

the prevalence of venous thrombosis was similar in PV and ET. The rates of bleeding events were similar among MPN subtypes. All bleeding events occurred in PV patients were major bleeding, while 60.0% of bleeding in ET patients were considered major bleeding. Half of bleeding episodes required blood transfusion. The most common bleeding site was gastrointestinal (GI) bleeding and the single event of bleeding in PMF was non-major bleeding (Table 2).

Survival

The median follow-up time for the whole cohort was 63 months (IQR 32 to 119). The cumulative rate of thrombosis in PV was 22.0% at 5 years, of which most of the events occurred within the first year after diagnosis. Cumulative rate of thrombosis in ET was 15.4% at five years. No thrombotic event occurred in PMF patients (Figure 2).

TFS at 5 years in PV and ET were similar. On the contrary, there was a trend of worse TFS in PMF. (Figure 3).

OS of patients with MPNs differed between the groups. PMF patients had the worst OS compared to PV and ET patients (Figure 4).

Discussion

The present study is a single-centered cohort

Table 2. Outcomes of all MPN patients

Variables	All patients (n=175)	PV (n=46)	ET (n=123)	PMF (n=6)	p-value
All thrombosis; n (%)	49 (28.0)	20 (43.5)	29 (23.6)	0 (0.0)	0.012
Thrombosis at diagnosis	12 (6.9)	5 (10.9)	7 (5.7)	0 (0.0)	
Thrombosis post-diagnosis	37 (21.1)	15 (32.6)	22 (17.9)	0 (0.0)	
Thrombosis more than 1 site/episode; n (%)	12 (24.5)	2 (10.0)	10 (34.5)	0 (0.0)	0.262
Time to first thrombosis (months); median (IQR)	7.4 (0.1 to 50.1)	2.9 (0.0 to 70.4)	14.8 (0.3 to 49.3)		0.504
Arterial thrombosis; n (%)	43 (24.6)	19 (41.3)	24 (19.5)	0 (0.0)	0.007
Coronary thrombosis; n (%)	11 (6.3)	3 (6.5)	8 (6.5)	0 (0.0)	0.812
Ischemic stroke; n (%)	29 (16.6)	14 (30.4)	15 (12.2)	0 (0.0)	0.019
PAOD; n (%)	7 (4.0)	3 (6.5)	4 (3.3)	0 (0.0)	0.525
Venous thromboembolism; n (%)	6 (3.4)	1 (2.2)	5 (4.1)	0 (0.0)	0.747
Bleeding complications; n (%)	24 (13.7)	8 (17.4)	15 (12.2)	1 (16.7)	0.503
Major bleeding; n (%)	17 (70.8)	8 (100)	9 (60.0)	0 (0.0)	0.018
AML transformed; n (%)	2 (1.1)	0 (0.0)	2 (1.6)	0 (0.0)	0.652
Dead; n (%)	54 (30.9)	9 (19.6)	42 (34.2)	3 (50.0)	0.085

AML=acute myeloid leukemia; ET=essential thrombocythemia; IQR=interquartile range; PMF=primary myelofibrosis; PV=polycythemia vera; PAOD=peripheral arterial occlusion disease

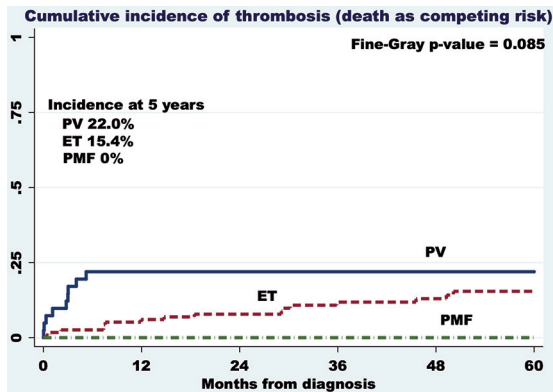


Figure 2. Cumulative incidence of thrombosis in MPN patients.

ET=essential thrombocythemia; PMF=primary myelofibrosis; PV=polycythemia vera

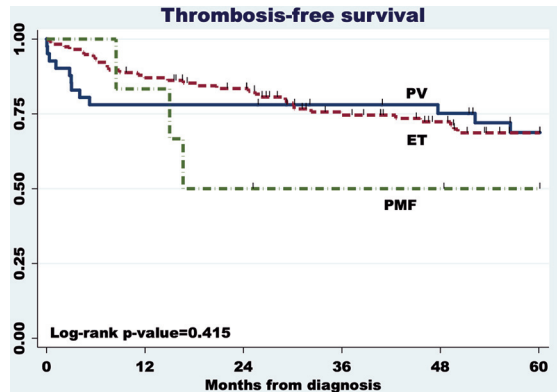


Figure 3. Thrombosis-free survival in MPN patients.

ET=essential thrombocythemia; PMF=primary myelofibrosis; PV=polycythemia vera

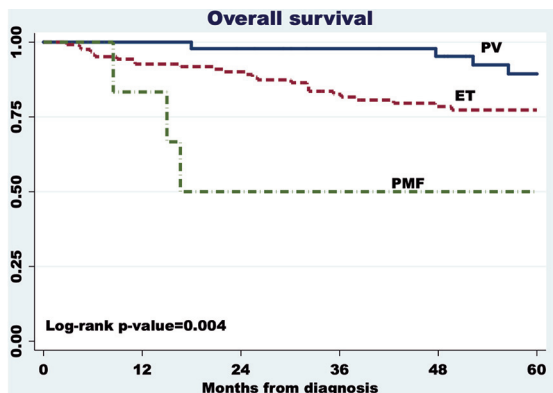


Figure 4. Overall thrombosis in MPN patients.

ET=essential thrombocythemia; PMF=primary myelofibrosis; PV=polycythemia vera

of 175 patients with *BCR::ABL1* negative MPNs in Thailand. The current study revealed the distribution of diagnoses as more prominent ET, followed by PV, and rarely PMF. The result was comparable with other studies from Northern Thailand⁽¹²⁾, South Korea⁽¹⁸⁾, and Brazil⁽¹³⁾. However, the result was different from another study from Germany, which reported equal prevalence between PV and ET⁽¹⁹⁾.

The present study also revealed an overall rate of thrombosis of 28.0%. With regards to the time of thrombosis, 6.9% of thrombotic events occurred at the onset of MPN diagnosis and a further 21.1% occurred after diagnosis. Two systematic review and meta-analyses^(7,10) have reported overall incidences of thrombosis of 20.0% across all MPN subtypes. The

present result had higher rate of thrombosis when compared to a previous study from Thailand⁽¹²⁾, but similar thrombotic rate when considering only thromboses that occurred after diagnosis. The reason behind this discrepancy is yet unknown and could be an interesting research question of different thrombotic rate in an urban population versus regional area in Thailand. There was no occurrence of thrombosis in patients with PMF in the present study. This could be due to the very small number of patients with PMF and most of these patients were classified as high risk for disease progression, which compete with the risk of thrombosis.

Bleeding events occurred in 13.7% of patients in the present study. The bleeding rate was twice as high as the reported rate of 6.2% in meta-analysis⁽⁷⁾ and 6.2% as published in a recent study⁽²⁰⁾. However, the rate of major bleeding in the present study was 9.7%, which was similar to 8% in the German MPN registry⁽¹⁹⁾, and merely a small difference to the rates reported in large meta-analysis. Moreover, another single-center study had reported overall bleeding event up to 17.2%⁽²¹⁾, but the rate of major bleeding in the present study was only 5.7%⁽²¹⁾. However, mucocutaneous bleeding, GI bleeding, and in central nervous system were the most common sites of bleeding complication among the previous and current studies^(7,19,21-23). The first limitation of the present study was that there was no data on *CALR* and *MPL* mutation. This is because the present study comprised contemporary cohort, of which the *CALR* and *MPL* mutation results are not available for most of the patients. Next generation sequencing result for myeloid gene panel was also not widely available in Thailand. Thus, absence of complete molecular genetic study is the major limitation of the current study. The authors look forward to including the molecular genetic data in further study, as multiple gene mutation may play important roles in the development of thromboses⁽¹⁰⁾. Secondly, the study comprised a very low number of patients with PMF, which was not sufficient to demonstrate the effect of disease characteristics on incidences of thrombosis and bleeding. Collaboration with nationwide registry that emphasizes the PMF subpopulation may give more insight on thromboses and bleedings in this rare entity. Thirdly, due to retrospective nature of the present study, some of the confounding factors on thrombosis such as underlying atherosclerotic condition prior to MPN diagnosis may not be well documented. The results from this single center study may be biased and not represent the broader

population or be applicable to nationwide settings. Fourthly, hematopathological reviews were not performed in the present study, as the current criteria have evolved and the discrimination between ET and early PMF may be problematic.

Conclusion

Thrombosis is a significant complication in MPN patients. More than a quarter of MPN patients had experienced thrombosis and the incidence of arterial thrombosis was seven-time higher than venous thrombosis. Ischemic stroke remained the most common site of thrombosis in the present cohort, followed by cardiovascular events similar to other cohorts. PV had the highest thrombotic event and all cases occurred in the first year of diagnosis. Bleeding was a common complication after thrombosis and was majorly located in gastrointestinal tract.

What is already known on this topic?

Thrombosis is a common and significant complication among *BCR::ABL1*-negative MPN patients. Arterial thromboses including cerebral and coronary arteries are much higher than venous site. Cytoreduction and antiplatelet can reduce thrombotic events in MPN patients.

What does this study add?

Thrombotic rates are varied in many cohorts. This study showed a slightly higher thrombotic rate than the meta-analysis and some cohorts, and a higher thrombosis in PV than ET. Bleeding incidence was twice as high as in the meta-analysis. However, the rate of major bleeding was similar in many studies. This study also demonstrated cumulative rate of thrombosis, TFS, and OS in Thailand.

Authors' contributions

DJ contributed to the study conception and design. Material preparation, data collection and acquisition of data were performed by DJ, SK, and CJ. Statistical analysis was done by DJ and WL. Writing the original draft was done by DJ. DJ and WL did the writing review and editing. All authors gave the writing approval.

Conflicts of interest

The authors declare no conflict of interest.

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