

The Frequency of Thromboembolism and Factors Associated with Thromboembolism in Patients Suffering from Polycythemia Vera

Mehmet Ali Uçar^{*}, Simten Dağdaş, Funda Ceran, Mesude Falay, Gülsüm Özet

Department of Hematology, Ankara Numune Training and Research Hospital, Ankara, Turkey

Email address:

mucardr@hotmail.com (M. A. Uçar)

^{*}Corresponding author

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Abstract: This study aimed to identify at what frequency of thromboembolic complications and the other risk factors that create a predisposition to thromboembolic complications occur in patients suffering from polycythemia vera (PV). In accordance with the 2001-2008 criteria put forth by World Health Organization, we reviewed the medical records of 207 patients who were diagnosed with PV between 2009 and 2017 at Ankara Numune Training and Research Hospital. We retrospectively looked at their demographical and clinical data, alongside their history of previous thrombotic events, what treatment they had received, and lab data at the time of diagnosis. We found that the mean hemoglobin and hematocrit levels, as well as their median white blood cell count and JAK2V617F positivity rate of those who had suffered thrombotic events were higher who had not. In addition, we also discovered that the mean age (60 vs. 55.3; $p=0.012$) and rate of tobacco use (62.9% vs. 23.7%; $p<0.001$) were both determined among the thrombotic groups versus the normal group. According to multivariate regression model of potential risk factors associated with thrombotic events, we had determined that smoking ($OR=7.21$; $p<0.001$), hypertension ($OR=5.44$; $p=0.008$), itching ($OR=6.7$; $p=0.001$), and JAK2V617F positivity ($OR=2.61$; $p=0.043$) were all independent risk factors that indicated the presence of an arterial event. We also arrived at the fact that smoking ($OR=7.07$; $p=0.001$) and itching ($OR=12.9$; $p=0.001$) were also independent risk factors predicting the presence of a venous event. Our findings conclusively reveal which risk factors are associated with thromboembolic events among PV patients. In light of that, we recommend that preventive measures be against these risk factors in order to decrease the frequency of thromboembolic complications that PV patients experience.

Keywords: Polycythemia Vera, Thrombosis, JAK2 Mutation

1. Introduction

Polycythemia vera (PV) is an acquired stem cell disease included among BCR-ABL-negative myeloproliferative neoplasms. It is a chronic and clonal in nature, and characterized by uncontrolled proliferation of the blood cells (erythroid, myeloid, and megakaryocytic, primarily erythroid series) at different rates as well as absolute increase in total blood volume as a result of heightened sensitivity of the hematopoietic precursor cells. This increase in erythroid series is frequently accompanied by the overproduction of granulocytes, thrombocytes, and splenomegaly [1]. Many

studies have cited JAK2 mutation in PV cases as being positive at a rate of 97%. Hence, describing the JAK2V617F mutation has since been an important milestone in medicine both for us in order to understand the pathogenesis of the disease as well as to establish a diagnosis. JAK2 is a tyrosine kinase and plays an important role both in development of hematopoietic cells, as well as in the synthesis of receptors involved in the signal transduction of the colony-stimulating factor [2].

Prognosis in PV depends on the severity of the complications that develop during the clinical course. 80% of patients at the time of diagnoses are asymptomatic, whereas

the remaining 20% may exhibit malaise, headaches, and itching [3]. Approximately 20% of patients may experience frequent arterial thromboembolic complications such as transient ischemic attack, cerebrovascular events, and myocardial infarction and, less frequently, venous thromboembolic complications such as deep vein thrombosis. Thrombotic complications thus are main causes of morbidity and mortality among PV sufferers [4-6]. Similarly, the risk of thrombosis increases proportionally to the elevation of the hematocrit. We know that thrombosis has been shown to be associated with neutrophil-thrombocyte complexes. JAK2 mutation is thought to cause a predisposition to a prothrombotic state because it builds up thrombocyte-neutrophil complexes [7]. The current approach to treating this focuses preventing thrombotic and hemorrhagic events from happening. Physicians chart out treatment plans in accordance with the risk of thrombotic complications, and this often means phlebotomy. Risk factors include being over 60 years of age, having a history of arterial/venous thrombosis, and having a thrombocyte count higher than $1,500 \times 10^9/L$ [8, 9]. Independent risk factors also include having hypertension, hyperlipidemia, and diabetes, and using tobacco products. As a cytoreductive treatment, hydroxyurea reduces the risk of developing thrombosis, a high thrombocyte count, and splenomegaly. Anagrelide is a prostaglandin synthesis inhibitor that selectively inhibits the production of thrombocytes, thus preventing thrombocytosis. Despite lacking any teratogenic potential, IFN- α tends to be the agent of choice particularly for patients who are pregnant or thinking of becoming pregnant, and can also be given to patients who cannot tolerate or who do not respond to other medications. Low-dose prophylactic aspirin use (100 mg/day) is also known to significantly reduce thromboembolic complications as well [10].

PV patients who have JAK2V617F mutation are known to suffer from thromboembolic complications. This study aims to assess within a Turkish context how frequently patients suffering from PV experience thromboembolic complications, as well as to look at what other factors create a predisposition for thromboembolic complications.

2. Materials and Methods

We conducted our study on PV patients who had been diagnosed at the Ankara Numune Training and Research Hospital Department of Hematology between 2009 and 2017.

A total of 207 patients who were diagnosed with PV and whose files were adequate were included in the study. We did not include those who lacked demographical information, clinical or lab findings within their medical files.

We diagnosed PV in accordance with the 2001-2008 criteria outlined by the World Health Organization.

We retrospectively looked at patients' demographical and clinical data, alongside their history of previous thrombotic events, what treatment they had received, and lab data at the time of diagnosis. We had screened JAK2V617F mutation screened using conventional methods. In the context of our

research, arterial thrombosis was defined as the patient suffering from either acute coronary syndrome (angina pectoris, acute myocardial infarction), ischemic stroke, or transient ischemic attacks. Venous thrombosis was defined likewise defined as the patient suffering from a pulmonary embolism, deep vein thrombosis, portal or mesenteric vein thrombosis, or sinus venous thrombosis. We had initiated our research only after obtaining approval from the hospital's scientific ethics committee.

Statistical Analysis

We performed our statistical evaluation using IBS SPSS 20 for Windows (IBM SPSS Inc., Armonk, NY, USA). We likewise used the Kolmogorov-Smirnov test to evaluate the normal distribution, whereupon we represented all numerical variables exhibiting normal distribution as mean \pm standard deviation, all the while treating any numerical variables that did not exhibit normal distribution as being a median (min-max). Categorical variables were represented in terms of counts and percentages. In order to determine the variables that differed by presence of a thrombotic event, we used the Student t-test for numerical variables exhibiting normal distribution as well as the Mann-Whitney U test for any numerical variables that did not exhibit normal distribution. Similarly, we drew upon the chi-square and Fisher exact chi-square tests in order to compare our clinical data, as well as benefited from a multivariate logistic regression in order to identify the presence of any potential risk factors for predicting a thrombotic event. In all of statistical analyses, $p < 0.05$ was deemed as being significant.

3. Results

Demographic characteristics of the patients by presence of a thrombotic event are represented in detail in Table 1. Accordingly, we had divided patients into two groups, including 118 patients with a history of having suffered previous thrombotic events (thrombotic group), and 89 patients who had no history of any previous thrombotic events (control group). 75.3% ($n=67$) of those in the thrombotic group had had a history of a previous arterial event, whereas 24.7% ($n=22$) had had a history of a previous venous event. Sex ratios exhibited similar distributions between both groups. We found that while the mean age was higher in the thrombotic group versus the control group (60.5 ± 14.5 vs. 55.3 ± 14.4 years; $p=0.012$), we nevertheless observed no significant difference in regard to either the presence of diabetes mellitus or a history of previous hemorrhagic events between either groups. On the other hand, we discovered that hypertension, acute coronary syndrome, and itching were statistically significantly higher in the thrombotic group. We found that tobacco use was high in both groups (62.9% vs. 23.7%; $p < 0.001$), and yet we did not observe any significant difference in regard to rates of tobacco use, diabetes mellitus, hypertension, and itching between those with histories of arterial versus venous events.

Table 1. Distribution of demographic characteristics according to thrombotic event development.

Variables	Thrombotic event				p value			
	No events n=118	Developing			No events vs			Arterial events vs Venous events
		All events n=89	Arterial n=67	Venous n=22	All events	Arterial events	Venous events	
Gender, n (%)								
Female	46 (39.0)	34 (38.2)	25 (37.3)	9 (40.9)	0.909	0.822	0.995	0.804
Male	72 (61.0)	55 (61.8)	42 (62.7)	13 (59.1)				
Age (year)	55.3±14.4	60.5±14.5	60.9±13.6	59.3±17.4	0.012*	0.011*	0.248	0.670
≤60	74 (62.7)	31 (34.8)	20 (29.9)	11 (50.0)	<0.001*	<0.001*	0.342	0.121
>60	44 (37.3)	58 (65.2)	47 (70.1)	11 (50.0)				
Smoking, n (%)	28 (23.7)	56 (62.9)	43 (64.2)	13 (59.1)	<0.001*	<0.001*	0.002*	0.800
Diabetes, n (%)	14 (11.9)	16 (18.0)	14 (20.9)	2 (9.1)	0.236	0.134	0.992	0.352
Hypertension, n (%)	59 (50.0)	76 (85.4)	58 (86.6)	18 (81.8)	<0.001*	<0.001*	0.009*	0.842
Heart disease, n (%)	2 (1.7)	42 (47.2)	41 (61.2)	1 (4.5)	<0.001*	<0.001*	0.963	<0.001*
Itching, n (%)	49 (41.5)	77 (86.5)	57 (85.1)	20 (90.9)	<0.001*	<0.001*	<0.001*	0.737

Normally distributed numerical variables were shown as mean ± standard deviation.

Numerical variables that do not show normal distribution were shown with median (min-max).

Categorical variables were shown as number (%).

* p <0.05 shows statistical significance.

In contrast, our findings reveal that the presence of an arterial or venous event, mean platelet count, mean hemoglobin, mean hematocrit, median white blood cell count, and median splenomegaly rate, as well as JAK2V617F positivity were statistically significantly higher among

patients in the thrombotic group (Table 2). We however did not find any significant difference in regard to the aforementioned parameters between patients with a history of arterial versus venous events.

Table 2. Distribution of laboratory findings according to thrombotic event.

Variables	Thrombotic event				p value			
	No events n=118	Developing			No events vs			Arterial events vs venous events
		All events n=89	Arterial n=67	Venous n=22	All events	Arterial events	Venous events	
Platelet (10 ³ μ/L)	409.5 (113-1352)	566 (127-1947)	570 (150-1947)	555.5 (127-808)	<0.001*	<0.001*	0.015*	0.645
Hemoglobin (g/dL)	17.8±1.4	18.4±1	18.5±1.0	18.3±1	0.001*	0.002*	0.005*	0.384
Hematocrit (%)	52.7±5.0	56.9±3.6	57.2±3.8	56.4±3.1	0.035*	0.032*	0.046*	0.442
WBC (10 ³ μ/L)	10500 (4900-35300)	14100 (5400-29800)	14100 (8000-29800)	14350 (5400-26500)	<0.001*	<0.001*	0.001*	0.693
Neutrophile (10 ³ μ/L)	3.2 (0.2-30.1)	4.2 (0.8-17.7)	3.8 (0.8-9.8)	4.6 (1.6-17.7)	0.181	0.200	0.487	0.966
Erythropoietin (U/mL)	2.3 (0-16.3)	2 (0.6-34)	2 (0.6-34)	2 (1-21)	0.994	0.802	0.628	0.413
Splenomegaly (mm)	130 (105-220)	145 (110-230)	145 (110-230)	149 (120-200)	<0.001*	<0.001*	0.041*	0.796

Normally distributed numerical variables were shown as mean ± standard deviation.

Numerical variables that do not show normal distribution were shown with median (min-max).

Categorical variables were shown as number (%).

* p <0.05 shows statistical significance.

Abbreviations: WBC: White blood cell

When we looked at treatment options, we saw that while the ratio of patients who underwent phlebotomy was lower among the thrombotic versus the control group, the ratio of patients who received a cytotoxic treatment was higher. Similarly, we also found that while the ratio of patients who

received interferon did not differ significantly between either groups, the ratio of patients who received interferon was higher in the thrombotic versus the control group, as well as among those with a history of previous arterial thrombosis (Table 3).

Table 3. Distribution of clinical findings according to the development of thrombotic event.

Variables	Thrombotic event				p value			
	No events n=118	Developing			No events vs			Arterial events vs venous events
		All events n=89	Arterial n=67	Venous n=22	All events	Arterial events	Venous events	
JAK2V617F, n (%)								
(+)	82 (69.5)	81 (91.0)	60 (89.6)	21 (95.5)	<0.001*	0.002*	0.009*	0.674
(-)	36 (30.5)	8 (9.0)	7 (10.4)	1 (4.5)				
Myelofibrosis conversion, n (%)								
(+)	33 (28.0)	22 (24.7)	14 (20.9)	8 (36.4)	0.636	0.380	0.450	0.240
(-)	85 (72.0)	67 (75.3)	53 (79.1)	14 (63.6)				

Variables	Thrombotic event				p value			
	No events n=118	Developing All events n=89	Arterial n=67	Venous n=22	No events vs All events	Arterial events	Venous events	Arterial events vs venous events
BM fibrosis grade, n (%)	0 (0-3)	0 (0-3)	0 (0-3)	0 (0-3)	0.658	0.251	0.254	0.069
Jack exon 12, n (%)								
(+)	-	1 (1.1)	1 (1.5)	-				
(-)	7 (5.9)	10 (11.2)	9 (13.4)	1 (4.5)	0.193	0.075	0.999	0.574
Absent	111 (94.1)	78 (87.6)	57 (85.1)	21 (95.5)				
Acetylsalicylic acid, n (%)	96 (81.4)	70 (78.7)	65 (97.0)	5 (22.7)				
Anticoagulant, n (%)	9 (7.6)	18 (20.2)	2 (3.0)	16 (72.7)	<0.001*	0.002*	<0.001*	<0.001*
Absent, n (%)	13 (11.0)	1 (1.1)	-	1 (4.5)				
Hydroxyurea, n (%)	87 (73.7)	83 (93.3)	61 (91.0)	22 (100.0)	<0.001*	0.004*	0.004*	0.335
Anagrelid, n (%)	4 (3.4)	5 (5.6)	5 (7.5)	-	0.503	0.378	0.858	0.432
Phlebotomy, n (%)	44 (37.3)	21 (23.6)	15 (22.4)	6 (27.3)	0.049*	0.048*	0.050*	0.858
Interferon, n (%)	7 (5.9)	12 (13.5)	7 (10.4)	5 (22.7)	0.087	0.408	0.030*	0.047*
Ruxolitinib, n (%)	2 (1.7)	2 (2.2)	1 (1.5)	1 (4.5)	0.999	0.999	0.963	0.993

Categorical variables were shown as number (%).

* p <0.05 shows statistical significance.

Our first multivariate regression model revealed that smoking (OR=7.41; p<0.001), hypertension (OR=4.44; p=0.003), and JAK2V617F positivity (OR=3.21; p=0.009) were independent risk factors that predicted the presence of a thrombotic event (Table 4).

Our second multivariate regression model had also revealed that smoking (OR=7.21; p<0.001), hypertension

(OR=5.44, p=0.008), itching (OR=6.7; p=0.001), and JAK2V617F positivity (OR=2.61; p=0.043) were independent risk factors for predicting the presence of an arterial event. Likewise, we found that smoking (OR=7.07; p=0.001) and itching (OR=12.9; p=0.001) potentially predicted the presence of a venous event (Table 4).

Table 4. Independent predictors of thrombotic event development.

Variables	OR	95% CI	p
All event			
Smoking	7.41	3,01-18,26	<0,001*
Hypertension	4.44	1,65-11,96	0,003*
Heart disease	22.24	4,90-101,1	<0,001*
Itching	7.80	3,01-20,22	<0,001*
jak2 v617f positivity	3.21	1,34-7,65	0,009
	Nagelkerke R ² =0.682; p<0.001*		
Arterial event			
Smoking	7.21	2,01-21,67	<0,001*
Hypertension	5.44	1,56-18,96	0,008*
Heart disease	39.0	8,13-187,50	<0,001*
Itching	6.70	2,10-21,34	0,001*
jak2 v617f positivity	2.61	1,03-6,59	0,043*
	Nagelkerke R ² =0.714; p<0.001*		
Venöz event			
Smoking	7.07	2,12-23,63	0,001*
Itching	12.90	2,66-62,49	0,001*
	Nagelkerke R ² =0.458; p<0.001*		

* p <0.05 shows statistical significance.

Abbreviations: OR: Odd ratio, CI: Confidence interval

4. Discussion

This study is the first of its kind to be conducted a large number of patients from a single center. According to our findings, we discovered that the rates of incidence of arterial and venous thrombosis were similar to results of a previous study conducted by Barbui and Finazzi (3/4 arterial and 1/4 venous thrombosis, respectively) [11]. Other studies have counted being over 60 years of age as being one of the most significant risk factors of thrombosis [10-12]. In our study, similarly, the mean age of patients with a history of

thrombosis was significantly higher.

A Spanish study, which looked at thrombotic risk factors in PV, revealed that sex did appear to be a contributing risk factor for any thrombotic events; the same held true in our study, as well [13]. We learned that the rate of tobacco use was high among patients in the thrombotic group, and that the ratios between the presence of arterial versus venous event in relation to tobacco use were similar [14]. We observed that tobacco use seemed to contribute to thrombotic events something that is already commonly known [15]. Not only does JAK2 increase one's risk of experiencing

thrombotic events, but it also causes a predisposition to thrombosis, and in turn leads to endothelial injury and activation of thrombocytes and procoagulants [16, 17]. Our findings demonstrate that tobacco use was significantly increased patients' risk of experience thrombotic events in the presence of the JAK2 mutation. Accordingly, we are of the belief that presence of tobacco use and JAK2 mutation are independent risk factors.

While we did not observe any significant correlation between diabetes mellitus and thrombotic events, we did notice that hypertension did increase the risk at similar rates in both arterial and venous cases. Other studies involving patients suffering from PV have also revealed that having arterial hypertension also increased the risk of one's developing thrombosis. We think that this is due a high flow-resistance during the passage of thrombocytes through the injured endothelium [18, 19].

Independent of arterial and venous events, we discovered that those with a thrombotic history had had high platelet, hematocrit, white blood cell, and splenomegaly counts. It is necessary that one's hematocrit count be kept below 45 in order to keep thrombotic events and the disease itself under control. A study on myeloproliferative diseases showed that the risk of all thrombotic events was higher in patients suffering from leukocytosis, as well as that the risk of cardiovascular events had especially increased in cases where one's white blood cell count was over $15 \times 10^9/L$. Falanga et al., too, had revealed that leukocytosis and the activation of polymorphonuclear cells in patients suffering from essential thrombosis and PV had also activated procoagulants and thrombocytes, and that this was associated with hypercoagulability [6, 20].

A compilation by Dentali et al. comprising of the data of 3,123 patients demonstrated that JAK2 mutation had significantly increased the risk of thrombosis. JAK2 is thought to lead to hypersensitivity alongside the increased mobilization and aggregation of megakaryocytes, as well as is thought to cause one to develop a predisposition to thrombosis by increasing the leukocyte and thrombocyte count. Another study that investigated the effect of JAK2 mutation on thrombotic events showed that the risk of arterial thrombosis had increased in patients with essential thrombocytosis. However, the study also reported that the risk of venous thrombosis had increased only in patients with primary myelofibrosis as opposed to arterial thrombosis. On the contrary, our own findings reveal that the JAK2V617F positivity rate was higher in patients within the thrombotic group. The rate between arterial thrombosis and venous thrombosis, on the other hand, was similar [21-23].

We found that itching, too, appeared to be more common among those with a history of thrombosis. Tefferi et al. proved that the JAK2V617F mutation both increased basophil counts as well as caused itching by causing cytokine activation, especially among PV patients [24]. This correlation between JAK2 also seems to explain the increased risk of thrombosis in JAK2-positive patients [25].

Patients who had a history of thrombosis were either unresponsive to phlebotomy or had undergone cytoreductive

treatment. On the other hand, those who were resistant to hydroxyurea and anagrelide and who had received interferon were found to have had a history of thrombosis as well. We think that the failure to reach target hematocrit levels and thrombocyte counts in these patients was associated with the increased risk of thrombosis.

We identified tobacco use, hypertension, and JAK2V617F positivity as being independent risk factors for thrombosis. Upon assessing arterial or venous thrombotic events in more detail, we found that tobacco use, hypertension, and JAK2V617F positivity, as well as the presence of itching were independent risk factors predicting the presence of an arterial event, whereas we identified tobacco use and itching as being independent risk factors predicting the presence of a venous event.

Two limitations of our study include its being focused on a single medical, having data that is retrospective data in nature.

5. Conclusion

This study is the first single-institution study with a high number of patients to be conducted in a Turkish context. Accordingly, we think that the data presented here will shed light on better understanding its association with the JAK2V617F mutation, identifying the risk of thrombosis, and identifying prophylactic measures and courses of treatment for PV patients. On a final note, we feel that a multi-center, controlled, randomized studies in which patients' thrombotic risk factors, their demographical data, and the types of treatment that they undergo are equally distributed will greatly contribute to identifying other potential risk factors.

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