Thrombotic Events and Risk Factors for Thrombosis in Polycythemia in Senegal, West Africa

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Abstract

Objectives: We aim to identify thrombotic events and risk factors for thrombosis (RFT) comparing polycythemia vera (PV) and secondary polycythemia (SP) patients.

Methods: We carried out a retrospective study of a cohort of 59 patients with PV (n=34) and SP (n=25) followed for a period of 14 years. Variables studied were the frequency and type of thrombosis, sociodemographic, clinical, and biological RFT. Statistical analysis was performed using SPSS software version 18. Multivariate analysis was performed to identify RFT.

Results: Mean age in PV was 53 years (33 - 79) and 44.5 years (5 - 78) in SP (p=0.74). The sex ratio in PV was 1.12 and 2.57 in PS (p=0.52). Sixteen patients had thrombotic events (27.1%) including 12 PV (35.3%) versus 4 SP (16%) (p=0.09). Twenty-two thrombotic events were identified; 14 (63.7%) of arterial thrombosis and 8 (36.3%) of venous thrombosis. There were 18 thrombotic events (81.8%) in PV versus 4 (18.2%) in SP (p=0.02). Arterial thrombosis was more frequent in PV (55.6%). Thrombosis events were more frequent in female patients (59.1%). RFT in PV were age (40-59 years), hematocrit >45% and thrombocytosis ≥ 600 G/L and in SP, RFT were hematocrit >45% and hypercholesterolemia. After multivariate analysis, hematocrit >45% was the only RFT independently associated with thrombosis occurrence.

Conclusion: We show through this study, a frequent occurrence of arterial thrombosis in polycythemia. Main RFT is the high hematocrit level (>45%). We insist on the interest of therapeutic bloodletting, sometimes associated with cytoreductive treatment in order to maintain a hematocrit level <45%.

Keywords: Hematocrit, Polycythemia vera, Secondary polycythemia, Thrombosis

Introduction

Polycythemia refers to an excessive proliferation of the erythrocyte lineage with permanent elevation of total blood volume [1]. There are two major groups of polycythemia disorders, the PV, which is a myeloproliferative syndrome characterized by the presence of a clonal abnormality (JAK2 gene mutation: JAK2V617F or exon 12), and SP, which are often reactive to hypoxic circumstances or to tumors inappropriately secreted erythropoietin [2,3].

Difficulties of diagnosis encountered in primary polycythemia are at the origin of the establishment of diagnosis criteria regularly revised by the WHO [4,5].

Polycythemia is characterized by blood hyperviscosity leading to venous or arterial thrombosis, which is the main cause of patient mortality [6-8]. Nevertheless, it is sometimes difficult to link thrombosis events directly to polycythemia because of frequent co-morbidities in patients. The prevention of thrombosis is based on maintaining a hematocrit below

45% through therapeutic phlebotomy and sometimes cytoreductive treatment [9].

While polycythemia is widely studied in the West due to the availability of molecular analyses, in Africa, polycythemia is a rarely reported condition and studies often involve small cohorts of patients [10,11].

In our country, two studies have been conducted on polycythemia and have compared the epidemiological, diagnosis and therapeutic aspects of primary and secondary polycythemia [11,12]. These studies had found that thrombotic events were the major cause of morbidity and early mortality in patients. Because polycythemia often occurs in elderly subjects, it is sometimes difficult to link thrombosis directly to polycythemia because of the frequent comorbidities in these patients [13]. In view of this, we initiated this study with the objective to describe thrombotic events and RFT in patients followed for polycythemia.

Methods

We followed a cohort of 59 polycythemia consisting of 34 PV and 25 SP patients over a 17-year period (2004-2020). Patients followed for PV were diagnosed according to the WHO 2016 criteria. The diagnosis of PS patients was retained in front of clinical data (young age, absence of splenomegaly, history of chronic respiratory or cardiovascular diseases, prolonged stay in altitude) and blood count data (absence of hyperleukocytosis and/or thrombocytosis) and biological inflammatory signs (accelerated blood sedimentation rate, polyclonal hypergammaglobulinemia, hyperfibrinemia). In the absence of these clinical and biological data, PV diagnosis was retained even the absence of molecular biological analyses.

The SP etiologies consisted of congenital cyanogenic heart disease (n=5), chronic lung disease (n=3), chronic renal failure (n=2), chronic hepatic disease (n=1), hypoxia without a specific cause identified (n=9) and 5 cases of unidentified etiologies without PV criteria.

Dependent variables were thrombotic events in polycythemia patients. The types of thrombosis were ischemic stroke confirmed by CT scan, myocardial infarction confirmed by ECG with persistent ST-segment elevation, deep venous thrombosis of the inferior members, of the superior members or superficial venous thrombosis confirmed by venous Doppler, pulmonary embolism confirmed on angioscan and portal thrombosis or Budd Thiari syndrome on abdominal CT scan or abdomino-pelvic ultrasound.

Independent variables consisted of sociodemographic data (age, sex, exposure to toxic substances, high altitude >2000 m), medical history such as chronic hepatic disease, chronic obstructive pulmonary disease, pulmonary neoplasia, heart disease, renal tumor), biological data (hematocrit,

hyperleukocytosis, thrombocytosis, Jak2V617F mutation). The therapeutic data consisted of phlebotomy (8 ml/kg without exceeding 500 ml in emergency or basic treatment 1 to 3 sessions per month), low-dose aspirin (100 mg/d), hydroxyurea (10-20 mg/kg/d), anticoagulants (antivitamin K dose adjusted to INR and low-molecular-weight heparin at 100 IU/kg/12h)

Cardiovascular risk factors studied were age, sex, hypertension defined as blood pressure >140/90 mm Hg, diabetes, current smoking or smoking stopped for less than 3 years, hypercholesterolemia (LDL >1.6 g/L), obesity (BMI >30).

Statistical analysis was performed using SPSS software (version 18). A univariate and bivariate descriptive study summarized the quantitative variables as means with their standard deviations and the qualitative variables as numbers and percentages. Fisher test was used to measure the strength of the association as Relative Risk (RR), with the 95% confidence interval (CI). Multivariate analysis was performed by binary logistic regression to further investigate the RFT. A p value <0.05 was considered statistically significant

An informed consent form was signed by all patients, and anonymity and confidentiality were respected for all personal data collected.

Results

General baseline characteristics of patients

Mean age was 53 years (33-79) in PV and 44.5 years (5-78) in SP patients (p=0.74). The sex ratio M/F was l, 12 in PV and 2.57 in SP (p=0.52).

Only PV patients had presented thrombocytosis ≥ 600 G/L (p=0.002) and JAK2V617F mutation (p=0.000) (mutational load was >50% in 75% of PV patients.

Therapeutic bloodletting for background treatment was performed more in PS patients (p=0.001). Hydroxyurea was used only in PV patients (p=0.000).

No progression to primary myelofibrosis or acute leukemia was noted. Seven patients (11.8%) had died, 2 deaths in PV (5.8%) and 5 deaths in SP (20%) (**Table 1**). Causes of death in PV consisted of thrombosis, whereas in SP, deaths were due to complications of the baseline pathology.

Frequency and type of thrombosis in PV and SP patients

Sixteen patients had thrombotic events (27.1%) including 12 PV patients (35.3%) and 4 SP patients (16%) (p=0.09) (**Figure 1**).

Twenty-two thrombotic events were identified including 18 thrombotic events (81.8%) in PV versus 4 cases (18.2%) in PS (p=0.02).

Table 1. General Baseline Characteristics of Patients.

| Data	PV (n=34)	PS (n=25)	p
Mean age (years)	53	44.5	0.74
Sex (M/F)	18/16	18/7	0.52
High blood pressure	41.10%	44%	1
History of diabetes	8.80%	4%	0.63
LDL cholesterol	8.80%	4%	0.63
Hematocrit > 45%	50%	32%	0.46
Thrombocytosis ≥ 600 G/L	38.20%	0	**0.002**
JAK2V617F mutation	47%	0	**0**
Leucocytosis > 15 G/L	32.30%	0	0.054
Bloodletting (emergency)	82.30%	88%	1
Bloodletting (basic treatment)	14.70%	84%	0.001
Acetyl salicylic acid	85.30%	48%	0.21
Hydroxyurea	85.20%	0	**0**
Number of deaths (n=7)	5.80%	20%	0.23
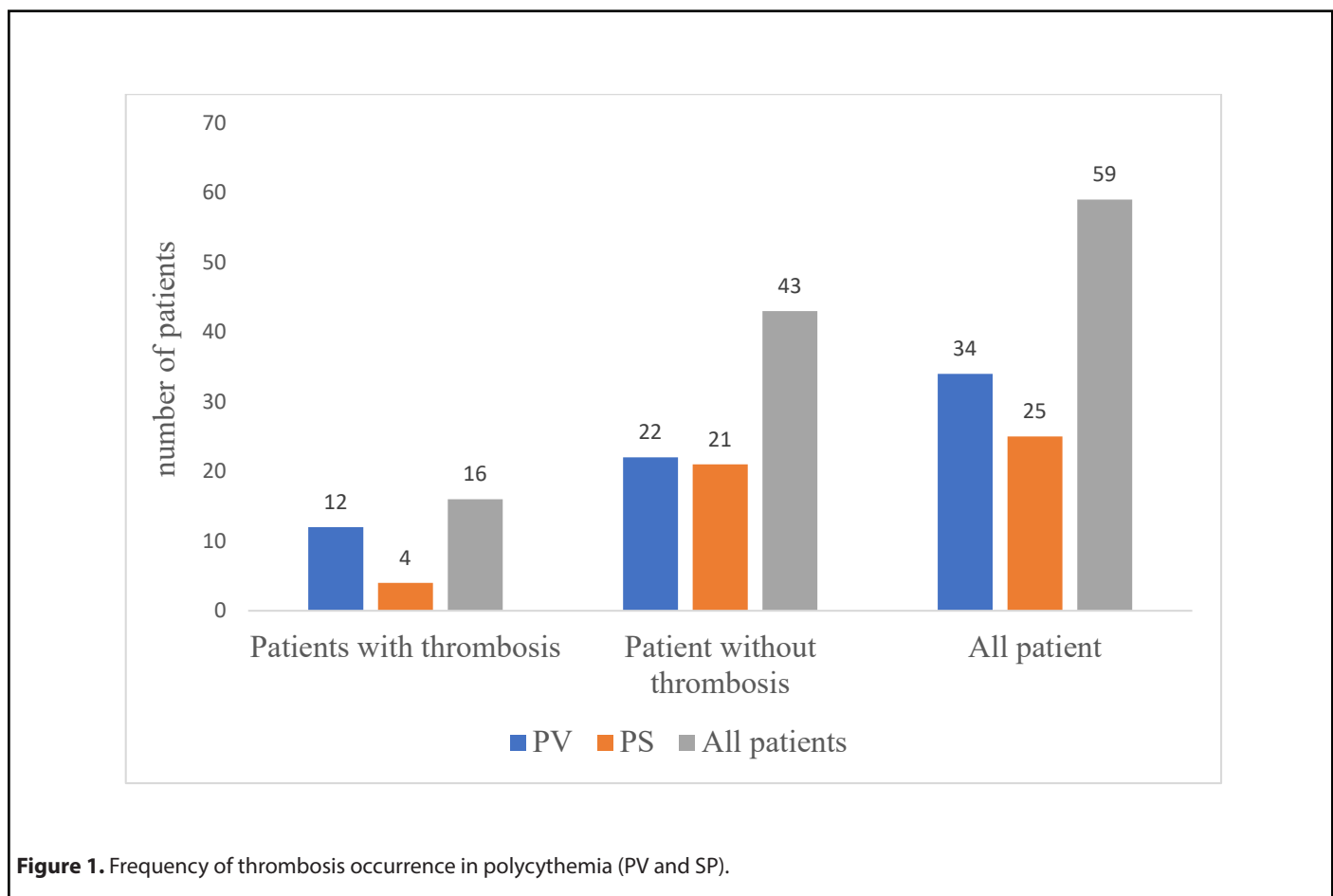
Figure 1. Frequency of thrombosis occurrence in polycythemia (PV and SP).

Arterial thrombosis was more frequent (63.7%) and represented 55.6% of thrombosis events for PV patients. IS type being more frequent (45.45%) but there was no significant difference in the type of thrombosis between PV and SP (p>0.05) (**Table 2**).

Thrombosis events were more frequent in female patients (59.1%) but there was no difference for thrombosis type in terms of frequency between PV and PS according to sex (p>0.05) (**Table 3**).

RFT identified in PV and SP patients

The RFTs identified were age range between 40 and 59 years (RR=3.32), hematocrit >45% (RR=3.54), thrombocytosis ≥ 600G/L (RR=5.89) and hypercholesterolemia (RR=3.17) (**Table 4**).

RFTs identified in PV were age (40-59 years) (p=0.02), hematocrit >45% (p=0.00), and thrombocytosis ≥ 600 G/L (p=0.00), whereas in SP, RFTs were hematocrit >45% (p=0.02) and hypercholesterolemia (p=0.01) (**Table 5**).

Table 2. Type of thrombosis and frequency according to the type of polycythemia.

Thrombotic events (n=22)	PV (n=18; 81.8%)	PS (n=4; 18.2%)	P
IS (n=11)	7 (63.6%)	4 (36.4%)	0.867
MI (n=3)	3	0	0.22
DVT IM (n=3)	3	0	0.127
SVT (n=2)	2	0	0.387
DVT SM (n=2)	2	0	0.22
PE (n=1)	1	0	0.387

IS: Ischemic Stroke; MI: Myocardial Infarction; DVT IM: Deep Venous Thrombosis of the Inferior Members; DVT SM: Deep Venous Thrombosis of the Superior Members; SVT: Superficial Venous Thrombosis; PE: Pulmonary Embolism

Table 3. Type of thrombosis for polycythemia patients according to gender.

	PV (n=18)		PS (n=4)		
	M	F	M	F	P
	(n=6)	(n=12)	(n=3)	(n=1)	
IS (n=11)	27.3%	36.4%	27.3%	9%	0.867
MI (n=3)	33.3%	66.7%	0	0	0.22
DVT IM (n=3)	66.7%	33.3%	0	0	0.127
SVT (n=2)	0	2	0	0	0.387
DVT SM (n=2)	0	2	0	0	0.22
PE (n=1)	0	1	0	0	0.387

Table 4. RFT identified in polycythemia patients (PV versus PS).

Data	Patients with thrombosis (PT+) (n=16)	Patients without thrombosis (PT-) (n=43)	P	RR
Age (years)				
≤40	18.7%	30.2%	0.38	0.62
40-59	68.7%	37.2%	**0.00**	**3.32**
≥60	12.5%	32.5%	0.12	0.38
Sex				

Male	19.4%	67.4%	0.09	0.49
Female	39.1%	32.5%	0.09	11.7
High blood pressure	43.7%	41.8%	0.92	0.916
History of diabetes	6.2%	7%	0.42	0.49
Smoking history	6.2%	14%	0.38	0
Hematocrit > 45%	81.2%	27.9%	**0.00**	**3.54**
Thrombocytosis ≥ 600G/L	50%	11.6%	**0.00**	**5.89**
JAK2V617F	37.5%	23.2%	0.27	1.61
Leukocytosis ≥15 G/L	25%	16.3%	0.44	1.45
LDL cholesterol	18.7%	2.3%	**0.02**	**3.17**

Table 5. RFT identified according to the type of polycythemia (PV versus PS).

Data	PV PT+ (n=12)	PT- (n=22)	P	PS PT+ (n=4)	PT- (n=21)	P
Age (years)						
≤40	8.3%	18.2%	0.43	50%	42.8%	0.79
40-59	75.0%	45.5%	**0.02**	50%	28.6%	0.40
≥60	16.7%	36.4%	0.23	0	28.6%	0.22
Sex						
Male	33.3%	63.6%	0.09	100%	71.4%	0.22
Female	66.7%	36.4%		0	28.6%	
High blood pressure	33.3%	9.1%	0.22	50%	42.9%	0.79
History of diabetes	8.3%	4.5%	0.45	0	4.8%	0.65
Smoking history	0	4.5%	0.45	25	33.3%	0.74
Hematocrit > 45%	66.7%	22.7%	**0.00**	75%	42.9	**0.02**
Thrombocytosis ≥ 600 G/L	66.6%	22.7%	**0.00**	0	0	NA
JAK2V617F	50%	45.5%	0.80	0	0	NA
Leukocytosis > 15 G/L	33.3%	4.5%	0.65	0	0	NA
LDL cholesterol	8.3%	4.5%	0.65	25%	0	**0.01**

After multivariate analysis, the only RFT independently associated with the occurrence of thrombosis in PV or SP was elevated hematocrit >45%.

Discussion

We observed a predominance of PV (34 PV versus 25 SP), which is not the case in several studies that had shown a predominance of SP compared to PV [14]. This difference can be explained on the one hand by the fact that our department focuses specifically the management of malignancy hemopathies, whereas SP have a multidisciplinary management including hematology and the specialty of the causative pathology.

It is noteworthy that patients with PV had a mean age of 53 years, which is lower than the mean age reported in the West, which is 60 years [15]. This finding has been found in other studies in sub-Saharan Africa where the mean age of patients was less than 60 years [6,16,17].

According to gender, approximately 53% of PV patients were male (sex ratio = 1.12). In SP, the sex ratio was 2.57. Male frequency in PV has also been described in other studies in the West and in Africa [4,16-18].

Cytoreductive therapy with hydroxyurea was used exclusively for the basic treatment of PV; of 85.3% of PV patients who received this treatment, 41.4% had at least one history of thrombosis. In patients without a history of thrombosis, this type of treatment was prescribed in 27.6% of patients over 60 years older, and in 31% of patients under 60 years who had hematocrit level >45%, leukocytosis >15 G/L, or thrombocytosis ≥ 600 G/L, resistant to therapeutic bloodletting. Due to the fact that we have a very young population at risk of thrombotic complications, the decision was made to use hydroxyurea in patients <60 years without a history of thrombosis, despite recommendations in the Western literature reserving Hydroxyurea for patients at high risk of thrombosis (age >60 years and/or a history of thrombosis). Therapeutic erythrocytapheresis is a more efficient strategy compared to therapeutic bloodletting to deplete levels of hematocrit in primary and secondary erythrocytosis [19-21]. The outcome of the treatment was favorable in most patients. It was marked by the control of hematocrit level at a value <45%. Contrary to the PVSG data, 1/3 of patients surviving the first thrombotic event will recur. In this study, 1/4 of patients with a history of thrombosis had at least one thrombosis recurrence. It was noted that thrombotic recurrence during follow-up occurred exclusively in patients with at least one history of venous thrombosis [22].

The frequency of JAK2V617F mutation was more than 60% in PV patients. Given the frequency of JAK2V617F mutation in PV (96%) [19], JAK2 mutation testing at exon 12 would have been requested if JAK2V617F-negative patients with strong suspicion of PV [20].

The therapeutic approach taken resulted in favorable outcomes, although two patients had recurrent thrombosis. This shows the difficulty of managing anticoagulant treatment in polycythemia. Anticoagulant treatment is often combined with therapeutic bloodletting to significantly reduce the blood hyperviscosity generated [21].

In this study, 27.1% of patients presented thrombotic events. We noted a predominance of arterial thrombosis as previously reported in several studies [4,23,24]. Female were more exposed to thrombosis but without any statistically significant difference compared to male patients. Nevertheless, female gender has been reported as a RFT in several studies [25].

Depending on the type of polycythemia, thrombotic events occurred more in PV patients. Laboratory studies show that coagulation activation markers are significantly higher in PV than in PS [24]. However, our results are better than other studies where the probability of thrombosis in PV was estimated to be more than 40% [26,27].

A total of 22 thrombotic events were identified with a predominance of ischemic stroke (more than 45%) followed by myocardial infarction, deep venous thrombosis of the members, superficial venous thrombosis and pulmonary embolism. All these types of thrombosis were observed in PV, but only ischemic stroke was noted in SP patients. This can be explained by the fact that the most frequent etiologies of SP in our study were pathologies at high risk of thrombosis such as heart disease and chronic broncho-pneumopathy.

Despite the higher frequency of thrombotic events and the presence of all types of thrombosis in PV [27], this study did not show any significant difference according to the type of thrombosis compared with SP.

This leads us to investigate, all factors that may influence the occurrence of thrombosis during primary or secondary polycythemia. Because polycythemia often occurs in elderly subjects, it is sometimes difficult to link thrombosis events directly to polycythemia because of the frequent comorbidities causing the occurrence of thrombosis in these patients [13].

The main sociodemographic or clinico-biological RFTs identified were the age range between 40 and 59 years, hematocrit level >45%, thrombocytosis ≥ 600 G/L and hypercholesterolemia. According to the type of polycythemia, RFTs identified in PV consisted of age, high hematocrit level and thrombocytosis, whereas in SP, RFTs identified were high hematocrit level and hypercholesterolemia. However, after multivariate analysis, the only RFT independently associated with the occurrence of thrombosis in PV or SP was hematocrit level >45%.

This study confirms the data in the literature that a hematocrit >45% is a cardiovascular risk factor in patients with PV or SP due to blood hyperviscosity [21,28,29].

Several studies have identified advanced age (>60 years) as a major RFT, due to vascular aging, and the tendency to hypercoagulability [30]. In our study, the predominance of young age would explain the fact that an age range between 40 and 59 years is considered an RFT.

Although somewhat unclear to some authors, thrombocytosis (>600 G/L) has been associated with a high risk of thrombosis in PV [31], as demonstrated in our study.

Hypercholesterolemia is a cardiovascular risk factor that favors the occurrence of thrombosis, as it would increase the risk of vascular injury through the action of arteriosclerosis. In addition, the concomitant presence of hypercholesterolemia with other factors such as hematocrit >45% would have an aditive pro-coagulant effect [25].

Some authors have suggested the presence of the JAK2V617F mutation, especially with a mutational load >50%, as a RFT in PV [32]; however, in this study, as in others [26,33],

JAK2V617F mutation, even with a mutational load >50% was not identified among RTF.

The therapeutic approach chosen in our patients resulted in favorable outcomes, although some patients had recurrent thrombosis. This shows the difficulty of managing anticoagulant treatment in polycythemia. Anticoagulant treatment is often combined with therapeutic bloodletting to considerably reduce blood hyperviscosity generated in polycythemia.

However, our study has two limitations: the small size of the cohort and the fact that some RFTs such as the concomitant presence of thrombophilia factors, obesity, sedentary lifestyle or oral contraceptives could not be evaluated due to the retrospective study.

We show through this study, a frequency of arterial thrombosis in polycythemia. The main RFT is the high hematocrit level (>45%), even if, others RFTs were identified such as the age range (40-59 years), thrombocytosis ≥ 600 G/L and hypercholesterolemia. We insist on the interest of therapeutic bloodletting, sometimes associated with cytoreductive treatment in order to maintain a hematocrit level below 45% to reduce occurrence of thrombotic events.

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