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– ORIGINAL PAPER –

Prognostic Factors in Polycythemia Vera

Sandor-Szilard PORTIK[1*], Laura URIAN[1,2], Mihnea ZDRENGHEA[1,2], Anca VASILACHE[1], Tunde TOROK[1,2], Andrada PARVU[1,2], Ciprian TOMULEASA[1,2], Delia DIMA[1], Ioana RUS[1], Oana MESAROS[1,2], Laura JIMBU[1,2], Anca BOJAN[1,2]

Abstract

Introduction: *Polycythemia vera is a chronic myeloproliferative neoplasm associated with an increased risk of thrombotic events, the main cause of morbidity and mortality. The established risk factors are age ≥60 years and prior thrombosis.*

Objectives*: To identify clinical, biological and therapeutic factors associated with thrombosis in PV patients.*

Materials and Methods*: We conducted a retrospective, single-center study of 89 JAK+ PV patients diagnosed and treated between January 2015 and August 2025 in the Hematology Department of the "Prof. Dr. Ion Chiricuță" Institute of Oncology, Cluj-Napoca. Demographic, clinical, treatment-related and laboratory data (erythrocytes, hemoglobin, hematocrit, RDW, leukocytes, platelets, ferritin) were analyzed. Statistical evaluation was performed in GraphPad Prism using t-tests, Chi-square tests and logistic regression.*

Results*: The median age at diagnosis was 61,3 years; 50,5% were female. Comorbidities were present in 53,9%, most frequently arterial hypertension (47,9%). Thrombosis occurred in 19 patients (21,3%): 7 pre-diagnosis, 11 post-diagnosis and 1 both pre- and post-diagnosis, with an equal arterial/venous distribution. In univariate analysis, patients with thrombosis were older (66,63 vs. 59,91 years; p=0,039) and had higher RDW (53,57 vs. 49,17; p=0,007). Other factors (comorbidities, treatment) were not significantly associated with thrombosis. Multivariate regression identified RDW as the only independent predictor of thrombotic risk (HR=1,7; 95%CI: 1,06–4,2; p<0,005). Age and lower hematocrit showed trends (HR=1,04 and HR=0,62) without statistical significance.*

Conclusion: *RDW, a simple and affordable hematologic parameter, was independently associated with thrombotic risk in PV and may serve as an additional marker for thrombotic risk stratification.*

Keywords: *polycythemia vera, thrombotic risk, RDW*

[1] Institute of Oncology "Prof. Dr. Ion Chiricuta", Cluj-Napoca, Romania

[2] University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania

Corresponding author:
*** Sandor-Szilard Portik,** Institute of Oncology "Prof. Dr. Ion Chiricuta", Cluj-Napoca, Romania
Email: portiksanyika@yahoo.ro

Introduction

Polycythemia vera is a clonal hematopoietic stem cell disease, in which the emergence of certain mutations, such as the gain-of-function mutation of JAK2 gene, causes the overproduction of red blood cells independent of the circulatory erythropoietin level. (1) (9) Clinical features include constitutional symptoms, aquagenic pruritus, palpable splenomegaly and microcirculatory symptoms (headaches, visual symptoms, erythromelalgia), while laboratory findings showcase an increased erythrocyte count and an elevated

hemoglobin/hematocrit level, as well as leukocytosis with granulocytosis and thrombocytosis. (2)

The clonal erythropoiesis in polycythemia vera is associated with both quantitative and qualitative abnormalities of red blood cells. The subsequent increase in red blood cells and hemoglobin leads to an elevated hematocrit, resulting in elevated blood viscosity and a series of microcirculatory disorders. In parallel, red blood cells exhibit reduced deformability, further contributing to hyperviscosity and overexpress adhesion proteins and release procoagulant extracellular microvesicles. Additionally, the chronic activation of leukocytes and platelets, driven by constitutively active JAK2 signaling, leads to the secretion of particles enriched in procoagulant factors, thereby promoting a prothrombotic state and facilitating the formation of thrombi. (1) (3) (9)

Thrombosis is an important complication of polycythemia vera and represents the main cause of morbidity and mortality, with an incidence of 3,8 per 100 patient-years. (4) Numerous factors such as age above 60 years old, history of thrombosis, JAK2V617F allele burden, the intensity of phlebotomy alongside the cardiovascular factors (hypertension, diabetes mellitus, dyslipidemia) increase the thrombotic risk. (1) (10) In clinical practice, thrombotic risk stratification is based on age and previous thrombotic events, with patients being divided into low risk, if their age is under 60 years or if patient history findings lack at least one thromboembolic event, or high risk, if both these factors are present. (4) However, recent evidence suggests that these variables do not capture the full complexity of risk, which appears to be influenced by a complex interaction of several factors. (5)

Several therapeutic options are available in polycythemia vera, which primarily focuses on improving quality of life and reducing the risk of complications. All patients with polycythemia vera, regardless of risk, require periodic phlebotomy at well-established time intervals, with a therapeutic target being achieving and maintaining a hematocrit below 45%, and daily aspirin therapy. In high-risk patients, the use of cytoreductive agents such as hydroxycarbamide, Janus kinase inhibitors such as ruxolitinib and other drugs such as pegylated interferon or anagrelide is advised, along with periodic venesections and anti-thrombotic therapy. (2) (11)

Materials and Methods

This retrospective unicentric study included JAK+ polycythemia vera patients diagnosed and treated between January 2015 and August 2025 in the Hematology Department of the “Prof. Dr. Ion Chiricuță” Institute of Oncology from Cluj-Napoca. By participating in the study, patients consented to the use of their personal clinical and paraclinical data.

The main objective was the identification of risk factors associated with thrombotic events in these patients. The secondary objectives included the characterization of these events and the assessment of the impact of treatment on thrombotic risk.

Information regarding each patient was collected from hospital medical records. Demographic data, including age, gender, medical history, the date of polycythemia vera diagnosis, signs and symptoms of the disease were collected. Further data included hematology laboratory parameters (RBC, hemoglobin, hematocrit, RDW, WBC, platelets), iron reserve status, phlebotomy history, applied hematological treatments and thrombosis history. Thrombotic events appearing more than 30 days after the date of diagnosis were considered post-diagnosis and others pre-diagnosis. A favorable response to therapy was defined as sustained hematocrit control (<45%), independent of treatment modality (phlebotomy and/or cytoreductive therapy); with a low phlebotomy need (≤3 procedures/year) considered an additional defining criterion. Phlebotomy dependence was defined as a requirement for ≥3 phlebotomies/year.

Statistical analysis was made using Microsoft Excel and GraphPad Prism using t-tests, Chi-square tests and logistic regression.

Results

89 patients were included in the study, of which 44 (49,5%) males and 45 (50,5%) females. The mean age was 61,3 years and the majority, 54 (60,6 %) patients, were over 60 years old. At the time of diagnosis, 57 (64,3%) patients presented clinical signs and symptoms consistent with polycythemia vera, the most frequently reported being hyperemia. Comorbidities were present in 48 (53,9%) cases, with arterial hypertension being the most common. Detailed distributions of clinical features at diagnosis and comorbidities are presented in *Table*. 73 (82%) and 6 (6,7%) patients received hydroxyurea and pegylated interferon as first line treatment, while 8 (8,9%) patients were treated only with periodic phlebotomies and low-dose aspirin. Two patients initially received anagrelide; subsequently removed and changed later, as current guidelines do not recommend its use in polycythemia vera. A favorable response to treatment, according to the predefined criteria, was observed at 26

(29,2%) patients, whereas 62 patients (69,6%) did not achieve or sustain hematocrit control under first line therapy. 30 patients (33,7%) required a change in first line therapy due to inefficacy or intolerance. 57 (64%) patients became phlebotomy dependent during the follow-up.

Table1. *Clinical features and comorbidities of patients with polycythemia vera at diagnosis*

Clinical features	
Asymptomatic, n (%)	32 (35,9%)
General symptoms, n (%)	15 (16,8%)
Hyperemia, n (%)	24 (26,9%)
Pruritus, n (%)	15 (16,8%)
Splenomegaly, n (%)	14 (15,7%)
Hepatomegaly, n (%)	3 (3,3%)
Neurological symptoms, n (%)	7 (7,8%)
Comorbidities	
Arterial hypertension, n (%)	23 (47,9%)
Ischemic heart disease, n (%)	18 (37,5%)
Diabetes mellitus, n (%)	5 (10,4%)
Periferic arterial disease, n (%)	3 (6,2%)
Atrial fibrillation, n (%)	3 (6,2%)

Median follow-up was 53,1 months during which 19 patients (21,3%) had ≥1 thrombotic event, of which 7 (36,8%) presented pre-diagnosis, 11 (57,8%) post-diagnosis and in one patient thrombosis occurred both before and after the diagnosis. Among the 19 patients, the majority (n=18; 94,7%) had a single thrombotic event, while one patient experienced multiple thrombotic events. The distribution of arterial and venous thromboses was equal (n=10; 50%) as can be seen in *Figure 1*, which presents a detailed breakdown of thrombotic events by type and location.

We found no significant correlations between the presence of clinical manifestations of polycythemia vera at diagnosis (HR= 0,7 [0,3-1,7]; p=0,59) or the presence of cardiovascular comorbidities (arterial hypertension, ischemic heart disease and diabetes mellitus) (HR= 2,1 [0,9-5,0]; p=0,11) and the subsequent risk of thrombotic events, although a trend of increased risk was observed in patients with these comorbidities.

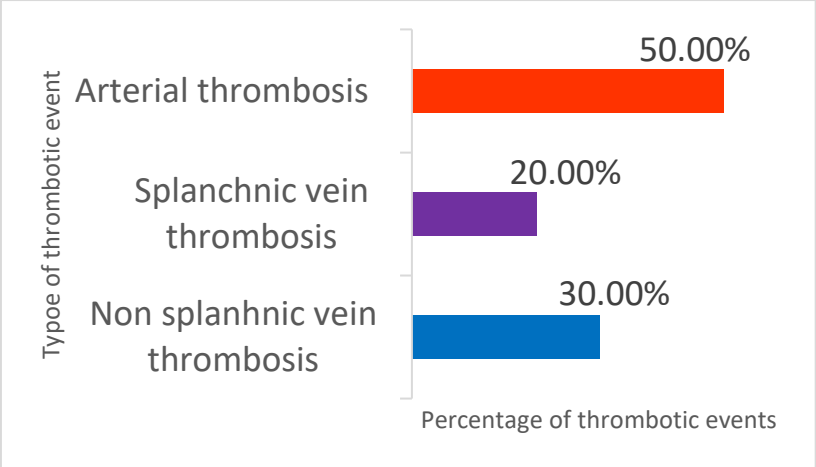

Figure 1. *Distribution of thrombotic events in patients with polycythemia vera. Arterial thrombosis included myocardial infarction, stroke and transient ischemic attack; non splanchnic venous thrombosis included deep vein thrombosis and pulmonary embolism; splanchnic vein thrombosis included Budd-Chiari syndrome*

Baseline characteristics, including age, hematological and biochemical parameters, are presented in *Table* 2 as mean values for the overall study population and according to the thrombotic status. Group comparisons were performed using univariate analysis, with corresponding p values reported.

Table 2 *Comparison of age and baseline laboratory parameters between patients with and without thrombotic events. Values are represented as mean (range)*

Analyzed factors	*Total study population (n=89)*	*Patients with thrombotic events (n=19)*	*Patients without thrombotic events (n=70)*	*P value*
Age (years)	*61,34 (27-86)*	*66,63 (41-79)*	*59,91 (27-86)*	*0,039*
RBC (10^6 /µL)	*6,26 (3,76-9,47)*	*6,06 (3,76-8,46)*	*6,32 (3,84-9,47)*	*0,455*
Hgb (g/dl)	*17,45 (11,3-24,2)*	*16,78 (12,5-21,5)*	*17,68 (11,3-24,2)*	*0,208*
HCT (%)	*52,76 (36,4-73)*	*50,7 (36,4-65,4)*	*53,33 (38-73)*	*0,234*
RDW-SD (fl)	*50,12 (35,5-77,4)*	*53,57 (43-77,4)*	*49,17 (35,5-64,7)*	*0,007*
WBC (/µL)	*10 844 (2 800-27 270)*	*11 581,05 (2 800-27 100)*	*10 644,86 (4 140-27 270)*	*0,459*
PLT (/µL)	*476 898 (92 000-1 628 000)*	*460 631,6 (155 000-833 000)*	*481 314,3 (92 000-1 628 000)*	*0,753*
Ferritin (µg /L)	*73,15 (8,03-410)*	*56,75 (20-157)*	*77,45 (8,03-410)*	*0,486*

Patients who developed thrombotic events were significantly older (p=0,03) and presented higher RDW values (p=0,007) compared to those without thrombosis, as shown in *Figure 2*. No statistically significant differences were observed for the other analyzed parameters.

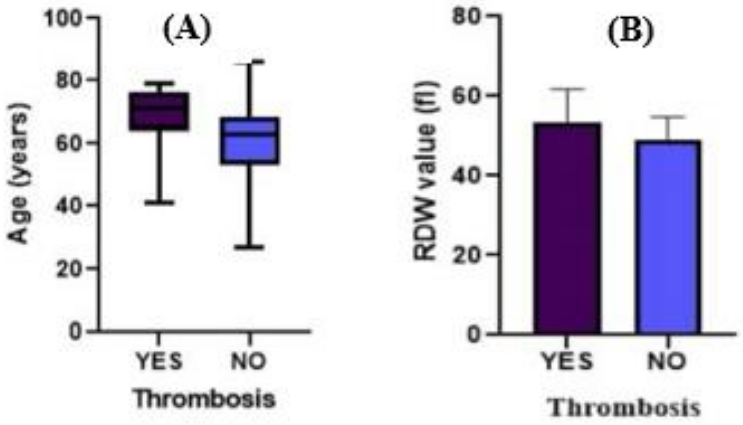

Figure 2. *Association of age and RDW values with thrombotic events in patients with polycythemia vera. (A) Patients with thrombotic events were significantly older compared to those without thrombosis. (B) RDW values were significantly higher in patients who developed thrombotic events.*

The evaluation of treatment-related factors on thrombotic risk showed that the cytoreductive therapy with hydroxyurea did not reduce significantly the thrombotic risk (HR= 0,7 [0,2-2,3]; p=0,69) compared to other

treatment modalities, although a non-significant trend toward risk reduction was observed. Elevated hematocrit level, above 45% (HR= 0,3 [0,1-0,8]; p=0,03), in patients who failed to maintain the hematocrit control with therapy, showed a significantly higher risk of thrombosis. Although patients who developed phlebotomy dependency during the follow-up period appeared to have a higher thrombotic risk (HR= 1,5 [0,2-1,2]; p=0,69), this association was not statistically significant.

In multi-variable analysis, RDW (HR= 1,7 [1,06-4,2]; p=0,04) was the only independent predictor for thrombotic events. Although older age (HR= 1,04 [0,9-1,1], p=0,24) demonstrated a trend toward elevated thrombotic risk and lower hematocrit levels appeared to confer a protective effect against subsequent thrombotic events, neither association reached statistical significance.

Discussions

Our study provides real-world data on thrombotic events, associated risk factors and treatment impact in patients with polycythemia vera. Our cohort's typical profile was characterized by older age, the presence of disease-related symptoms at diagnosis and the presence of cardiovascular comorbidities, placing the majority of patients within a high risk category according to conventional risk stratification models, which are primarily based on age and thrombotic history.

The overall incidence of thrombotic events in our study (21,3%) is comparable to that reported in the literature, with previous studies reporting a thrombotic risk of approximately 26% (1), confirming thrombosis as a major complication of the disease.

The presence of cardiovascular comorbidities in our cohort was associated with a trend toward increased thrombotic risk without reaching statistical significance, further underscoring the complex and multifactorial nature of thrombosis in polycythemia vera. These findings are in line with the different results reported in the literature. The ECLAP study did not demonstrate a significant association between arterial hypertension or diabetes mellitus and the risk of arterial or venous thrombotic events (5), whereas other studies have identified these conditions as contributors, particularly to arterial thrombosis. (6) (7) In addition, the role of hematologic parameters as predictors of thrombotic risk remains inconsistent across studies. Large cohorts such as the REVEAL study and the CYTO-PV study have suggested that leukocytosis, particularly values exceeding 11×10^9/L, is associated with an increased risk of thrombosis, while the contribution of thrombocytosis remains controversial, with conflicting results reported in the literature. (5) In our cohort, however, no statistically significant associations were identified between leukocyte or platelet counts and thrombotic risk.

We observed a similar pattern as in the original polycythemia vera study group (PVSG) and ECLAP study, which demonstrated an increased risk of cardiovascular complications in patients older than 65 years with polycythemia vera, forming the basis for current risk stratification models. (1) (5) In our analysis, patients who developed thrombotic events were significantly older in the univariate analysis compared to those without thrombosis. However, this correlation did not remain significant in multivariate analysis. This result confirms the role of age as a useful component of traditional risk stratification, while also suggests that thrombotic risk in polycythemia vera is multifactorial and may be more precisely assessed by integrating additional biological parameters.

In our cohort, patients with hematocrit values above 45% presented a significantly higher risk of thrombotic events, underscoring the clinical importance of maintaining hematocrit below this level. These results are in agreement with the CYTO-PV study, which demonstrated a significantly lower incidence of cardiovascular death and thrombotic events in patients maintained at a hematocrit level <45% compared to those with levels between 45–50% (2,7% vs 9,8%). (1) (4) Therefore, hematocrit control below 45% remains a therapeutic goal, but represents also an important modifiable factor in prevention of thrombotic events.

Perhaps the most important finding of our study is related to the significance of the hematological parameter RDW in the mechanism of thrombosis. Known as a parameter which reflects the variability in size and volume of red blood cells, recent studies have reported RDW as a predictor of thrombotic events in patients with polycythemia vera, although the underlying mechanisms are not completely understood. Elevated RDW values are associated with reduced erythrocyte deformability, which may impair microcirculatory flow and increase blood viscosity. It is recognized as a marker of ineffective erythropoiesis and systemic inflammation, contributing to a prothrombotic state. (5) (3) Our study identified higher RDW values in patients with thrombotic events in univariate analysis and identified RDW as the only independent predictor of thrombotic risk in multi-variable analysis. This is in line with a study conducted on 92

patients with myeloproliferative neoplasms (41 with polycythemia vera), where higher RDW was associated with worse thrombosis-free survival (12), and is opposite to another study which included 902 newly diagnosed polycythemia vera patients, where the same outcome was observed with lower RDW values (<14,5%) in high risk patients. (8) Despite the contradictory findings, RDW variations may reflect disturbances in erythrocyte homeostasis impacting the thrombotic risk.

Conclusions

Our findings confirm the risk of thrombotic complications in patients with polycythemia vera and highlight the critical importance of strict hematocrit control. Furthermore, our study emphasizes that RDW, a simple and widely available parameter from the complete blood count, could serve as an additional marker for thrombotic risk stratification alongside traditional factors.

Abbreviations

PV – polycythemia vera
RDW – red cell distribution width
RBC – red blood cell count
WBC – white blood cell count
HGB – hemoglobin
HCT – hematocrit
PLT – platelets

Ethics Statement and Conflict of Interest Disclosures

Financial support and sponsorship: All authors have declared that no financial support was received from any organization for the submitted work.

Ethics Consideration: The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national laws. Written informed consent was provided by the participant in this study.

Conflict of interest: No known conflict of interest correlated with this publication.

Availability of data and materials: The data used and/or analyzed throughout this study are available from the corresponding authors upon reasonable request.

Competing interests: The authors declared that they have no competing interests.

The use of generative AI and AI-assisted technologies: AI technologies were used solely to refine English language and spelling.

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