

Symptomatic Profiles of Patients With Polycythemia Vera: Implications of Inadequately Controlled Disease

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A B S T R A C T

Purpose

Polycythemia vera (PV) is a myeloproliferative neoplasm (MPN) associated with disabling symptoms and a heightened risk of life-threatening complications. Recent studies have demonstrated the effectiveness of *JAK* inhibitor therapy in patients with PV patients who have a history of prior hydroxyurea (HU) use (including resistance or intolerance), phlebotomy requirements, and palpable splenomegaly. We aimed to determine how these features contribute alone and in aggregate to the PV symptom burden.

Patients and Methods

Through prospective evaluation of 1,334 patients with PV who had characterized symptom burden, we assessed patient demographics, laboratory data, and the presence of splenomegaly by disease feature (ie, known HU use, known phlebotomy requirements, splenomegaly).

Results

The presence of each feature in itself is associated with a moderately high symptom burden (MPN symptom assessment form [SAF] total symptom score [TSS] range, 27.7 to 29.2) that persists independent of PV risk category. In addition, symptoms incrementally increase in severity with the addition of other features. Patients with PV who had all three features (PV-HUPS) faced the highest total score (MPN-SAF TSS, 32.5) but had similar individual symptom scores to patients with known HU use (PV-HU), known phlebotomy (PV-P), and splenomegaly (PV-S).

Conclusion

The results of this study suggest that patients with PV who have any one of the features in question (known HU use, known phlebotomy, or splenomegaly) have significant PV-associated symptoms. Furthermore, it demonstrates that many PV symptoms remain severe independent of the number of features present.

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INTRODUCTION

Polycythemia vera (PV) is a myeloproliferative neoplasm (MPN) that evolves from dysregulated clonal erythropoiesis. The condition is recognized for its distinct molecular profile (*JAKV617F*), burdensome symptoms, predilection for thrombosis, and capacity to transform into acute myelogenous leukemia (AML) or myelofibrosis (MF). Treatments are primarily directed at preventing life-threatening complications (eg, thrombosis),

and the choice of interventions is typically based on risk assessment.^{1,2} Despite many treatment advancements, studies continue to demonstrate that the PV symptom burden remains under-managed.³ In a 2007 internet survey of 405 patients with PV who were receiving standard treatment, the authors found that symptoms—including fatigue (85%), pruritus (65%), night sweats (49%), bone pain (43%), fevers (13%), and undesired weight loss (10%)—directly contributed to poor overall quality of life and compromised functionality.³ Palpable splenomegaly, present in up to

36% of patients with PV, is especially bothersome and contributes to other symptoms and complications, including early satiety, bloating, pain, portal hypertension, weight loss, and exacerbation of cytopenias.⁴⁻⁶

A variety of therapies have been used in PV, most of which aim to reduce thrombotic risk, because inadequately controlled hematocrit levels have resulted in higher rates of cardiovascular events (10.9% v 4.4%) and death (4.4 v 1.1 per 100 person-years) and have perpetuated symptoms such as headaches and coughing.⁷ The CYTO-PV study clearly demonstrated improved thrombotic outcomes with maintenance of a hematocrit less than 45% through phlebotomy.⁸ However, recent studies have shown that strict control of hematocrit levels also may be associated with a higher symptom burden, including worsened fatigue, pruritus, concentration issues, insomnia, weight loss, and night sweats.⁷ Hydroxyurea (HU) remains first-line treatment for patients with PV who need cytoreductive therapy.⁹ However, resistance and intolerance to HU has been reported in 11% and 13% of patients, respectively, and, furthermore, may contribute to a 5.6-fold increased risk of death.^{10,11}

More recently, attentions have turned to the development of treatments that specifically address PV symptoms. The phase III prospective Randomized Study of Efficacy and Safety in Polycythemia Vera with *JAK* Inhibitor INCB018424 versus Best Supportive Care (RESPONSE) evaluated the *JAK2* inhibitor ruxolitinib against best available therapy (BAT) in patients with PV who had the following features: resistance or intolerance to HU; baseline splenomegaly ($> 450 \text{ cm}^3$); and phlebotomy dependence.¹² The study demonstrated that patients with PV who had all three features suffered from a significant symptom burden and that ruxolitinib effectively alleviated these symptoms. As a result, on December 4, 2014, the FDA approved ruxolitinib for a select subset of the PV population: patients resistant or intolerant to HU.

This tremendous advancement for the PV population is limited by the issue of the restricted availability of ruxolitinib to select PV patients whose baseline symptomatology has not yet been fully characterized or compared to other PV patients who lack HU resistance/intolerance but still potentially face high symptom burdens. In this study, we sought to compare and contrast the baseline symptoms of patients with PV who have known HU use (PV-HU), known phlebotomy (PV-P), palpable splenomegaly (PV-S), or all three features (PV-HUPS).

PATIENTS AND METHODS

Survey Development and Collection

PV patients were recruited from international academic, private, and government medical institutions during routine office visits in a format previously published for validation of the MPN symptom assessment form (MPN-SAF)¹³ and through an online international survey (MPN fatigue project).¹⁴ In this study, anemia, thrombocytopenia, and leukopenia were defined as hemoglobin less than 11 g/dL, platelet count less than 150×10^9 cells/L, and white blood cell count less than 3.5×10^9 cells/L, respectively. Data were collected in English, Chinese, Dutch, French, German, Italian, Spanish, and Swedish languages.

Symptom Assessment

Assessment of MPN symptoms was performed by using the validated MPN-specific patient-reported outcome tool, the MPN-SAF total

symptom score (MPN-SAF TSS; MPN-10).² Assessed symptoms were fatigue, early satiety, abdominal discomfort, inactivity, concentration problems, night sweats, itching, bone pain, fevers, and weight loss. All items were evaluated on a 0 (absent) to 10 (worst imaginable) scale. For individuals who completed at least six of the 10 MPN-SAF TSS items, the survey was scored by multiplying the average score across items by 10 to achieve a 0-to-100 scaled score. The survey was collected in the aforementioned languages, and original language validations were conducted with a patient-reported outcome translation method.

Clinical Feature Subgroup Assignment

Clinical feature subgroups of PV were grouped according to the type and number of features present. Features were defined as known HU use, known phlebotomy, and splenomegaly. Subgroups consisted of those with no features or with one, two, or all three features present. Patient demographic and clinical variables, MPN-10 TSS score, and individual MPN-10 TSS items were compared among feature subgroups. In the MPN database, both current and prior use of HU/phlebotomy were assessed as separate questions. In the fatigue survey, however, only use of these therapies was assessed, and current versus previous use was not distinguished. Patients with a history of prior splenectomy were excluded. Control groups for each PV feature were derived from the remaining total PV patient cohort that lacked the specified feature (PV-cHU, PV-cP, PV-cS, PV-cHUPS); patients in whom the trait status was unknown were excluded from each respective control group.

Prognostic Scoring

Prognostic scoring for PV survival was calculated with the Leukemia 2013 prognostic scoring model developed by Tefferi et al.⁶ This scoring system includes the variables of age 67 years or older (5 points), age 57 to 66 years (2 points), WBC $15 \times 10^9/\text{L}$ or greater (1 point), and prior thrombosis (1 point) to risk stratify patients into high risk (≥ 3 points), intermediate risk (1 to 2 points), or low risk (0 points).

MPN Symptom Burden Severity Assessment

Determination of clinically meaningful difference in symptom severity for patients with PV was based on the 2013 MPN symptom burden response thresholds criteria.¹⁵ With this criteria, the TSS for each patient was analyzed to place the patient into the quartiles of low symptom burden (TSS, zero to seven), intermediate symptom burden (TSS, eight to 17), moderately high symptom burden (TSS, 18 to 31), or high symptom burden (TSS, ≥ 32).

Statistical Analysis

Continuous variables were compared with an analysis of variance, and dichotomous data were compared with the χ^2 test. Overall MPN-10 TSS score and individual symptoms were compared among various subgroups with the *t* test. Comparison of symptoms among groups used *t* tests. Statistical significance was set to $P < .05$. SAS version 9.3 (Cary, NC) was used for analysis.

RESULTS

Demographics

A total of 1,334 patients were included for analysis and had the following characteristics: known HU use (PV-HU, $n = 499$), known phlebotomy (PV-P, $n = 646$), palpable splenomegaly (PV-S, $n = 369$), or all three features (PV-HUPS, $n = 148$; Table 1). Included patients were recruited from the MPN-10 TSS validation study ($n = 717$) and the 2014 FATIGUE study ($n = 617$). Patients on the MPN-10 TSS validation study were slightly older than those

Table 1. Demographic and Clinical Characteristics by Features

Characteristic	No. (%) of Patients by Feature																			
	Known HU Use					Known Phlebotomy					Enlarged Spleen					All Three Features				
	No. (n = 807)	Yes (n = 499)	Total (n = 1,306)	P	No. (n = 688)	Yes (n = 646)	Total (n = 1,314)	P	No. (n = 852)	Yes (n = 369)	Total (n = 1,221)	P	No. (n = 1,026)	Yes (n = 148)	Total (n = 1,174)	P				
Mean (SD) age, years	60.9 (12.1)	61.7 (12.2)	60.9 (12.2)	.08	61.4 (12.7)	60.3 (11.5)	60.9 (12.1)	.11	61.3 (12.3)	59.7 (12.1)	60.8 (12.3)	.03	60.8 (12.5)	61.9 (10.1)	60.9 (12.3)	.311				
Age ≥ 60 years (%)	715 (66.4)	269 (53.6)	704 (56.7)	.33	385 (68.2)	323 (64.9)	708 (56.6)	.25	472 (68.1)	178 (51.7)	650 (56.2)	.048	550 (66.2)	82 (59.9)	632 (56.6)	.422				
Mean (SD) MPN duration, years	6.9 (6.4)	8.8 (7.0)	6.9 (6.4)	.008	7.0 (6.5)	6.4 (6.0)	6.9 (6.4)	.49	6.5 (6.1)	8.6 (7.2)	7.0 (6.5)	.005	7.0 (6.5)	11.5 (10.7)	7.0 (6.5)	.331				
Language				<.001				<.001				<.001				<.001				
Chinese	168 (12.6)	31 (6.2)	168 (12.9)		168 (25.1)	0 (0.0)	168 (12.8)		149 (17.5)	16 (4.3)	165 (13.5)		165 (16.1)	0 (0.0)	165 (14.1)					
Dutch	119 (8.9)	104 (12.9)	119 (9.1)		119 (17.8)	0 (0.0)	119 (9.1)		2 (0.2)	37 (10.0)	39 (3.2)		39 (3.8)	0 (0.0)	39 (3.3)					
English	656 (49.2)	408 (81.8)	628 (48.1)		72 (10.8)	564 (87.3)	636 (48.4)		390 (45.8)	253 (68.6)	643 (52.7)		450 (43.9)	146 (98.6)	596 (50.8)					
French	172 (12.9)	143 (17.7)	172 (13.2)		159 (23.8)	13 (2.0)	172 (13.1)		143 (16.8)	19 (5.1)	162 (13.3)		162 (15.8)	0 (0.0)	162 (13.8)					
German	47 (3.5)	40 (5.0)	47 (3.6)		24 (3.6)	23 (3.6)	47 (3.6)		33 (3.9)	11 (3.0)	44 (3.6)		42 (4.1)	2 (1.4)	44 (3.7)					
Italian	64 (4.8)	61 (7.6)	64 (4.9)		37 (6.5)	27 (4.2)	64 (4.9)		46 (5.4)	18 (4.9)	64 (5.2)		64 (6.2)	0 (0.0)	64 (5.5)					
Spanish	56 (4.2)	55 (6.8)	56 (4.3)		48 (7.2)	8 (1.2)	56 (4.3)		38 (4.5)	14 (3.8)	52 (4.3)		52 (5.1)	0 (0.0)	52 (4.4)					
Swedish	52 (3.9)	47 (5.8)	52 (4.0)		41 (6.1)	11 (1.7)	52 (4.0)		51 (6.0)	1 (0.3)	52 (4.3)		52 (5.1)	0 (0.0)	52 (4.4)					
PV risk				.09				.18				.81				.122				
Low (%)	288 (23.6)	161 (25.2)	247 (23.1)		116 (23.0)	136 (23.7)	252 (23.4)		187 (23.9)	67 (22.9)	254 (23.6)		216 (24.0)	22 (16.4)	238 (23.0)					
Intermediate (%)	343 (31.4)	189 (29.6)	336 (31.4)		146 (29.0)	192 (33.5)	338 (31.4)		240 (30.7)	96 (32.8)	336 (31.3)		275 (30.6)	49 (36.6)	324 (31.3)					
High (%)	493 (45.1)	288 (45.1)	487 (45.5)		242 (48.0)	245 (42.8)	487 (45.2)		354 (45.3)	130 (44.4)	484 (45.1)		409 (45.4)	63 (47.0)	472 (45.6)					
Anemia* (%)	14 (2.5)	10 (2.1)	14 (2.5)	.11	14 (2.9)	0 (0.0)	14 (2.5)	.12	10 (2.2)	4 (4.9)	14 (2.6)	.16	14 (2.6)	0 (0.0)	14 (2.6)	.822				
Leukopenia† (%)	20 (3.6)	15 (3.1)	20 (3.6)	.15	20 (4.2)	0 (0.0)	20 (3.6)	.06	15 (3.3)	5 (6.1)	20 (3.7)	.21	20 (3.7)	0 (0.0)	20 (3.7)	.782				
Thrombocytopenia‡ (%)	45 (8.1)	38 (7.9)	45 (8.1)	.75	38 (8.0-24.5)	7 (8.5)	45 (8.1)	.87	39 (8.5)	5 (6.1)	44 (8.1)	.47	44 (8.1)	0 (0.0)	44 (8.1)	.672				
Mean (range) Hgb, g/dL	14.9 (8.0-24.5)	15.0 (8.0-24.5)	14.4 (10.0-22.1)	.04	15.0 (2.6)	14.7 (11.3-19.6)	14.9 (8.0-24.5)	.44	14.9 (8.0-24.5)	14.9 (10.0-22.7)	14.9 (8.0-24.5)	.92	14.9 (8.0-24.5)	14.4 (12.4-16.4)	14.9 (8.0-24.5)	.761				
Mean (range) WBC, × 10 ⁹ /L	9.2 (2.3-74.3)	9.3 (2.3-74.3)	7.3 (2.3-74.3)	.54	8.8 (2.3-74.3)	11.7 (3.5-34.0)	9.2 (2.3-74.3)	<.001	8.7 (2.3-44.2)	11.8 (2.8-74.3)	9.1 (2.3-74.3)	<.001	9.1 (2.3-74.3)	20.3 (16.6-24.0)	9.1 (2.3-74.3)	.011				
Mean (range) platelets, × 10 ⁹ /L	355.4 (2.0-1211.0)	360.0 (2.0-1211.0)	355.4 (2.0-1211.0)	.19	336.9 (2.0-1205.0)	462.8 (55.0-1211.0)	355.4 (2.0-1211.0)	<.001	341.0 (2.0-1157.0)	425.3 (79.0-1211.0)	353.7 (2.0-1211.0)	<.001	352.4 (2.0-1211.0)	703.5 (616.0-791.0)	353.7 (2.0-1211.0)	.011				
Laboratory abnormality, %	68 (12.2)	55 (11.5)	68 (12.2)	.19	61 (12.8)	7 (8.5)	68 (12.2)	.27	56 (12.2)	11 (13.4)	67 (12.4)	.75	67 (12.4)	0 (0.0)	67 (12.4)	.582				
Prior thrombosis (%)	322 (24.6)	194 (24.7)	317 (24.8)	.98	179 (27.7)	140 (21.8)	319 (24.8)	.02	197 (23.2)	103 (28.5)	300 (24.8)	.05	285 (25.0)	37 (25.2)	292 (25.1)	.972				
Prior hemorrhage (%)	136 (10.2)	66 (8.2)	134 (10.3)	.002	44 (6.6)	89 (13.8)	133 (10.2)	<.001	69 (8.1)	58 (15.8)	127 (10.4)	<.001	88 (8.6)	35 (23.8)	123 (10.5)	<.001				
Current phlebotomy (%)	646 (49.2)	249 (31.0)	370 (76.4)	<.001	—	—	—	—	305 (36.6)	175 (48.7)	480 (40.2)	<.001	—	—	—	<.001				
Enlarged spleen§ (%)	369 (30.2)	184 (25.8)	359 (30.1)	<.001	121 (21.4)	238 (37.5)	359 (29.9)	<.001	—	—	—	<.001	—	—	—	<.001				
Spleen size, cm below left costal margin	(0.0-24.5)	2.1 (0.0-24.5)	2.0 (0.0-24.0)	.33	2.1 (0.0-24.5)	1.2 (0.0-15.0)	2.0 (0.0-24.5)	.06	0.2 (0.0-2.0)	8.9 (2.3-24.5)	2.0 (0.0-24.5)	<.001	2.0 (0.0-24.5)	4.0 (3.0-5.0)	2.0 (0.0-24.5)	.0531				

Abbreviations: Hgb, hemoglobin; HU, hydroxyurea; MPN, myeloproliferative neoplasm; PV, polycythemia vera; SD, standard deviation; WBC, white blood cell count.

*Hgb < 11 g/dL

†WBC < 3.5 × 10⁹/L

‡Platelets < 150 × 10⁹/L

§Less than 2 cm below left costal margin.

on the fatigue survey (mean [deviation {SD}], 61.8 [12.7] years ν 59.7 [11.3] years; $P = .003$), and a higher proportion of patients on the validation study than on the fatigue survey had high-risk scores (49.2% ν 40.8%; $P = .017$). In addition, the MPN-10 TSS database included an international cohort of patients, and the fatigue survey was completed only by patients from the United States. Each PV subgroup (PV-HU, PV-P, PV-S, and PV-HUPS) was compared with a control group composed of the remaining total PV population that lacked the trait, including those without a history of known HU use (PV-cHU, $n = 807$), without known phlebotomy (PV-cP, $n = 668$), without splenomegaly (PV-cS, $n = 852$), or without all three features (PV-cHUPS, $n = 1,026$). Patient ages were similar among subgroups (PV-HU, 61.7 years; PV-S, 59.7 years; PV-P, 60.3 years; PV-HUPS, 61.9 years) and their respective comparison groups (range, 60.8- to 61.3 years).

Clinical Variables

Disease duration varied among PV-HU, PV-P, PV-S, and PV-HUPS subgroups (range, 6.5 to 11.5 years; [Table 1](#)). Patients in both the PV-HU and PV-S subgroups demonstrated significantly longer disease durations than those patients in the respective control groups that lacked the descriptive feature (PV-HU, 8.8 years ν PV-cHU, 6.6 years [$P = .008$]; PV-S, 8.6 years ν PV-cS, 6.5 years [$P = .005$]). No statistical differences in PV risk scores were noted among any of the subgroups or their respective comparison groups, and most patients met high-risk criteria (range, 42.8% to 47.0%). The prevalence of prior thrombosis among subgroups ranged from 21.8% to 28.5%, and a statistical difference was noted in the prevalence of PV-P and PV-S in relation to their control groups (PV-P, 21.8% ν PV-cP, 27.7% [$P = .02$]; PV-S, 28.5% ν PV-cS, 23.2% [$P = .05$]). History of prior hemorrhage and splenomegaly were statistically more prominent in all subgroups when compared to their respective comparison groups.

Laboratory Abnormalities

The presence of laboratory abnormalities varied among subgroups ([Table 1](#)). For patients in the PV-HU, PV-P, and PV-S groups, rates of anemia (range, 0% to 5.1%) leukopenia (range, 0% to 6.4%), and thrombocytopenia (range, 0% to 9.0%) were low and were without statistical difference when compared with their respective control groups. Mean hemoglobin levels were similar among patients in the PV-HU, PV-P, and PV-S subgroups (range, 14.4 to 14.9 g/dL). Patients in the PV-HUPS subgroup had the highest levels of leukocytosis and thrombocytosis among feature groups. Wide variability was noted in the mean WBC and platelet counts between subgroups; counts in patients with PV-HUPS ($20.3 \times 10^9/L$ and $703.5 \times 10^9/L$, respectively) were markedly higher than those in the PV-HU ($8.8 \times 10^9/L$ and $327.5 \times 10^9/L$, respectively), PV-P ($11.7 \times 10^9/L$ and $462.8 \times 10^9/L$, respectively), or PV-S ($11.8 \times 10^9/L$ and $425.3 \times 10^9/L$, respectively) subgroups. Statistical differences in WBC and platelet counts were also noted between patients when comparing PV-P, PV-S, or PV-HUPS subgroups and their respective control groups.

High Symptom Burden in Individual Feature Subgroups

Intermediate to high symptom burdens were noted in all feature subgroups, and the highest symptom burden was expressed by patients in the PV-HUPS subgroup (TSS, 32.5; range, 27.7 to 32.5; [Figs 1 and 2](#)). Patients in the PV-HUPS subgroup also had

higher individual scores for all symptoms assessed, with the exception of fever. However, numerous scores for individual symptoms, including abdominal discomfort, inactivity, night sweats, bone pain, and weight loss, were similarly high between PV-HUPS and other single-feature PV subgroups. MPN-10 total symptom scores were similar between PV-HU (29.2), PV-P (27.7), and PV-S (28.8) subgroups. Patients in the PV-HU subgroup had the highest mean symptom scores for microvascular and cytokine-related complaints, including fatigue, inactivity, concentration problems, night sweats, and bone pain. Patients in the PV-P subgroup had the lowest mean symptoms scores for items related to abdominal complaints, including early satiety, abdominal discomfort, and weight loss. They also had the lowest overall score for pruritus. Patients in the PV-S subgroup were most likely to have abdominal-related complaints, including early satiety and weight loss, and were least likely to have fatigue. When each feature subgroup was compared with their respective control group, the TSS and most of the individual symptoms were higher in patients who possessed the feature in comparison to those who lacked it ([Figs 1 and 2](#)).

Worsening Symptom Burden With Increasing Number of Features

Data also were compared between PV cohorts on the basis of the number of features present within each patient ([Table 2](#)). A total of 362 patients with PV had zero features; 348 had one feature (PV-HU, $n = 82$; PV-P, $n = 165$; PV-S, $n = 101$); 315 had two features (PV-HU + PV-P, $n = 215$; PV-P + PV-S, $n = 80$; PV-HU + PV-S, $n = 20$); 617 had one or two features; and 148 had all three features (PV-HUPS).

Mean age statistically differed among patients by the number of features they possessed ($P = .002$). Patients who had zero features were slightly older (62.5 years) than those with one to two features (59.8 years). Patients who had all three features had the highest mean WBC count ($20.3 \times 10^9/L$ ν 8.5 to $10.0 \times 10^9/L$; $P = .001$), highest platelet levels ($703.5 \times 10^9/L$ ν 332.8 to $384.7 \times 10^9/L$; $P < .001$), and highest history of prior hemorrhage (23.8% ν 4.7% to 10.7%; $P < .001$). No differences were noted in PV risk scores; the presence of anemia, leukopenia, or thrombocytopenia; mean hemoglobin level; or history of prior thrombosis.

When symptom burdens were compared, scores for all individual questions statistically differed by the number of features present, with the exception of fever and weight loss ([Figs 3 and 4](#)). Patients who had one feature had higher total and individual symptom scores than patients who had zero features. Similarly, patients who had two features had higher individual and total symptom scores than patients who had one feature (PV-P + other ν PV-P, $P = .05$; PV-HU + other ν PV-HU, $P = .01$), and patients who had all three features (PV-HUPS) had higher individual and total symptom scores (all $P < .01$) than patients who had one or two features. Overall, symptom scores were highest and most prevalent for the item of fatigue followed by microvascular-related symptoms, including concentration difficulties and pruritus.

DISCUSSION

The results of this study clearly demonstrate that the symptom burden in patients with PV is substantial, independent of whether a patient has used HU, has received phlebotomy, or has splenomegaly.

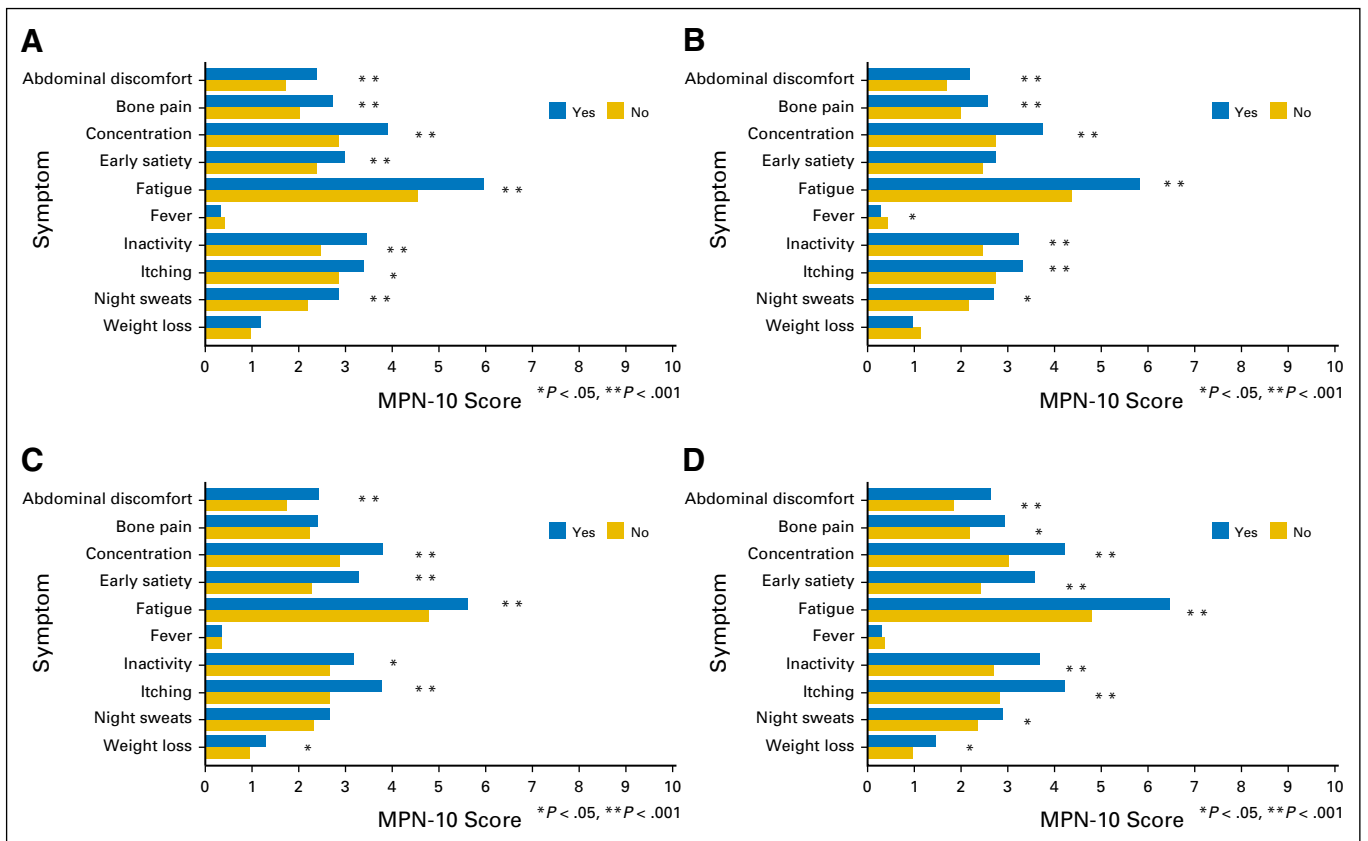


Fig 1. Myeloproliferative neoplasm symptom assessment form (MPN-10) with individual symptoms by features. Mean symptom scores by (A) known hydroxyurea use, (B) known phlebotomy, (C) enlarged spleen, or (D) all three features.

With the 2013 symptom response thresholds criteria,¹⁵ patients with PV who had all three features (PV-HUPS) met criteria for symptom quartile 4 (TSS, 32.5; high symptom burden profile). To put this into perspective, the average TSS of patients with myelofibrosis falls within symptom quartile 3 (TSS, 25.3), which suggests that disease burden is exceptionally high within this PV population.² Importantly, all patients with PV who had only one feature (PV-P, PV-S, or PV-HU) also ranked within symptom quartile 3 (moderately high symptom burden profile), which demonstrates suboptimal symptom control. Patients with PV who had any given feature were statistically more symptomatic by MPN-10 TSS than their control group that lacked the individual feature, which suggests that the presence of splenomegaly, HU use, or phlebotomy requirement is independently associated with a substantial symptom burden.

This study also identified an additive relationship between the number of features present and the degree of symptoms expressed. This is especially true for participants in the PV-P and PV-HU subgroups. For all categories, patients who possessed two features were significantly more symptomatic than those who had one feature. Similarly, those who had three features had more symptoms than those who had one or two features. This finding corresponds with the results in Table 2 that demonstrate a statistical difference in risk scores on the basis of the number of features present. Positive associations were also noted between the severity of thrombocytopenia, leukocytosis, or prior hemorrhage and the presence of multiple

features, as demonstrated by patients in the PV-HUPS subgroup.

It is notable that many scores for individual symptoms in patients with PV-HUPS were similar to those of patients in the single-feature PV-HU, PV-P, and PV-S subgroups (Fig 1). This is especially true for cytokine-driven items (night sweats, bone pain, weight loss) and abdominal-related complaints (abdominal discomfort, weight loss) in patients in the PV-HU subgroup. Of interest, the TSS of patients in the PV-HU subgroup was similar to that of patients in the PV-P and PV-S subgroups (29.2 v 27.7 to 28.8). Historically, HU has been reserved for high-risk PV. Given that patients in the PV-P and PV-S subgroups did not statistically differ by risk category compared with their respective control groups, the higher symptom score of patients in the PV-P and PV-S subgroups implies that high symptomatic burden exists independent of risk category and, furthermore, that symptoms remain undermanaged in low-risk patients with PV who are not deemed candidates for cytoreductive therapy. Although still meeting criteria for moderately high symptom burden, PV patients with a history of phlebotomy had a slightly lower symptom burden than patients in the other PV cohorts for both total score and individual items. Patients in the PV-P group did not differ from those in their respective control groups by risk category, so it is possible that phlebotomy in itself has symptom-ameliorating characteristics that have yet to be elucidated.

It is also worth noting that the items of weight loss and fevers were least likely to differ between feature groups and their

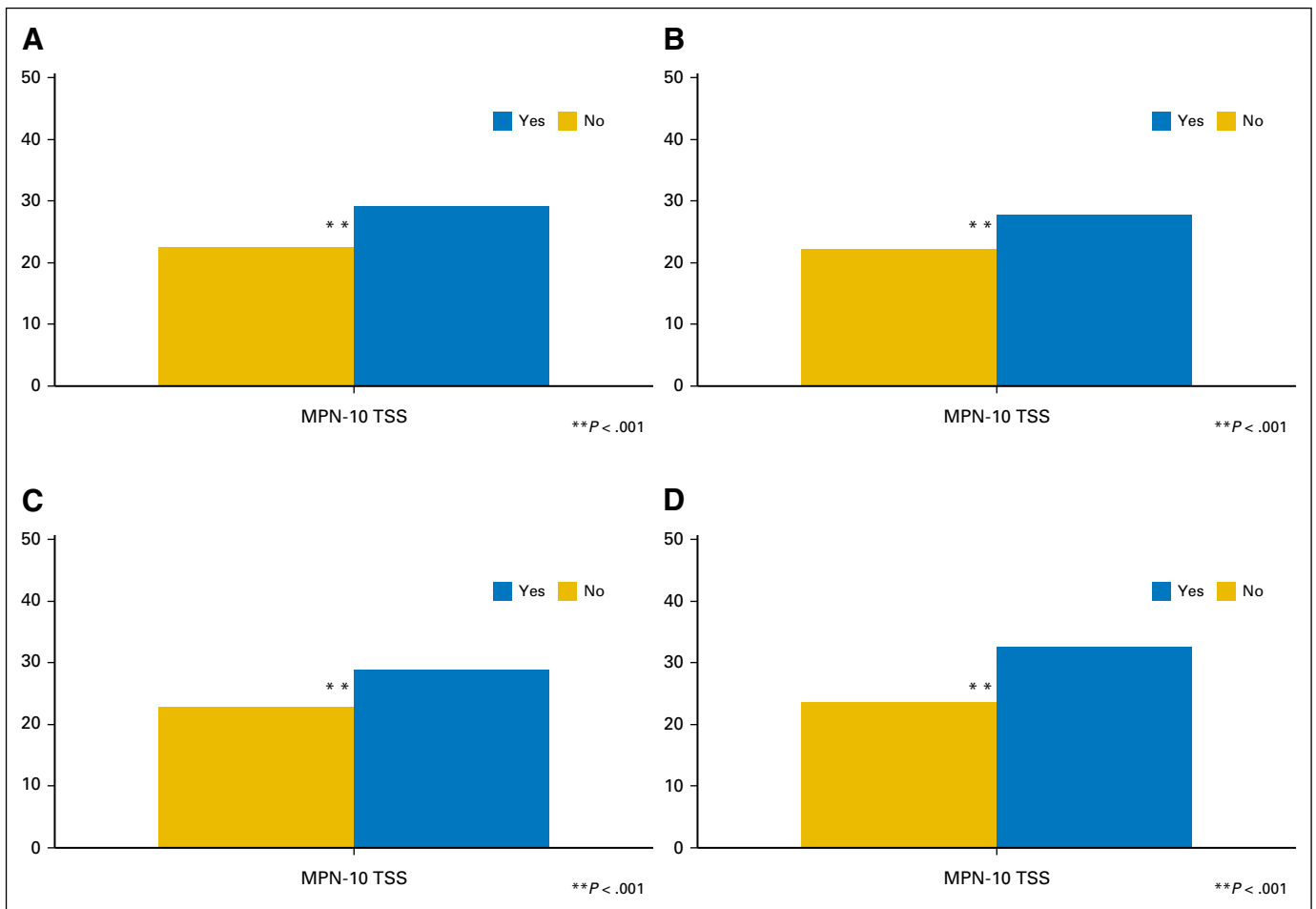


Fig 2. Myeloproliferative neoplasm symptom assessment form (MPN-10) total symptom score (TSS) by features. Mean MPN-10 TSS by (A) known hydroxyurea use, (B) known phlebotomy, (C) enlarged spleen, or (D) all three features.

associated controls or to vary by the number of features possessed. This observation implies that these disease features are not altered by the interventions (phlebotomy, HU) or the presence of splenomegaly. It is possible that the unique neurohormonal and cytokine environment (interleukin 4 [IL-4], fibroblast growth factor b [FGF-b], hepatocyte growth factor [HGF], and RANTES) induced by PV results in hypothalamic sensitization that contributes to weight loss and fever development.¹⁶ Alternatively, it is also possible that these are the two easiest symptoms to externally validate with objective information, directing the patient away from subjective reporting. It is worth noting that patients in both the PV-S and PV-HU subgroups differed in disease length from their respective control groups. However, the compared cohorts did not differ by risk scores, which suggests that disease length had a minimal impact on disease burden.

It is important to emphasize that there are limitations in making direct comparisons between patients in this study and the population represented in the RESPONSE trial.¹² First, this study did not differentiate whether therapies (HU/phlebotomy) were being provided currently or had been used remotely. The RESPONSE trial specifically included patients with resistance or intolerance to HU (which suggested that patients were no longer receiving therapy) and phlebotomy dependence, defined as two or more phlebotomies within 24 weeks prior to screening and at

least one within 16 weeks before screening. It is plausible that patients in whom HU has failed and/or patients who have current phlebotomy requirements may face a different symptom burden than that of patients who have a different timeline of therapy use. However, our population was a mixture of patients with current and prior therapy use, so we feel that the differences would likely be minimal. Furthermore, patients with resistance or intolerance to HU would be likely to express more symptoms, not less, which additionally substantiates our concerns that this population remains symptomatically undermanaged. It also is worth noting that our patient sample was composed of two different cohorts acquired from separate databases (the MPN-10 TSS validation survey and the FATIGUE survey). Participation in the survey for both groups was voluntary, and neither population received compensation for involvement. As such, we believe that selection bias was minimal but not directly investigated within this study.

The results of this investigation plainly show that symptoms in patients with PV who have known HU use, known phlebotomy requirements, and splenomegaly are greater than in those patients who lack these features. Furthermore, there is an additive effect on symptom burden as more features are included in a patient's profile. As discussed, the symptom burdens of patients with PV who have splenomegaly and/or phlebotomy requirements remain

Table 2. Clinical Characteristics of Patients With PV by Number of Features

Characteristic	No. (%) of Patients by Number of Features			All Patients (N = 1,116)	P
	0 (n = 362)	1-2 (n = 617)	3 (n = 137)		
Mean (SD) age, years	62.5 (12.8)	59.8 (12.3)	61.9 (10.1)	60.9 (12.3)	.002
Age ≥ 60 years	224 (61.9)	326 (52.8)	82 (59.9)	632 (56.6)	.02
Mean (SD) PV duration, years	6.6 (6.2)	7.4 (6.8)	11.5 (0.7)	7.0 (6.5)	.30
PV risk					.04
Low	75 (22.0)	141 (25.2)	22 (16.4)	238 (23.0)	
Intermediate	94 (27.6)	181 (32.4)	49 (36.6)	324 (31.3)	
High	172 (50.4)	237 (42.4)	63 (47.0)	472 (45.6)	
Anemia*	7 (2.1)	7 (3.4)	0 (0.0)	14 (2.6)	.62
Leukopenia†	13 (3.9)	7 (3.4)	0 (0.0)	20 (3.7)	.93
Thrombocytopenia‡	29 (8.6)	15 (7.4)	0 (0.0)	44 (8.1)	.80
Mean (SD) Hgb, g/dL	15.0 (2.7)	14.8 (2.3)	14.4 (2.8)	14.9 (2.5)	.42
Mean (SD) WBC, × 10 ⁹ /L	8.5 (5.5)	10.0 (7.4)	20.3 (5.2)	9.1 (6.4)	.001
Mean (SD) platelets, × 10 ⁹ /L	332.8 (174.8)	384.7 (226.1)	703.5 (123.7)	353.7 (198.0)	< .001
Laboratory abnormality	43 (12.8)	24 (11.8)	0 (0.0)	67 (12.4)	.82
Prior thrombosis	95 (26.2)	160 (24.4)	37 (25.2)	292 (25.1)	.83
Prior hemorrhage	17 (4.7)	71 (10.7)	35 (23.8)	123 (10.5)	< .001

Abbreviations: Hgb, hemoglobin; PV, polycythemia vera; SD, standard deviation; WBC, white blood cell count.

*Hgb < 11 g/dL.

†WBC < 3.5 × 10⁹/L.

‡Platelets < 150 × 10⁹/L.

unacceptably high and rival those of patients who meet high-risk criteria and who, therefore, become candidates for HU treatment. These findings are far-reaching because emerging therapies offer the potential to reduce phlebotomy requirements, protect against vascular events, improve the symptomatic burden, and potentially offer protection against disease transformation. Recent studies to characterize the symptoms inherent to phlebotomy⁷ and HU use^{10,11} have made the philosophy of individualized PV treatments according to symptom response an increasingly appealing approach.¹⁷ As demonstrated in the RESPONSE trial, ruxolitinib improves symptoms and controls hematocrit in patients who have the combined three features.¹² The results of this study suggest that

patients with PV who have even one or two features may benefit from *JAK2* inhibitor treatment as well. Other novel therapies, including histone deacetylase (HDAC) inhibitors and heat-shock protein-90 (HSP-90) inhibitors, are under active investigation in PV, and results are anxiously anticipated.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org

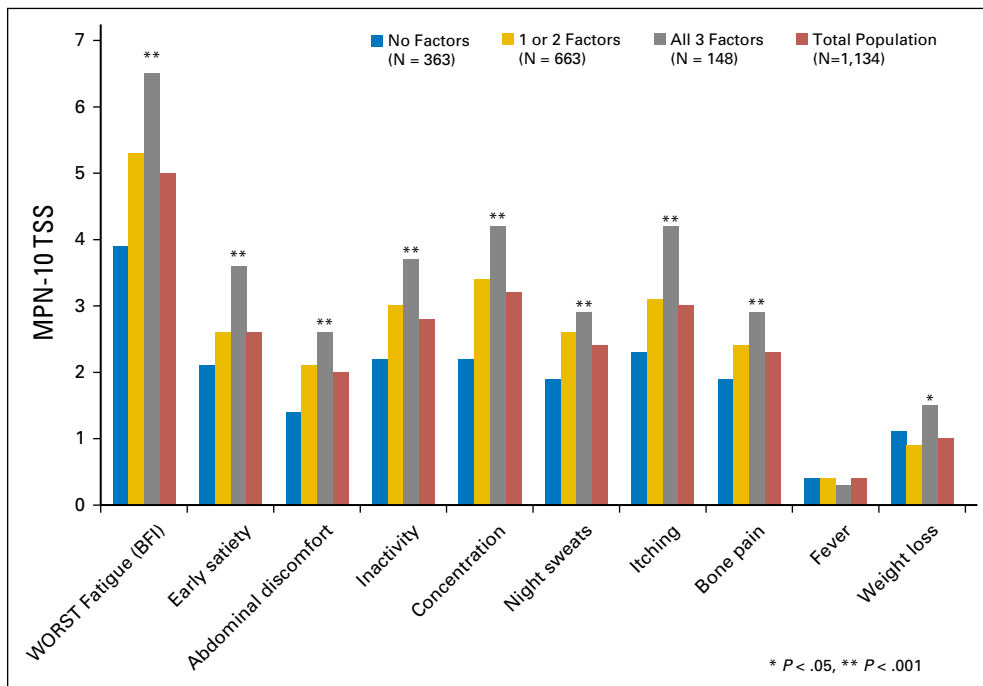


Fig 3. Myeloproliferative neoplasm symptom assessment form (MPN-10) total symptom score (TSS) symptoms according to the number of features present. BFI, Brief fatigue inventory scale.

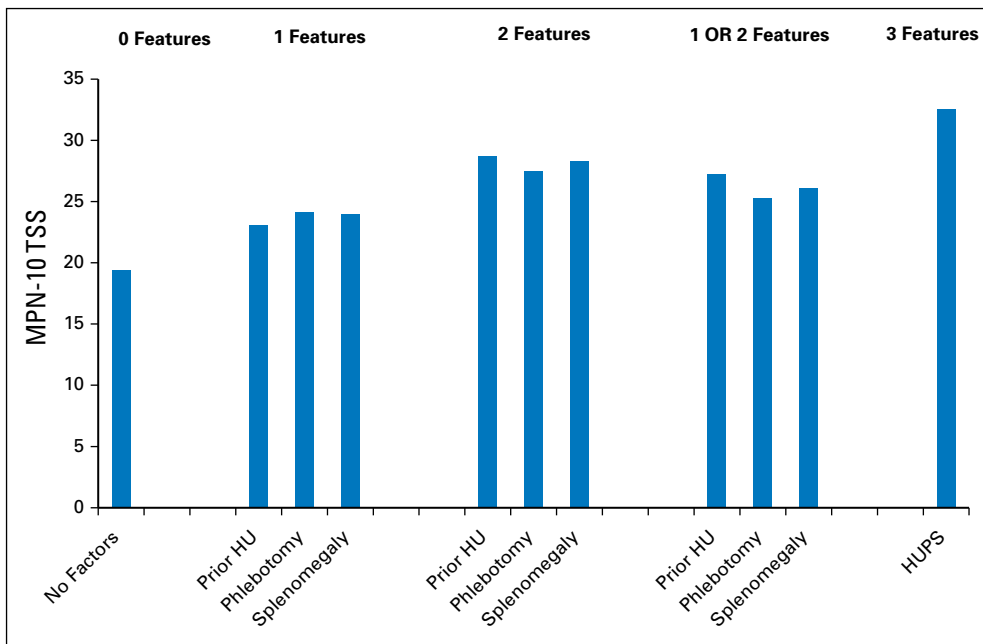


Fig 4. Myeloproliferative neoplasm symptom assessment form (MPN-10) total symptom score (TSS) according to the number of features. HU, hydroxyurea; HUPS, all three features (known HU use, known phlebotomy, and enlarged spleen).

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Symptomatic Profiles of Patients With Polycythemia Vera: Implications of Inadequately Controlled Disease

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