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A dynamic prognostic model for polycythemia vera long-term outcomes in patients treated with ruxolitinib

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Key Points

- PV-RR6 is a dynamic risk model integrating spleen response, hematocrit control, and dose intensity in ruxolitinib-treated PV.
- Maintaining full-dose ruxolitinib despite mild anemia was associated with superior 5-year EFS.

Ruxolitinib is widely used in polycythemia vera (PV) following hydroxyurea failure. However, validated response criteria to predict long-term outcomes in ruxolitinib-treated patients are lacking, complicating clinical decision-making. We investigated predictors of event-free survival ([EFS]; including progression to post-PV myelofibrosis, thrombosis, hemorrhages, or death) after 6 months of ruxolitinib in 178 patients with PV enrolled in the observational PV-ARC study. After a median follow-up from ruxolitinib start of 3.50 years, 15 patients died, 7 had a thrombosis, 9 had a hemorrhage, and 21 progressed to myelofibrosis. Overall, 5-year EFS was 70.4%. Leukocytosis, thrombocytosis, phlebotomy need, lack of spleen length reduction ≥50% (SR50), and ruxolitinib dose <10 mg twice daily at 3 time points (baseline and months 3 and 6), were tested for association with EFS. Multivariable analysis identified 3 independent risk factors: (1) ruxolitinib dose <10 mg twice daily at ≥1 time point (hazard ratio [HR], 1.94; P = .047), (2) no SR50 at months 3 and 6 (HR, 2.65; P = .009), (3) phlebotomy requirement at ≥2 time points (HR, 2.11; P = .039). Points were assigned as follows: 1 to phlebotomies at 1 time point; 2 to phlebotomies at ≥2 time points and to ruxolitinib <10 mg twice daily at ≥1 time point; and 2.5 to lack of SR50. Based on cumulative scores, we developed the PV–response to ruxolitinib after 6 months (PV-RR6) prognostic model, identifying 3 risk categories: low (score 0: 5-year EFS, 89.4% [n = 63]), intermediate (score 1-2.5: EFS, 71.0% [n = 82]), and high (score >2.5: EFS, 38.9% [n = 33]). PV-RR6 enables early identification of patients at risk of poor outcomes, supporting

Submitted 27 February 2026; accepted 3 May 2026; prepublished online on *Blood Advances* First Edition 11 June 2026; final version published online 3 August 2026. https://doi.org/10.1182/bloodadvances.2026020255.

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The data that support the findings of this study are available from the corresponding author, Chiara Sartor (chiara.sartor2@unibo.it), on request, at the following DOI: https://doi.org/10.5281/zenodo.17484861.

The full-text version of this article contains a data supplement.

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timely treatment optimization in ruxolitinib-treated patients. This trial was registered at www.clinicaltrials.gov as NCT06134102.

Introduction

Polycythemia vera (PV) is a chronic Philadelphia-negative myeloproliferative neoplasm characterized by the clonal proliferation of hematopoietic stem cells, leading to erythrocytosis and frequently associated leukocytosis, thrombocytosis, burdensome systemic symptoms, and progressive splenomegaly.[1-4] The disease carries a substantial burden of morbidity, mainly due to thromboembolic complications,[5-7] and may evolve over time into post-PV myelofibrosis (post-PV MF) or secondary acute myeloid leukemia.[8-10]

The primary therapeutic goal is to prevent vascular events, which can be achieved by strictly controlling hematocrit levels and using low-dose aspirin. Phlebotomies and rigorous control of cardiovascular risk factors (CVRFs) are the cornerstone of PV management in all patients. In high-risk cases, cytoreductive agents must be prescribed.[11] Hydroxyurea (HU) remains the standard first-line cytoreductive treatment; however, ~20% to 25% of patients eventually develop resistance or intolerance.[12-18] These conditions are clinically relevant because they have been consistently associated with a higher probability of thrombosis, disease progression, and shorter survival.[19-22] Therefore, the identification of effective therapeutic strategies in this setting represents a crucial unmet need.[23,24]

Ruxolitinib, a selective JAK1/2 inhibitor, is currently the only targeted agent approved for patients with PV who are resistant or intolerant to HU.[25] Its approval was based on the pivotal RESPONSE and RESPONSE-2 trials,[26-28] which demonstrated significant efficacy in controlling hematocrit without phlebotomy, reducing splenomegaly, and improving disease-related symptoms. Long-term follow-up of these studies, as well as real-world observational series, have confirmed durable efficacy and a manageable safety profile, supporting the use of ruxolitinib in routine clinical practice.[29-32] Nevertheless, the clinical course of PV under ruxolitinib therapy remains heterogeneous, with a subset of patients experiencing progression despite treatment.

In myelofibrosis, early on-treatment variables such as spleen volume reduction, red blood cell transfusion requirement, and ruxolitinib dosage have emerged as relevant prognostic markers, correlating with survival and disease evolution.[33,34] Although the Mutation-Enhanced International Prognostic Scoring System for Polycythemia Vera[35] score may enhance survival prediction in PV using static variables at diagnosis, the potential for dynamic, treatment-related factors to further refine risk assessment in PV remains unexplored. In clinical practice, the assessment of spleen size and hematologic parameters (hematocrit, leukocytes, platelets, and phlebotomy requirement) represents the cornerstone of response evaluation, collectively summarized by the concept of complete hematologic response (CHR).[36] However, these markers have never been incorporated into a unified, dynamic prognostic framework during ruxolitinib therapy.

This knowledge gap is particularly relevant in a disease in which treatment decisions are often prolonged over many years, and early recognition of suboptimal responders may allow for timely intervention or consideration of alternative strategies.

On this background, we designed a large, multicenter, real-world analysis to develop a new prognostic score based on routinely available clinical parameters reflecting both disease control and treatment intensity. This new score aims to provide an early and practical tool to identify patients with PV at a higher risk of adverse outcomes while receiving ruxolitinib, supporting more individualized management strategies.

Materials and methods

Patient enrollment and study design

This is an observational, retrospective cohort study (PV-ARC, ClinicalTrials.gov identifier: NCT06134102)[37] that was promoted by the IRCCS Azienda Ospedaliero-Universitaria S. Orsola-Malpighi, Bologna, Italy.

The study now involves 1197 patients with PV diagnosed between January 1985 and December 2023. Among them, 178 patients were treated with second-line ruxolitinib for at least 6 months; only these patients were included in this analysis.

Following the approval of each Institutional Review Board, participating centers collectively submitted diagnostic and follow-up information. The total number of medical files from each center was reported via data input into an electronic database that was developed to label all study data with an alphanumeric code after the deidentification of patients to protect personal privacy.

The data collected included patient demographics, medications, clinical/laboratory test results at diagnosis and during follow-up, type of PV therapy and events including thrombosis, disease progression into post-PV MF, and death. All information about concomitant diseases, body mass index, CVRFs, thrombosis history, and drug usage was recorded in each case history and, thereafter, used for retrospective evaluation. Any treatment decision, including the use of phlebotomies, ruxolitinib, and antiplatelet/anticoagulant drugs, was at the physician's discretion and independent from participation in this study. The *JAK2*^{V617F} variant allele frequency (VAF) was assessed using the routine laboratory methods adopted by each participating hematology center.

After the first data entry, follow-up information was validated with revision of the clinical data, and specific queries were addressed to the participating centers in cases of inconsistent data. All patients were followed up until death or the data cutoff date (March 2025).

Definitions

PV was diagnosed according to the World Health Organization 2022 classification.[38] In patients diagnosed before 2022, bone marrow biopsies were internally reviewed to adhere the data to the current criteria.[39] In patients without a bone marrow histology, PV diagnosis was based on the presence of elevated hemoglobin

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(Hb) levels (ie, >18.5 and 16.5 g/dL in males and females, respectively), the *JAK2* exon 14 or exon 12 mutations, and low serum erythropoietin levels.

Conventional criteria were used for the diagnosis of post-polycythemia vera myelofibrosis[38]; leukemic transformation was defined by blast cells being at least 20% in the peripheral blood and/or bone marrow.[39]

Thromboses and hemorrhage were defined according to the International Classification of Diseases (ninth revision)[40] and graded according to the Common Terminology Criteria for Adverse Events version 5.0.[41] Only grade ≥2 thromboses and hemorrhages occurring during ruxolitinib therapy were recorded and analyzed in this study.

CVRFs included active smoking, hypertension, overweight (body mass index, ≥25 kg/m^2), diabetes, and dyslipidemia.[42]

CHR required a leukocyte count <10 ×10^9/L, platelet count <400 ×10^9/L, and hematocrit <45%, with no requirement for phlebotomy. Spleen response was defined as a ≥50% reduction in spleen length (SR50).

Statistical analysis

Statistical analysis was conducted at the biostatistics laboratory of the Myeloproliferative Neoplasms Unit, IRCCS Azienda Ospedaliero-Universitaria S. Orsola-Malpighi, Bologna, Italy.

Continuous variables are expressed as mean ± standard deviation (SD), whereas categorical variables are presented as frequencies and percentages. Comparisons of quantitative variables between 2 groups of patients were conducted using the Wilcoxon-Mann-Whitney rank-sum test and among 3 groups using the Kruskal-Wallis equality-of-populations rank test. Associations between categorical variables were tested using the χ^2 test.

The incidence rate (IR) of thrombotic and hemorrhagic events was calculated as the number of events per 100 patient-years, considering the time from ruxolitinib initiation to the last follow-up (95% confidence intervals [CIs] were calculated assuming a Poisson distribution).

Myelofibrosis-free survival (MF-FS), including progression to post-PV MF and death, and event-free survival (EFS), including thrombosis, hemorrhages, progression to post-PV MF, or death, were estimated from the start of ruxolitinib treatment to the first event or last follow-up. Survival curves were estimated using the Kaplan-Meier method, and comparisons between groups were performed using the log-rank test. Hazard ratios (HR) with 95% CIs were estimated using Cox proportional hazards regression. *P* values from pairwise comparisons of survival outcomes across groups were adjusted for multiple testing using the Benjamini-Hochberg false discovery rate procedure.

To identify early predictors of reduced EFS after the first 6 months of ruxolitinib therapy, a Cox proportional hazards model was applied to the following clinically plausible variables, each recognized as a surrogate marker of disease activity, treatment response, and dose intensity, evaluated at baseline and 3 and 6 months: (1) persistent or worsening leukocytosis (leukocyte count >10 ×10^9/L); (2) persistent or worsening thrombocytosis (platelet count >400 ×10^9/L); (3) phlebotomy requirement; (4) subtherapeutic ruxolitinib dosing, defined as the administration of <10 mg twice daily. The lack of SR50 or emergence of new palpable splenomegaly at 3 and 6 months was also included among tested variables.

Variables with *P* value <.05 in univariate analysis were entered into a multivariate Cox model. Independent predictors of inferior EFS were subsequently incorporated into the new prognostic model, with weighted points assigned proportionally to their HR. Patients were stratified into 3 risk categories (low, intermediate, and high) according to cumulative score values. EFS according to the derived prognostic score was subsequently evaluated using both nonparametric and model-based approaches. Kaplan-Meier estimates were used to describe unadjusted survival distributions, whereas a parametric accelerated failure time model assuming a log-logistic distribution was fitted to assess the association between the PV–response to ruxolitinib after 6 months (PV-RR6) model and EFS after adjustment for age at ruxolitinib initiation.

The tests were 2-sided. Statistical significance was set at *P* value < .05. The analyses were performed using Stata/SE software version 18.0 (StataCorp).

The PV-ARC study was performed in accordance with the guidelines of the Institutional Review Boards of the participating centers and the standards of the Helsinki Declaration. The promoter of this study was the IRCCS Azienda Ospedaliero-Universitaria S. Orsola-Malpighi, Bologna, Italy, which obtained approval from the Area Vasta Emilia Centro Ethics Committee (approval number: 483/2018/Oss/AOUBo). This study was also approved by the local ethics committees of participating centers (protocol code: PV-ARC) and has no commercial support.

Results

Baseline patient characteristics

A total of 178 patients with PV were included. Median age was 65.8 years (SD, 10.9); 58.7% were male. At least 1 CVRF was present in 132 patients. The most common risk factors were hypertension (n = 80 [44.9%]), overweight (n = 61 [34.3%]) and active smoking (n = 43 [24.2%]). All patients were at high thrombotic risk according to conventional criteria; a thrombotic event before ruxolitinib occurred in 50 patients (28.1%). The *JAK2*^{V617F} VAF was available in 77 patients, and the mean VAF was 50.4% (SD, 28.2), with 35 patients (45.5%) having a VAF ≥50%. Median time on HU therapy was 2.9 years (range, 0.2-24.5); reasons for HU discontinuation were resistance in 96 patients (53.9%) and intolerance in 67 patients (37.7%), whereas a combination of resistance and intolerance was reported in 15 patients (8.4%).

At ruxolitinib initiation, 92 patients (51.7%) had palpable splenomegaly; of these, 40 (22.5%) had the spleen margin palpable at ≥5 cm below the costal margin; only 13 patients (7.3%) had the spleen size palpable at ≥10 cm below the costal margin. In 86 patients, the spleen was not palpable nor detected by ultrasound echography at baseline.

No patient started ruxolitinib while in CHR. Requirement for phlebotomy was present in 42.1% of patients, leukocytosis (white blood cell count of ≥10 ×10^9/L) in 44.4% of patients, and thrombocytosis (platelet count of ≥400 ×10^9/L) in 47.2% of patients. PV-related symptoms, mainly aquagenic pruritus, were reported by 60.7% of patients.

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Table 1. Disease-specific characteristics and ruxolitinib dose at baseline and 3 and 6 months from treatment initiation

	Baseline	At 3 mo	At 6 mo
Ruxolitinib dose, n (%)			
5 mg bid	8 (4.5)	13 (7.3)	26 (14.6)
10 mg bid	164 (92.1)	134 (75.3)	112 (62.9)
15 mg bid	5 (2.8)	19 (10.7)	22 (12.4)
20 mg bid	1 (0.6)	12 (6.7)	18 (10.1)
Hb level, mean (SD), g/dL	14.0 (1.5)	12.5 (1.5)	12.7 (1.4)
Male, mean (SD), g/dL	14.2 (1.5)	12.8 (1.5)	12.8 (1.4)
Female, mean (SD), g/dL	13.7 (1.5)	12.0 (1.3)	12.2 (1.2)
Hb level ≤12 g/dL, n (%)	13 (7.3)	51 (28.7)	47 (26.4)
Hematocrit, mean (SD), %	45.1 (4.6)	43.2 (5.0)	42.0 (5.5)
Male, mean (SD), %	45.8 (4.3)	44.1 (4.7)	43.2 (5.1)
Female, mean (SD), %	44.1 (4.8)	42.3 (5.6)	40.4 (5.6)
Hematocrit ≥45%, n (%)	100 (56.2)	70 (39.3)	53 (29.8)
Leukocytes count, mean (SD), $\times 10^9$/L	10.8 (6.1)	8.9 (5.6)	9.6 (5.4)
Leukocyte count ≥10 $\times 10^9$/L, n (%)	79 (44.4)	46 (25.8)	56 (31.5)
Platelet count, mean (SD), $\times 10^9$/L	451 (281)	413 (233)	397 (170)
Platelet count ≥400 $\times 10^9$/L, n (%)	84 (47.2)	78 (43.8)	68 (38.2)
Palpable spleen length BCM, mean (SD), cm	2.6 (3.6)	1.6 (3.1)	1.4 (2.9)
Palpable spleen, n (%)	92 (51.7)	66 (37.1)	56 (31.5)
Palpable spleen length ≥5 cm, n (%)	40 (22.5)	21 (11.8)	22 (12.4)
PV-related symptoms, n (%)	108 (60.7)	50 (28.1)	31 (17.4)
Phlebotomies requirement, n (%)*	75 (42.1)	23 (12.9)	17 (9.6)

BCM, below the costal margin; bid, twice daily.
*Defined as at least 1 phlebotomy within the 3-month time frame.

All patients received antithrombotic prophylaxis (antiplatelet or anticoagulant agents, based on medical history).

Evolution of disease features and ruxolitinib dosing over the first 6 months

Changes of disease-specific features and ruxolitinib dose during the first 6 months of ruxolitinib therapy are reported in Table 1.

At baseline, 57.9% of patients were phlebotomy-free. This proportion increased to 87.1% at 3 months and reached 90.4% at 6 months, corresponding to a relative increase of 56.1% (supplemental Figure 1). Similarly, the percentage of patients without leukocytosis and thrombocytosis rose from 55.6% and 52.8% at baseline to 68.5% and 61.8% at 6 months, reflecting relative improvements of 23.2% and 17.0%, respectively. The proportion of patients with a palpable spleen ≥5 cm decreased from 23.0% at baseline to 12.4% at 6 months, corresponding to a 46.1% relative reduction (supplemental Figures 2-4).

Overall, 36 patients received ruxolitinib at <10 mg twice daily at least once during follow-up (supplemental Figure 5). Five were underdosed only at baseline, 3 at all time points, and 28 exclusively at months 3 and/or 6. Accordingly, dosing patterns shifted over time: the proportion receiving 5 mg twice daily increased from 4.5% at baseline (n = 8) to 14.6% at 6 months (n = 20). Notably, in 20 of the 28 patients who began standard dosing and later required reductions (71.4%), the change was triggered by isolated, transient mild anemia (Hb, 10-12 g/dL). In the remaining patients, including those starting at reduced doses, no clear rationale for underdosing was identifiable.

Response to ruxolitinib at 3 and 6 months

The response rates and distribution are summarized in Figure 1. At 3 months, a CHR was achieved in 40 of the 178 patients (22.5%). Among the 92 patients with baseline splenomegaly, 46 (50.0%) achieved SR50; of these, 11 patients (12.0%) achieved both spleen and hematologic responses. Among the 86 patients without baseline splenomegaly, 19 achieved a CHR.

At 6 months, both hematologic and spleen responses improved. CHR rose from 22.5% to 35.4% (40-63 of 178 total patients), reflecting a 57.3% relative increase. The SR50 rate increased from 50.0% to 63.0% (46-58 of 92 patients with baseline splenomegaly), a relative gain of 26.0%. The proportion achieving both responses nearly doubled, from 12.0% (11 patients) to 22.8% (21 patients), an 89.1% relative improvement.

No emergence of new splenomegaly was reported at 3 and 6 months among patients without baseline splenomegaly. Overall, 36 (39.1%) and 24 (26.1%) patients showed no measurable response at 3 and 6 months, respectively, indicating a 31.4% reduction. No significant differences were observed in response rates between HU-resistant and HU-intolerant patients.

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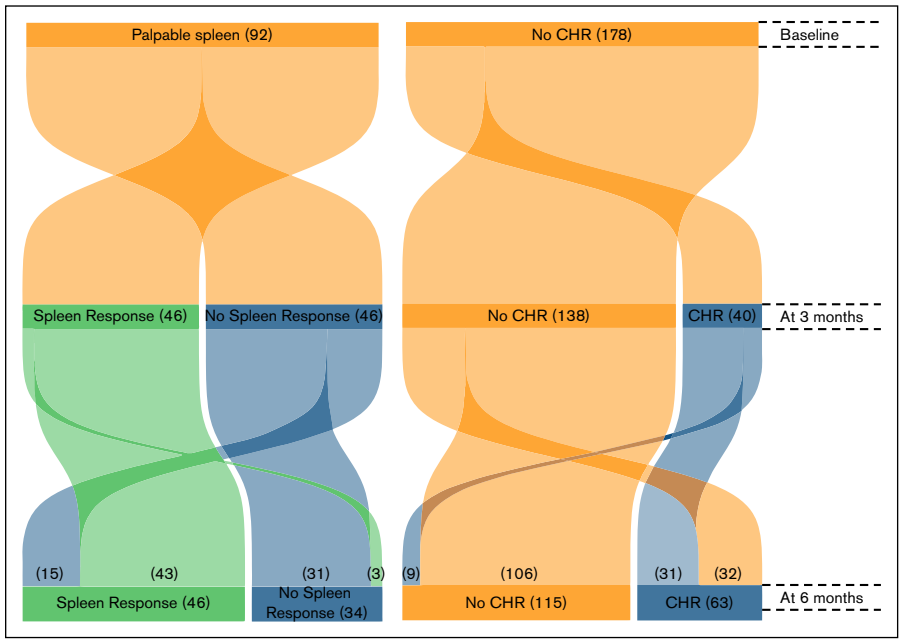


Figure 1. Spleen and CHR over time.

Long-term outcomes

During a median follow-up from ruxolitinib start of 3.50 years (range, 0.5-8.7), 7 had a thrombotic event, including 3 lower limb deep vein thromboses, 1 upper limb deep vein thrombosis, 2 ischemic strokes, and 1 splenic vein thrombosis, with an overall IR of 1.12 per 100 patient-years (95% CI, 0.41-2.21). In addition, 9 patients had a hemorrhagic event, including 3 cases of mucosal hemorrhage (ocular subconjunctival, epistaxis, and hemorrhoids), 3 cases of hematoma (1 gluteal and 2 limb hematomas), and 3 cases of internal bleeding (gastrointestinal, bladder, and rectal bleeding), with an IR of 1.32 per 100 patient-years (95% CI, 0.42-4.16).

Overall, 15 (8.4%) patients died, 21 progressed to myelofibrosis, and following transformation to post-PV MF, 2 patients developed acute leukemia.

Globally, 5-year EFS was 70.4% (95% CI, 60.8-78.0), with a median EFS of 7.73 years (95% CI, 6.32 to not reached), comparable between HU-resistant and HU-intolerant patients (7.95 vs 7.68 years; log-rank $P = .45$).

Baseline parameters (including thrombocytosis, leukocytosis, phlebotomy need, or starting dose <10 mg twice daily) did not correlate with EFS. In contrast, baseline splenomegaly was prognostic: patients without a palpable spleen had a higher 5-year EFS than those with splenomegaly (78.6% vs 63.6%). The degree of splenomegaly did not influence outcomes ($P = .75$), likely due to the narrow baseline distribution.

Importantly, patients with baseline splenomegaly who achieved SR50 at 3 or 6 months had EFS comparable with patients without splenomegaly. At 6 months, SR50 responders showed superior 5-year EFS compared with nonresponders (72.9% vs 46.8%; HR, 0.44; $P = .031$). Patients without splenomegaly at both baseline and 6 months had the best prognosis (79.8%; $P = .018$). A similar pattern was observed for MF-FS, with 5-year rates of 83.8% in SR50 responders, 52.6% in nonresponders, and 95.3% in patients who never had splenomegaly (global log-rank test $P < .001$). CHR at 6 months was associated with improved outcomes: 5-year EFS was 82.6% in CHR achievers vs 65.9% in nonresponders (HR, 0.44; $P = .039$). MF-FS showed a similar trend (90.2% vs 80.3%; $P = .12$; Figure 2).

No differences in overall, thrombosis-, or hemorrhage-free survival were observed by SR50 or CHR (supplemental Figure 6).

New prognostic model to predict EFS based on clinical response after 6 months of ruxolitinib in patients with PV

Table 2 summarizes the results of univariate and multivariate analyses of features evaluated for association with EFS. In multivariable Cox proportional hazard regression analysis, the following risk factors remained prognostically relevant: (1) lack of SR50 at 3 and 6 months (HR, 2.65; 95% CI, 1.25-5.82; $P = .009$); (2) ruxolitinib dose lower than 10 mg twice daily at ≥1 time point (HR, 1.94; 95% CI, 1.01-3.99; $P = .047$); (3) phlebotomies requirement at ≥2 time points (HR, 2.27; 95% CI, 1.03-4.95; $P = .039$). In univariate analysis, phlebotomies requirement at 1 time point was also significantly correlated with a lower EFS (HR, 1.69; 95% CI, 1.03-3.14; $P = .037$).

All 3 patients underdosed at every time point experienced an event, with markedly higher risk vs never underdosed (HR, 5.63; 95% CI, 1.68-18.38; $P = .005$) and vs those underdosed at 1 to 2 time points (HR, 3.89; 95% CI, 1.06-14.23; $P = .040$). To integrate the independent prognostic variables into a usable tool, we developed the PV-RR6 model. Point values were assigned according to HR: 1 point for phlebotomy at 1 time point; 2 points for phlebotomy at ≥2 time points and for ruxolitinib <10 mg twice daily at ≥1 time point; and 2.5 points for the absence of SR50 at both 3 and 6 months. The total scores ranged from 0 to 6.5.

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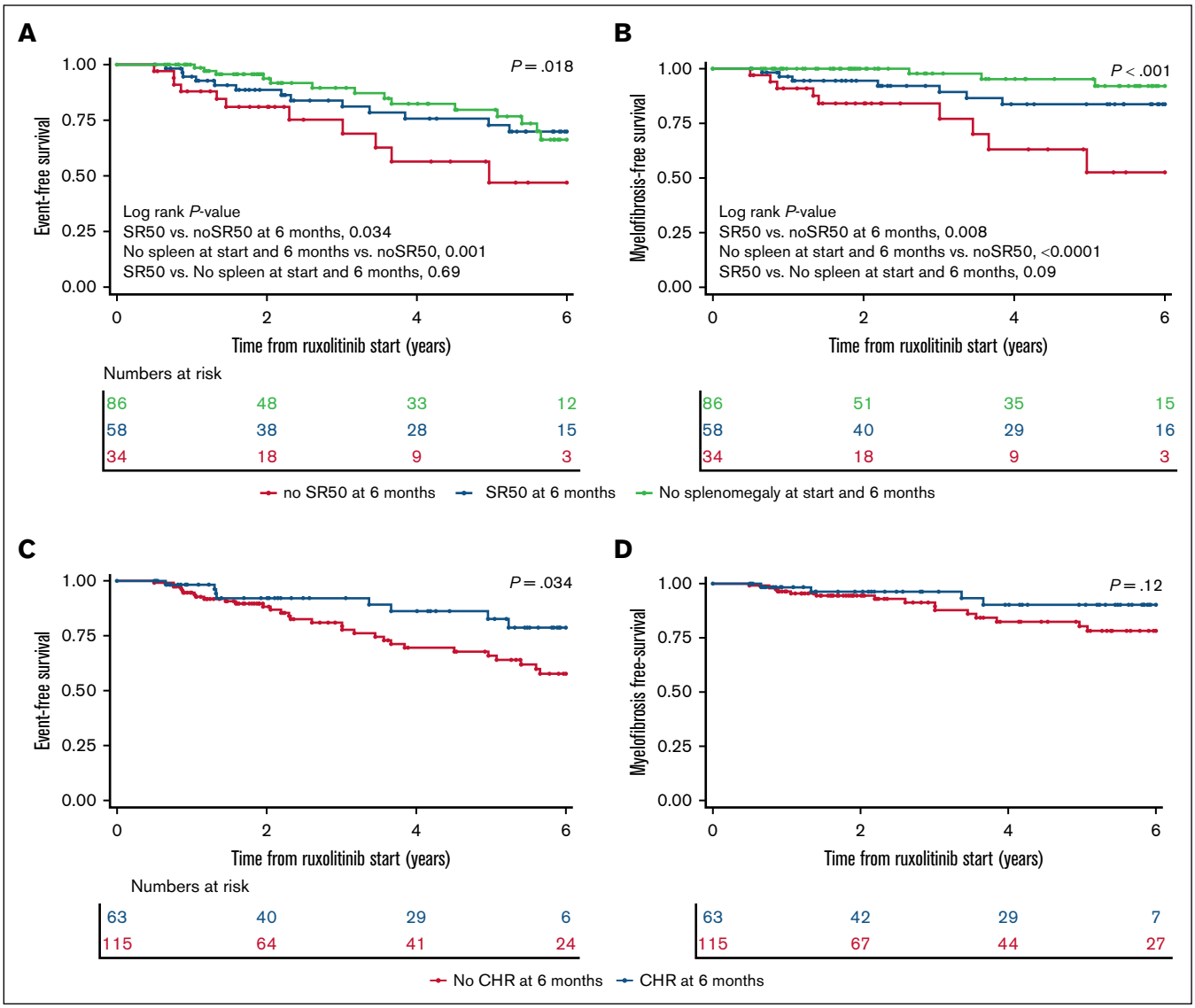


Figure 2. Impact of 6-month responses on outcomes. Kaplan-Meier curves for EFS and MF-FS by spleen response at 6 months (A-B) and CHR status (C-D).

To avoid small strata and group patients with similar EFS, scores 1 to 2.5 were classified as intermediate risk and ≥3 as high risk. Three groups emerged: low (score 0; n = 63; median EFS not reached), intermediate (score 1-2.5; n = 82; median EFS, 7.72 years), and high (score ≥3; n = 33; median EFS, 4.96 years) (log-rank $P < .001$; Figure 3). Compared with low-risk patients, HR were 2.61 (95% CI, 1.05-6.48; $P = .038$) for intermediate and 6.15 (95% CI, 2.29-16.49; $P < .001$) for high risk. The PV-RR6 model remained significant after adjusting for age ($P = .001$).

The score stratified risk in both HU-resistant and HU-intolerant patients. In HU-resistant cases, median EFS was not reached (low-risk), 8.15 years (intermediate), and 4.96 years (high-risk) (log-rank $P = .002$). Similarly, in HU-intolerant cases, median EFS was not reached, 7.63 years, and 4.96 years across the 3 risk groups ($P = .02$).

In the cohort of 170 patients who started ruxolitinib at the standard dose of 10 mg twice daily, 76 and 31 patients belonged to the intermediate- and the high-risk group, respectively. In the intermediate-risk group, 9 of 76 patients (11.8%) required a dose reduction at 3 and/or 6 months, in 8 patients (10.5%) associated with mild Hb decline (Hb level, 10-12 g/dL). In the high-risk group, 19 of 31 patients (61.3%) underwent dose reduction due to concomitant mild anemia in 12 patients (38.7%).

Overall, 20 patients reduced ruxolitinib in response to mild anemia, whereas 30 maintained 10 mg twice daily despite a similar Hb decline. Patients who retained full-dose therapy showed superior 5-year EFS (81.0%; 95% CI, 59.7-91.8) compared with those whose dose was reduced (53.1%; 95% CI, 23.9-75.6; log-rank $P = .019$; Figure 4).

Discussion

In this large real-world PV cohort, ruxolitinib showed progressive benefit, with CHR and SR50 rates of 35.4% and 32.6% at 6 months, respectively, and no cases of new or worsening

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Table 2. Univariate and multivariate Cox regression analysis of factors influencing EFS

Variable	Univariate HR (95% CI); *P* value	Multivariate HR (95% CI); *P* value
Persistent/increasing leukocyte count >10 ×10^9/L		
Single time point	1.80 (0.24-12.5); .51	
Multiple time points	1.87 (0.64-9.35); .31	
Persistent/increasing platelet count >400 ×10^9/L		
Single time point	1.15 (0.45-1.45); .51	
Multiple time points	1.35 (0.56-1.89); .45	
Persistent/increasing hematocrit >45%		
Single time point	1.81 (0.71-4.27); .16	
Multiple time points	1.65 (0.81-2.83); .27	
Phlebotomies requirement		
Single time point	1.69 (1.03-3.14); .037	1.07 (0.49-2.34); .86
Multiple time points	2.27 (1.07-4.54); .031	2.11 (1.03-4.95); .039
Lack of SR50 or emergence of splenomegaly at 3 and 6 months	3.39 (1.61-7.05); .001	2.65 (1.25-5.82); .009
Subtherapeutic ruxolitinib dosing*	2.01 (1.05-4.21); .034	1.94 (1.01-3.99); .047

bid, twice daily.
*Subtherapeutic ruxolitinib dosing, defined as administration of <10 mg bid at any of the following time points: baseline, 3 months, or 6 months.

splenomegaly. Although early spleen response is an established dynamic predictor in myelofibrosis, its prognostic significance in PV had not been defined.[33,34,43] In our study, achieving SR50 within 6 months was associated with significantly better EFS and MF-FS, with outcomes comparable with those of patients without splenomegaly. These findings indicate that early spleen response may counterbalance the adverse impact of baseline splenomegaly; conversely, failure to achieve spleen reduction was linked to poorer outcomes. Similarly, achieving an early CHR was associated with better EFS, largely due to a lower rate of progression to myelofibrosis. This aligns with the MAJIC-PV trial, in which CHR, under ruxolitinib or best available therapy, predicted favorable long-term outcomes.[44] Uncontrolled hematocrit is also known to increase thrombotic risk during HU therapy.[45,46] In our cohort, only 7 thrombotic events (all grade ≥2) occurred (3.9%; incidence, 1.12 per 100 patient-years), a rate lower than that reported in the Masciulli-Barbui meta-analysis (3.09 per 100 patient-years)[47] and comparable with the 5-year results of the RESPONSE-2 trial (1.50 per 100 patient-years).[28,47] Although retrospective underreporting cannot be fully excluded, our findings are consistent with real-world data from Theocharides et al, who reported a thrombotic rate of 3.9% during follow-up.[48] Additional real-world data will be important to confirm the generalizability of these findings. Nonetheless, our results highlight the need for regular monitoring during ruxolitinib therapy; lack of spleen response, absence of CHR, and especially persistent phlebotomy requirements should be

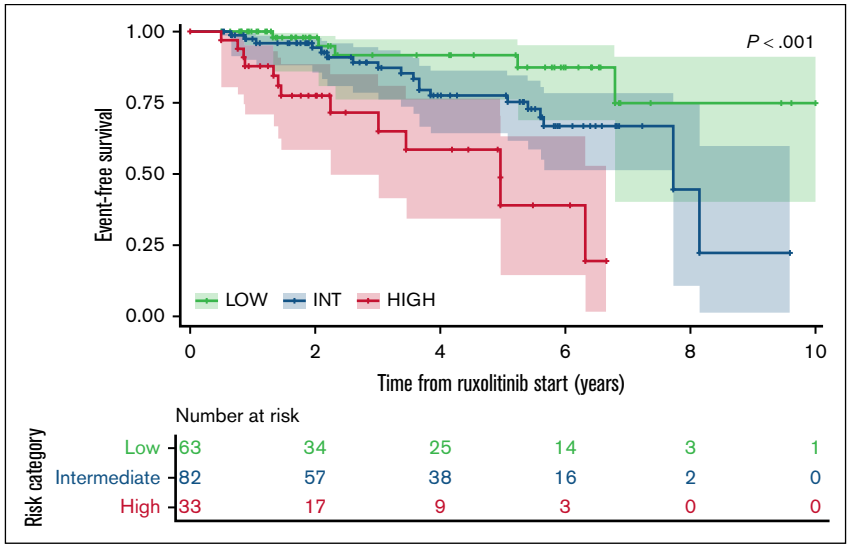


Figure 3. EFS curves of the 3 risk groups of patients according to the PV-RR6 model developed in ruxolitinib-treated patients with PV. INT, intermediate.

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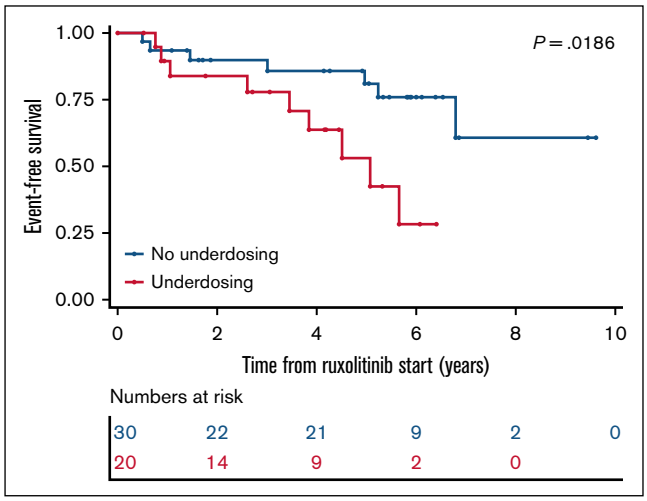


Figure 4. EFS stratified by ruxolitinib dose reduction in patients with partial anemia.

regarded as clinically relevant warning signals, prompting consideration of dose optimization or treatment switch.[44]

Building on these findings, we developed the PV-RR6 model, a dynamic prognostic tool that integrates 3 readily available measures of disease control and treatment dose intensity.

In our cohort, <5% of patients started ruxolitinib at a suboptimal dose and ~15% received suboptimal dosing during follow-up. These rates are consistent with a US real-world study of 69 patients with PV, in which nearly all began treatment at 10 mg twice daily and few required adjustments,[20] and with an Italian series reporting that 94% of patients received a mean dose of 10 mg twice daily.[49] In contrast, a larger chart review of 249 patients found that only 53% initiated therapy at 10 mg twice daily and 27% subsequently required dose modifications.[50]

Recent evidence in myelofibrosis has shown that ruxolitinib underdosing is associated with reduced response rates and inferior outcomes.[51,52] In our study, we identified ruxolitinib doses below the standard 10 mg twice daily at 1 or more time points as an independent adverse prognostic factor in PV, a finding that warrants further investigation.

The main driver of ruxolitinib underdosing was an early decline in Hb levels in the absence of moderate to severe anemia, which occurred in 50 of 170 (29.4%) patients starting with a standard ruxolitinib dose and led to dose reduction in 20 cases. Although such reductions are not recommended in the drug label, our data show that they are frequently adopted in clinical practice and are associated with worse outcomes. Indeed, patients who maintained the full ruxolitinib dose had significantly better EFS than those who reduced dosing due to mild anemia.

Dose-reduction patterns also differed markedly across the PV-RR6 risk groups. Anemia-driven reductions were uncommon among intermediate-risk patients (≈11%) but frequent in high-risk patients (≈39%). In intermediate-risk patients, inadequate spleen and/or hematocrit control typically underlies risk classification; therefore, increasing ruxolitinib above 10 mg twice daily should be considered to optimize disease control. Conversely, in high-risk patients, the development of mild anemia is common and often triggers dose reductions. In this setting, alternative causes of anemia, including iron or vitamin deficiencies, should be corrected before lowering the ruxolitinib dose. Nevertheless, early mild anemia may also reflect reduced bone marrow reserve and a more advanced disease biology, despite a seemingly similar baseline phenotype.

This study has limitations, including its retrospective design and the absence of external validation. Furthermore, external validation is warranted to further confirm the generalizability of the PV-RR6 model. Importantly, the robustness of these findings is supported by the large multicenter real-world cohort, rigorous data curation, standardized variables, and consistent longitudinal follow-up. Molecular data on *JAK2*^{V617F} VAF were also not routinely available, reflecting current practice in which quantitative molecular profiling is neither standardized nor systematically incorporated.

The PV-RR6 model stratified patients into 3 groups with clearly distinct EFS, integrating early response–based variables to capture the risk of thrombosis, bleeding, progression to post-PV myelofibrosis, and death. This dynamic tool offers a practical readout of disease activity and treatment adequacy, enabling early identification of higher-risk patients who may benefit from dose optimization or consideration of alternative strategies, including ropeginterferon alfa-2b.[53-56]

An important nuance in the clinical interpretation of PV-RR6 relates to the composite nature of the EFS end point, which encompasses biologically and clinically heterogeneous events.[57,58] Although persistent phlebotomy requirement, the absence of spleen response, and suboptimal ruxolitinib dosing signal insufficient disease control and should prompt reassessment of cytoreductive strategy and treatment intensity, the individual events captured by the composite end point may warrant distinct management approaches beyond the optimization of cytoreduction.[1,45] Specifically, recurrent thrombosis may require tailored antithrombotic strategies, including combined anticoagulation and antiplatelet therapy, in addition to hematocrit control and cytoreductive intensification. In parallel, hemorrhagic events necessitate the evaluation of bleeding risk factors, including acquired von Willebrand syndrome, and concomitant antithrombotic therapies,[59,60] along with appropriate supportive measures. Finally, progression to post-PV MF calls for a distinct diagnostic and therapeutic pathway, including bone marrow reassessment, dedicated prognostic scoring, and consideration of myelofibrosis-directed therapies or allogeneic transplantation.[61,62] Therefore, despite PV-RR6 providing a clinically actionable signal of suboptimal disease control that should trigger a comprehensive treatment reassessment, the specific nature of each event must guide individualized downstream management decisions.

In a treatment landscape where prognostication in PV remains anchored to baseline features, PV-RR6 introduces a time-dependent, treatment-responsive framework, similar in concept to the RR6 and iRR6 models developed for myelofibrosis.[33,34] This represents a shift toward dynamic risk assessment in PV, emphasizing the prognostic relevance of early therapeutic response and dose optimization rather than static baseline features.

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Acknowledgments

This work was supported by the Ministero della Salute Ricerca corrente and AIL Bologna. F. Palandri and F.H.H. were supported (in part) by the European Partnership for Personalized Medicine grant EPPERMED2025-134. The work reported in this article was funded by the Italian Ministry of Health (RC-2025-2797275 project).

Authorship

Contribution: F. Palandri, A. Dedola, G.C., C.S., V.D.S., and M.B. contributed to conceptualization, investigation, review and editing of the manuscript, and resources; F.P. contributed to funding acquisition, writing of the original draft, data curation, and visualization; E.R., E.M.E., R.L., N.P., E.M., G. Binotto, F.M., A.T., G. Benevolo, B.M., A. D'Addio, M.T., D.C., M.C., F.C., E.S., F.L., F. Pane, and G.A.P. contributed to investigation, review and editing of the manuscript, and resources; F.H.H. contributed to review and editing of the manuscript and investigation; and F.B. contributed to writing, review, and editing of the manuscript, formal analysis, conceptualization, data curation, and visualization.

Conflict-of-interest disclosure: F. Palandri reports honoraria and consulting fees from Novartis, GSK, Bristol Myers Squibb (BMS), Incyte, Sanofi, Takeda, Sobi, and AOP Health. E.M.E. reports meeting/advisory board participation for Novartis, GSK, AbbVie, and AOP Health. M.B. reports honoraria from Novartis, BMS, Pfizer, and Incyte. G. Benevolo reports honoraria from Novartis, Janssen, Amgen, Takeda, and BMS. G. Binotto reports honoraria from Novartis, Incyte, BMS-Celgene, and Pfizer. M.T. reports honoraria from, and has served on speakers' bureaus, for Novartis, BMS, Pfizer, and Incyte. M.C. reports honoraria from Novartis and Amgen. F. Pane reports honoraria from Incyte, Novartis, Jazz, BMS-Celgene, Amgen, and Gilead. G.A.P. reports consultancy for, and honoraria from, AbbVie, AOP Health, AstraZeneca, BMS, Incyte, GSK, MorphoSys, and Novartis. F.H.H. reports consultancy for BMS/Celgene, Novartis, CTI, AOP Health, Janssen, GSK, Merck Sharp & Dohme, AbbVie, Takeda, Kartos, Geron, Silence, Prelude, and Sumitomo; and research funding from BMS/Celgene and Novartis. V.D.S. participated in the speaker's bureau and advisory board of AbbVie, AOP Health, BMS, GSK, Grifols, Novartis, Novo Nordisk, Sanofi, Sobi, and Takeda. The remaining authors declare no competing financial interests.

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