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ARTICLE

Health-related quality of life and symptom profile of patients with *BCR::ABL1*-negative myeloproliferative neoplasms: Real-world evidence from the GIMEMA-PROPHECY observational study

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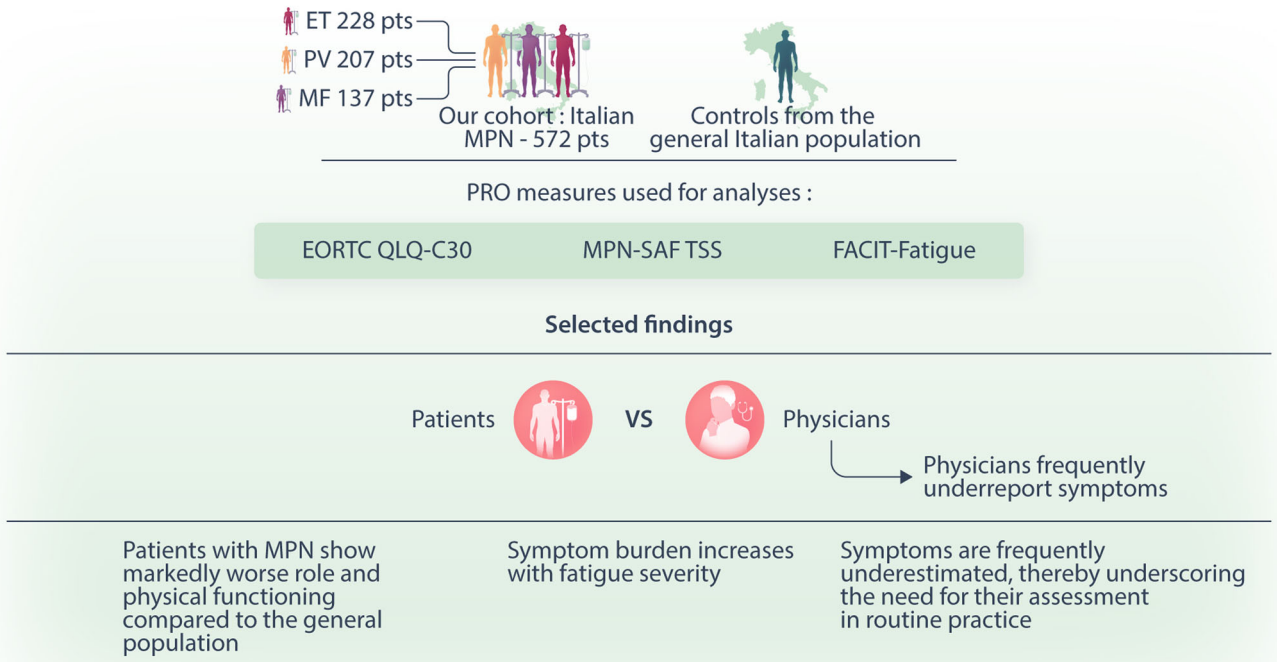
Graphical Abstract



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Abstract

Health-related quality of life (HRQoL) of patients with myeloproliferative neoplasms (MPNs) may be impaired across several domains. In this multicenter observational study, we evaluated HRQoL and symptoms in a cohort of MPN patients with validated measures, including the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), the Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS), and the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue) questionnaire. The primary objective was to compare the HRQoL profile of patients, by disease subtype, with that of the general population according to the EORTC QLQ-C30. A total of 572 patients with essential thrombocythemia (ET, $n = 228$), polycythemia vera (PV, $n = 207$), and myelofibrosis (MF, $n = 137$) were assessed. Worse statistically and clinically significant differences were observed for role functioning (ET: $\Delta = 8.9$, $P < 0.001$; PV: $\Delta = 11$, $P < 0.001$; MF: $\Delta = 16.7$, $P < 0.001$) and fatigue (ET: $\Delta = 5$, $P < 0.001$; PV: $\Delta = 8.3$, $P < 0.001$; MF: $\Delta = 11.5$, $P < 0.001$) in all three diagnostic groups. However, patients with MF also reported impairments in other important health domains. Fatigue was the most frequently reported and burdensome symptom, with greater severity correlating with a broader and more complex array of associated symptoms. Our analysis also revealed a substantial underestimation of symptoms by treating hematologists in paired physician–patient reports. Current findings may help to disentangle specific HRQoL limitations and symptomatology experienced by patients with MPNs, and underscore the importance of incorporating patient-reported outcomes into routine practice to better reflect the patient's perspective of the disease and treatment-related burden.

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INTRODUCTION

BCR::ABL1-negative myeloproliferative neoplasms (MPNs), comprising polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF),[1] are defined by distinct biological features, life-threatening complications, and a substantial impact on health-related quality of life (HRQoL).[2,3] Over the past two decades, HRQoL and other types of patient-reported outcomes (PROs)[4] have become central to evaluating disease burden and treatment benefits, both in clinical trials and routine practice.[5] These types of data have also been shown to provide independent prognostic information for survival across several cancer diagnoses,[6] including patients with MF,[7] thereby underscoring the importance of more systematically collecting this information. The Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS; MPN-10) is now frequently used to assess the full spectrum of symptoms and inform treatment decisions.[8] Notable evidence supporting the integration of PROs comes from the Phase III trial COMFORT-I trial,[9] which established the efficacy of ruxolitinib in alleviating MF-associated symptom burden, and the Phase III RESPONSE trial, where ruxolitinib proved superior to standard therapy in improving symptoms in PV.[10] Likewise, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) used in the JAKARTA-2 trial documented meaningful symptomatic improvement in MF patients receiving fedratinib.[11] More recently, the MOMENTUM trial confirmed the advantage of momelotinib over danazol in patients with MF with earlier and broader improvements across symptom domains, physical function, and overall HRQoL.[12,13] Notably, the approval of momelotinib was granted by the Food and Drug Administration (FDA) based on the primary PRO endpoint, which was the Myelofibrosis Symptom Assessment Form (MFSAF) TSS response rate at Week 24.[13]

Despite the remarkable contribution of PRO inclusion in MPN trials over the years, less is known about HRQoL and symptom profile of patients treated in real-life. Also, there is substantial evidence from the literature on patients with solid tumors indicating that physicians tend to underestimate patients' symptom severity.[14,15] However, there is limited evidence on patients with MPN in this regard.

The primary objective of this study was to compare the HRQoL profile of MPN patients with that of the general population. Secondary objectives were the following: (1) to describe symptom profile across MPN subtypes; (2) to examine the relationships between fatigue and other symptoms; and (3) to compare the reporting of symptom severity between patients and their treating physicians.

PATIENTS AND METHODS

Study population

The "Patient-Reported Outcome in Philadelphia-negative cytogenetic myeloproliferative neoplasm" (PROPHECY) was a multicenter prospective observational study enrolling Italian patients with *BCR::ABL1*-negative MPNs and coordinated by the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) Foundation. Local investigators carried out patient enrollment at each participating site. Eligibility criteria included age ≥ 18 years and a diagnosis of PV, ET, pre-fibrotic primary myelofibrosis (pre-PMF), overt PMF, and secondary MF (post-PV and post-ET), as defined by the 2016 World Health Organization (WHO) classification.[16] Only patients diagnosed within 12 months preceding enrollment were included. A known prognostic risk category at the time of initial diagnosis based on IPSS[17] for PV, IPSET[18] for ET, and DIPSS[19] for MF was required. Completion of a baseline PRO assessment was mandatory for study inclusion. Exclusion criteria included any psychiatric or cognitive condition that could interfere with self-reporting, as well as an inability to read and understand the local language. The study is registered at ClinicalTrials.gov NCT04378855. The ethics committees of all participating centers approved the study. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Study design and data collection

Patients completed survey booklets at baseline (study inclusion) and thereafter at predefined time points (3, 6, 12, 18, and 24 months). At baseline, a corresponding physician-reported data collection form was also included to gather insights on patient–physician communication and the clinical decision-making process. Physicians' basic demographic data were collected as well as other information, such as number of years in practice, frequency of patient encounters, and perceived patient involvement in the clinical decision-making process. Physicians' perception on patients' health status/quality of life (QoL) and symptoms (by the MPN-SAF TSS questionnaire) was also collected.

Concurrently with the PRO assessments, detailed longitudinal data on treatment type, duration, and regimen were documented throughout the follow-up period and at study completion. Clinical responses were assessed in accordance with established response criteria for PV, ET, and MF as outlined by the International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWMRT)[20] and European LeukemiaNet (ELN) consensus guidelines.[21,22] Adverse events were graded according to the National Cancer Institute

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Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0. Disease progression events were systematically captured and recorded.

PRO assessment measures

At baseline, participants were required to complete a set of validated PRO questionnaires, including the EORTC QLQ-C30,[23] Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue),[24] MPN-SAF TSS,[8] and FACIT-Treatment Satisfaction-General version 4 (FACIT-TS-G).[25] For the purpose of the present work, we present baseline data from the EORTC QLQ-C30, FACIT-Fatigue, and MPN-SAF TSS.

The EORTC QLQ-C30 is a 30-item multidimensional questionnaire that includes five functional scales: physical, role, emotional, cognitive, and social functioning, as well as a global health status/QoL scale. It also evaluates a core set of cancer-specific symptoms, including fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties.[23] Raw scores are transformed to a linear scale ranging from 0 to 100, where higher scores indicate better functioning or health status for functional and global scales or greater symptom severity for symptom scales.[26]

The FACIT-Fatigue is a 13-item scale that evaluates fatigue, weakness, and difficulty in performing daily activities due to fatigue.[24] Responses are recorded on a 5-point Likert scale (0 = "not at all" to 4 = "very much"), with a total score ranging from 0 to 52. Higher scores reflect lower levels of fatigue.

The MPN-SAF TSS is a concise 10-item tool designed to assess the prevalence and severity of symptoms in MPN. Symptoms evaluated include fatigue, concentration problems, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers. Each symptom is scored from 0 (absent) to 10 (worst imaginable) based on the symptoms experienced during the preceding week. Symptom severity is categorized as absent (0), mild (1–3), moderate (4–6), and severe (7–10). The total score was calculated by taking the mean of the completed items and multiplying it by 10, thereby producing the MPN-SAF TSS on a standardized 0–100 scale.[8,27]

Statistical analysis

Descriptive statistics were conducted for the demographic and clinical characteristics of patients. Continuous variables were summarized using the mean, standard deviation (SD), median, and interquartile range (IQR), while categorical variables were presented as frequency and percentage. Mean scores of the EORTC QLQ-C30 scales were calculated, and physical, emotional, and role functioning, as well as global health status/QoL and fatigue, were prespecified in the protocol as the main scales of relevance for our patient population. A sample of 576 patients was calculated to ensure 80% power to detect a small clinically meaningful difference in at least one of the prespecified EORTC QLQ-C30 scales. Mean scores were compared to normative data from the general Italian population.[28] For this reference population, adjusted mean scores were estimated accounting for sex, age, and comorbidity to allow an appropriate comparison. Evaluation of clinically meaningful differences between estimated mean differences of the two groups (i.e., general population and MPN patients) was based on previously published scale-specific thresholds[29] and reported if considered at least of small magnitude. Statistical significance was evaluated using the Wilcoxon rank sum test. The statistical significance of the above prespecified EORTC QLQ-C30 scale comparisons was set as $\alpha = 0.01$, to account for multiple testing, according to the Bonferroni correction. Descriptive statistics of MPN-SAF scales and TSS including mean scores and prevalence rates were calculated for the overall cohort as well as stratified by disease subtype (MF, PV, and ET) and by sex. Comparisons among MPN subtypes and sex were performed using the chi-square test for symptom prevalence and one-way analysis of variance (ANOVA) for symptom severity. Physician-reported symptoms were analyzed and compared with the corresponding symptoms reported by patients according to the MPN-SAF TSS. The percentage of agreement and Cohen's kappa coefficient were used to assess the concordance between patient and physician reports. Based on previous work[30] underreporting was defined as cases where the physician reported no symptom (Grade 0), while the patient reported at least Grade 1 of the same symptom. We also examined underestimation of severe symptoms (≥7), defined as discordant cases where the physician's rating did not exceed 6, whereas the patient's rating for the same symptom was 7 or higher. For descriptive purposes, and to ease interpretation of data, the cohort was divided into two groups based on the FACIT-Fatigue scores median value: lower fatigue (>42) and higher fatigue (≤42). MPN-SAF items and patient-reported symptom intensity were summarized according to fatigue levels. Correlation between the FACIT-Fatigue score and individual symptoms, including the TSS, was assessed using Spearman's correlation coefficients. Statistical tests for descriptive analyses were two-sided, with Type I error $\alpha = 0.05$ and were not adjusted for multiple testing. All analyses were performed using R software (version 4.4.2.).

RESULTS

Between June 2020 and November 2023, 580 patients were screened across 26 centers in Italy. Of these, 572 met the inclusion criteria and were evaluable for analysis. Eight patients were excluded: six due to missing baseline PROs, one for an unconfirmed diagnosis, and one following reclassification as chronic myeloid leukemia (Figure S1).

The median time from diagnosis to enrollment was 3.0 months (IQR: 1.0–7.0). The median age at diagnosis was 67.2 years (IQR: 55.5–74.7), and 51.2% of the patients were male.

Overall, 228 patients (39.9%) were diagnosed with ET, 207 patients (36.1%) with PV, and 137 patients (24.0%) with MF. Patients' characteristics by diagnostic category are summarized in Table 1. Driver mutation status was available in 562 patients (98.3%). Among these, 454 (79%) harbored a *JAK2* mutation; 58 patients (10.1%) carried *CALR* mutations, including 46 (8.0%) with Type 1/Type 1-like and 12 (2.1%) with Type 2/Type 2-like variants; and 14 patients (2.4%) carried *MPL* mutations. Twenty-one patients (3.7%) were triple-negative for *JAK2*, *CALR*, and *MPL* mutations.

Of the 572 patients included, 430 (76%) had initiated therapy before study inclusion, most commonly those with PV (84%), followed by ET (73%) and MF (69%). Hydroxyurea was administered in 43% of ET, 49% of PV, and 39% of MF patients, either as monotherapy or combined with other treatments (Table S1). Median duration of treatment was 2.7 months (IQR: 0.9–6.8). The HRQoL and symptom profile of patients who received previous therapy versus those who did not were broadly similar (Tables S2 and S3).

HRQoL profile comparison of MPN patients by diagnostic group with the general population

With regard to the main EORTC QLQ-C30 scales, worse statistically and clinically significant differences were observed for role functioning (ET: $\Delta = 8.9$, 95% CI: 6.4–11.4, $P < 0.001$; PV: $\Delta = 11$, 95% CI: 7.9–14.2, $P < 0.001$; MF: $\Delta = 16.7$, 95% CI: 12.2–21.1, $P < 0.001$) and

TABLE 1 Demographic and clinical characteristics of myeloproliferative neoplasm (MPN) patients, overall and by disease type (*N* = 572).

Characteristic	Overall, *N* = 572	Essential thrombocythemia, *n* = 228	Polycythemia vera, *n* = 207	Myelofibrosis, *n* = 137
Age, years				
Mean (SD)	64.4 (14.1)	62.8 (14.6)	64.4 (13.4)	67.0 (14.2)
Median (IQR)	67.2 (55.5–74.7)	66.7 (52.8–73.9)	66.7 (54.3–74.5)	68.5 (60.3–75.3)
Sex, *n* (%)				
Male	293 (51.2%)	102 (44.7%)	115 (55.6%)	76 (55.5%)
Female	279 (48.8%)	126 (55.3%)	92 (44.4%)	61 (44.5%)
Education level, *n* (%)				
Compulsory school education or less	211 (37%)	81 (39%)	78 (35%)	52 (38%)
High school	248 (44%)	84 (41%)	103 (46%)	61 (45%)
University degree or higher	108 (19%)	41 (20%)	43 (19%)	24 (18%)
Missing	5	1	4	0
Living arrangements, *n* (%)				
Living alone	90 (16%)	35 (17%)	33 (15%)	22 (16%)
Living with partner/spouse	415 (73%)	149 (72%)	167 (75%)	99 (72%)
Living with other relatives, except partner or spouse	53 (9.3%)	19 (9.2%)	21 (9.4%)	13 (9.5%)
Living with other person, except relatives, partner, or spouse	9 (1.6%)	3 (1.5%)	3 (1.3%)	3 (2.2%)
Missing	5	1	4	0
Comorbidities,[a] *n* (%)				
Yes	184 (32.2%)	62 (27.0%)	69 (33.7%)	53 (38.7%)
No	385 (67.8%)	165 (73.0%)	136 (66.3%)	84 (61.3%)
Missing	3	1	2	0
Time since diagnosis, months				
Mean (SD)	4.2 (3.7)	4.0 (3.7)	4.1 (3.8)	4.5 (3.6)
Median (IQR)	3 (1.0–7.0)	2.7 (0.9–6.8)	2.8 (0.9–7.4)	3.6 (1.5–6.9)
Previous treatment,[b] *n* (%)				
Yes	430 (76.1%)	164 (72.9%)	173 (84.0%)	93 (69.4%)
No	135 (23.9%)	61 (27.1%)	33 (16.0%)	41 (30.6%)
Missing	7	3	1	3
Transfusion dependency,[c] *n* (%)				
Yes	15 (2.7%)	3 (1.4%)	2 (1.0%)	10 (7.3%)
No	547 (97.3%)	218 (98.6%)	202 (99%)	127 (92.7%)
Missing	10	7	3	0
Previous thrombotic event, *n* (%)				
Yes	117 (20.6%)	42 (18.5%)	51 (24.6%)	24 (17.8%)
No	452 (79.4%)	185 (81.5%)	156 (75.4%)	111 (82.2%)
Missing	3	1	0	2
Driver mutation (*N* = 562/572),[d] *n* (%)				
JAK2 V617F	454 (79%)	161 (71%)	197 (95%)	96 (70%)
CALR Type 1/like	46 (8.0%)	33 (14%)	0	13 (9.5%)
CALR Type 2/like	12 (2.1%)	5 (2.2%)	0	7 (5.1%)
MPL	14 (2.4%)	7 (3.1%)	0	6 (4.4%)
Triple negative	21 (3.7%)	14 (6.1%)	0	6 (4.4%)
Not done	29 (5.1%)	11 (5.3%)	11 (4.8%)	7 (5.1%)

TABLE 1 (Continued)

Characteristic	Overall, *N* = 572	Essential thrombocythemia, *n* = 228	Polycythemia vera, *n* = 207	Myelofibrosis, *n* = 137
Hb level, g/dL				
Mean (SD)	14.7 (2.7)	14.0 (1.8)	17.0 (1.9)	12.5 (2.7)
Median (IQR)	14.9 (13.3–16.5)	14.3 (13.0–15.2)	16.9 (16.0–18.0)	12.8 (10.6–14.7)
Missing	5	2	1	2
Hematocrit value, %				
Mean (SD)	45.7 (8.2)	43.1 (5.1)	52.9 (5.9)	39.3 (7.3)
Median (IQR)	46.1 (41.2–50.2)	43.2 (40.3–46.6)	52.2 (49.0–56.2)	40.5 (34.8–45.1)
Missing	18	11	4	3
PLT count, $\times 10^9$/L				
Mean (SD)	586.1 (367.3)	699.4 (452.2)	497.9 (212.4)	529.5 (345.4)
Median (IQR)	562.0 (409.5–722.5)	649.5 (539.0–783.0)	485 (345.3–631.5)	525.0 (223.0–752.0)
Missing	8	2	3	3

Abbreviations: Hb, hemoglobin; IQR, interquartile range; PLT, platelets; SD, standard deviation.

[a]Presence of comorbidities has been assessed using the Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI). For descriptive purposes, we reported the prevalence of comorbidities without reporting the total score.

[b]Refers to the treatments received by the patient, from MPN diagnosis up to baseline patient-reported outcome (PRO) evaluation.

[c]Transfusion dependency is defined according to International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) consensus report as transfusion of at least six units of packed red blood cells (PRBCs) in the 12-week period before study enrollment, for a Hb level of <8.5 g/dL, in the absence of bleeding or treatment-induced anemia. In addition, the most recent transfusion episode must have occurred in the 28 days prior to study enrollment.

[d]Multiple-answer question.

fatigue (ET: Δ = 5, 95% CI: 2.2–7.9, P < 0.001; PV: Δ = 8.3, 95% CI: 5.0–11.5, P < 0.001; MF: Δ = 11.5, 95% CI: 7.6–15.5, P < 0.001) in all three diagnostic groups (Figures 1 and 2). However, patients with MF also reported statistically and clinically significant worse scores for physical functioning (Δ = 10.5, 95% CI: 6.9–14.1, P < 0.001) and global health status/QoL (Δ = 6.1, 95% CI: 2.2–10.1, P = 0.003). No differences were observed in the emotional functioning scale.

With regard to other scales, all three patient groups also reported worse scores for cognitive functioning (ET: Δ = 3.4, 95% CI: 1.0–5.9, P = 0.006; PV: Δ = 5.6, 95% CI: 3.1–8.2, P < 0.001; MF: Δ = 6.1, 95% CI: 2.7–9.5, P < 0.001) (Figure 1). Worse statistically and clinically meaningful differences were also observed for dyspnea in patients with PV and MF and for insomnia in patients with PV and ET. Interestingly, pain severity was lower (albeit not significant) in all three MPN subtypes compared to the general population (Figure 2). We note that positive differences observed in both functional and global HRQoL scales, as well as in symptoms, reflect worse HRQoL outcomes for MPN patients.

Patient-reported symptom severity and prevalence by the MPN-SAF TSS

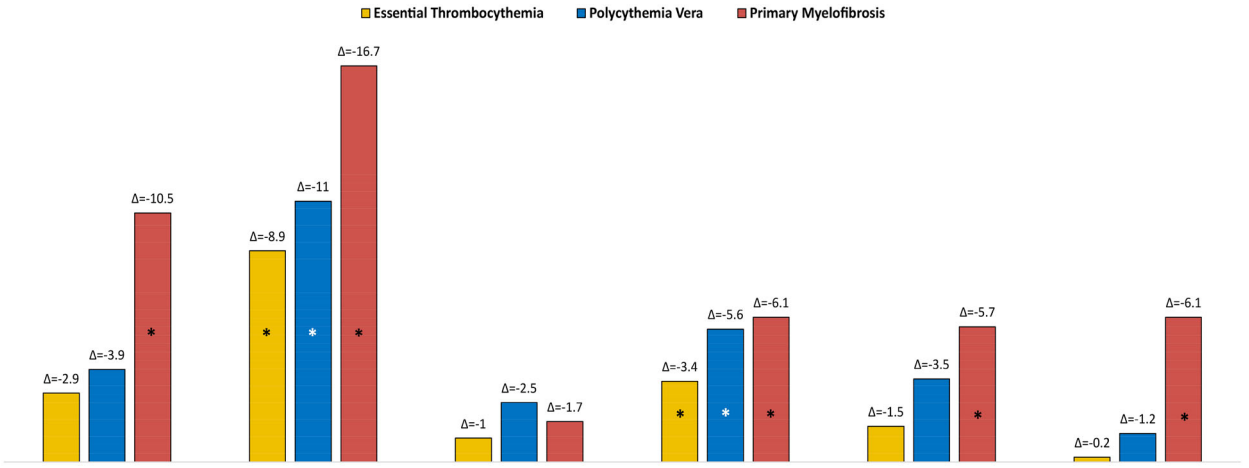
At least one symptom on the MPN-SAF TSS was reported by 506 patients (89%), with higher rates in PV (92%) and MF (91%) compared to ET (85%). The mean TSS for the entire cohort was 13.2 ± 13.9, highest in MF (14.9 ± 14.0), followed by PV (14.2 ± 14.9) and ET (11.3 ± 12.5). Female patients reported significantly greater symptom burden than males. For example, fatigue was more severe in females (3.2 ± 2.5) compared to males (2.4 ± 2.5) (Table S4). Fatigue was the most frequently reported symptom (77%) in the overall population, and it was more severe in patients with MF (3.3 ± 2.6) compared to PV (2.7 ± 2.6) and ET (2.5 ± 2.3) (Table 2). The proportion of patients reporting a mean MPN-SAF TSS of more than 20 points is reported in Table S5. By diagnostic group, inactivity (54%) and concentration problems (55%) were more frequent and severe in MF patients compared to ET and PV. Early satiety was also more common in MF (51%), although severity scores were comparable across groups. Intergroup differences were found for itching and night sweats. Itching was more frequent and severe in PV (55%, mean score 2.2 ± 2.7) compared to ET (0.9 ± 2.0) and MF (1.2 ± 2.3). Night sweats were also more common in PV (42%), though severity did not differ across subtypes. Further details and statistical significance for the corresponding prevalence and/or severity measures are reported in Table 2.

Fatigue severity and its relationship with other disease-specific symptoms

Investigation of fatigue severity (by the FACIT-Fatigue) and other disease-specific symptoms (by the MPN-SAF TSS) revealed a greater overall symptom burden in patients reporting higher fatigue. For example, 64% of patients reporting higher fatigue also reported concentration problems, compared to 17% of patients in the lower fatigue group. Although with different percentages, this pattern was broadly consistent across all symptoms investigated. Details are depicted in Figure 3. Additional correlation analyses between fatigue and other symptoms revealed that inactivity ($r = -0.63$; P < 0.001), concentration problems ($r = -0.60$; P < 0.001), and early satiety ($r = -0.55$; P < 0.001) were the three most strongly correlated symptoms with fatigue. A strong correlation ($r = -0.78$; P < 0.001) was also observed between the FACIT-Fatigue score and the TSS of the MPN-SAF questionnaire. Correlation between hemoglobin levels and FACIT-Fatigue score was weak being ($r = 0.215$).

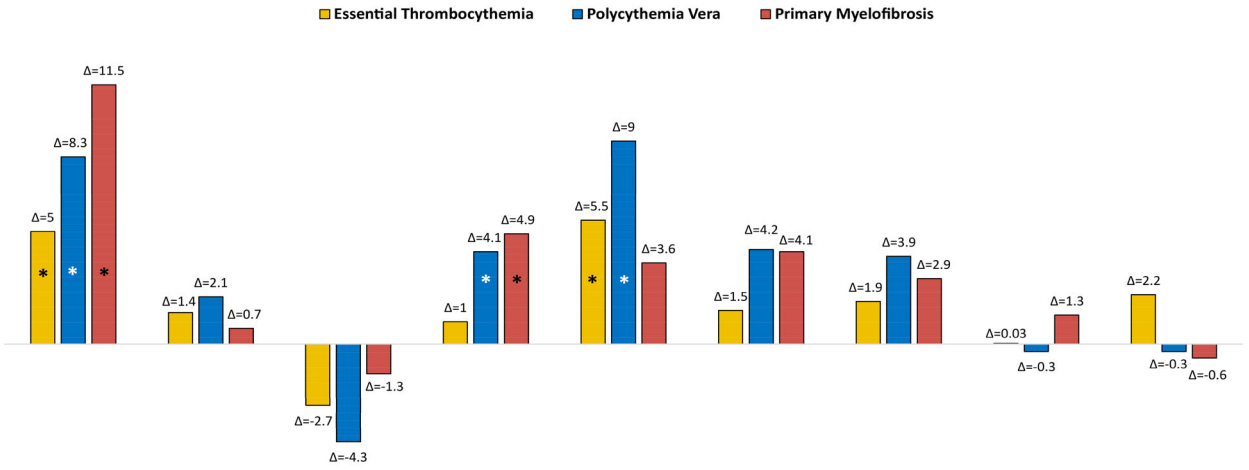
Physician-assessed symptom burden using the MPN-SAF TSS questionnaire and concordance with patient-reported scores

Analyses are based on 456 patients for whom both the patient- and physician-reported MPN-SAF TSS questionnaires



	Physical functioning		Role functioning		Emotional functioning		Cognitive functioning		Social functioning		Global quality of life	
Diagnosis	Mean (95% C.I.)	P	Mean (95% C.I.)	P	Mean (95% C.I.)	P	Mean (95% C.I.)	P	Mean (95% C.I.)	P	Mean (95% C.I.)	P
ET	2.9 (0.8;5.0)	0.007	8.9 (6.4;11.4)	<0.001	1 (-1.5;3.5)	0.433	3.4 (1.0;5.9)	0.006	1.5 (-0.7;3.7)	0.181	0.2 (-2.1;2.5)	0.865
PV	3.9 (1.2;6.5)	0.004	11 (7.9;14.2)	<0.001	2.5 (-0.2;5.1)	0.064	5.6 (3.1;8.2)	<0.001	3.5 (0.8;6.1)	0.010	1.2 (-1.4;3.7)	0.356
MF	10.5 (6.9;14.1)	<0.001	16.7 (12.2;21.1)	<0.001	1.7 (-1.8;5.3)	0.348	6.1 (2.7;9.5)	<0.001	5.7 (2.0;9.5)	0.003	6.1 (2.2;10.1)	0.003

FIGURE 1 **Adjusted mean differences in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) functional scales and global quality of life between patients with myeloproliferative neoplasm (MPN) and the general population, by MPN subtype.** Positive values indicate worse functioning or global quality of life in MPN patients compared to matched individuals from the general population. Estimates are adjusted for sex, age, and comorbidity. An asterisk (*) indicates a clinically meaningful difference (of small magnitude). ET, essential thrombocythemia; MF, myelofibrosis; PV, polycythemia vera.



	Fatigue		Nausea/vomiting		Pain		Dyspnea		Insomnia		Appetite loss		Constipation		Diarrhea		Financial difficulties	
Diagnosis	Mean (95% C.I.)	P	Mean (95% C.I.)	P	Mean (95% C.I.)	P	Mean (95% C.I.)	P	Mean (95% C.I.)	P	Mean (95% C.I.)	P	Mean (95% C.I.)	P	Mean (95% C.I.)	P	Mean (95% C.I.)	P
ET	5 (2.2;7.9)	<0.001	1.4 (0.4;2.5)	0.009	-2.7 (-0.1;-5.3)	0.042	1 (-1.5;3.6)	0.442	5.5 (2.1;8.9)	0.002	1.5 (-0.5;3.4)	0.132	1.9 (-1.1;4.8)	0.207	0.03 (-1.5;1.5)	0.969	2.2 (-0.5;4.9)	0.110
PV	8.3 (5.0;11.5)	<0.001	2.1 (0.8;3.5)	0.002	-4.3 (-7.0;-1.7)	0.002	4.1 (0.9;7.4)	0.013	9 (5.1;12.9)	<0.001	4.2 (1.7;6.8)	0.001	3.9 (0.7;7.1)	0.017	-0.3 (-1.8;1.1)	0.685	-0.3 (-2.5;1.9)	0.789
MF	11.5 (7.6;15.5)	<0.001	0.7 (-0.3;1.8)	0.191	-1.3 (-4.8;2.3)	0.473	4.9 (0.6;9.1)	0.024	3.6 (-0.9;8.1)	0.117	4.1 (0.8;7.4)	0.015	2.9 (-1.0;6.8)	0.145	1.3 (-1.3;4.0)	0.336	-0.6 (-2.7;1.6)	0.584

FIGURE 2 **Adjusted mean differences in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) symptoms between patients with myeloproliferative neoplasm (MPN) and the general population, by MPN subtype.** Positive values indicate greater symptom severity in MPN patients compared to matched individuals from the general population. Estimates are adjusted for sex, age, and comorbidity. An asterisk (*) indicates a clinically meaningful difference (of small magnitude). ET, essential thrombocythemia; MF, myelofibrosis; PV, polycythemia vera.

TABLE 2 Patient-reported symptom severity and prevalence at baseline by myeloproliferative neoplasm (MPN) subtype, assessed using the Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) questionnaire.

Patient reporting	Total, *N* = 572			Polycythemia vera, *n* = 207			Essential thrombocythemia, *n* = 228			Myelofibrosis, *n* = 137		
Symptoms	Mean	SD	Prevalence (%)[a]	Mean	SD	Prevalence (%)[a]	Mean	SD	Prevalence (%)[a]	Mean	SD	Prevalence (%)[a]
MPN-SAF TSS	13.2[b]	13.9	-	14.2	14.9	-	11.3	12.5	-	14.9	14	-
Worst fatigue (one-item BFI)	2.8[b]	2.5	77	2.7	2.6	77	2.5	2.3	75	3.3	2.6	81
Early satiety	1.4	2.2	41[b]	1.3	2.3	40	1.4	2.2	36	1.6	2.2	51
Abdominal discomfort	1.3	2.2	38	1.4	2.2	39	1.4	2.4	37	1.1	1.9	39
Inactivity	1.4[b]	2.2	41[b]	1.2	2.1	40	1.1	1.9	34	1.9	2.5	54
Concentration problems	1.4[b]	2.2	43[b]	1.4	2.2	42	1.1	2	35	1.8	2.4	55
Night sweats	1.4	2.4	36[b]	1.6	2.5	42	1.1	2.3	29	1.4	2.6	39
Itching	1.4[b]	2.4	39[b]	2.2	2.7	55	0.9	2	26	1.2	2.3	35
Bone pain	1.4	2.4	35	1.4	2.6	33	1.3	2.3	34	1.5	2.4	40
Fever	0.1	0.8	3	0.1	0.8	3	0	0.4	2	0.2	1.1	4
Weight loss	0.7	1.9	21	0.9	2	24	0.5	1.6	16	0.9	2.1	24

Note: Symptom severity was rated on a scale from 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be). The total MPN-SAF TSS score ranges from 0 to 100, with higher scores indicating greater symptom burden.
Abbreviations: BFI, Brief Fatigue Inventory; SD, standard deviation.

[a]Prevalence refers to the proportion of patients with a score > 0.

[b]Statistically significant difference between MPN subtypes ($P < 0.05$); prevalence differences were tested with χ^2 tests and severity differences with ANOVA F tests.

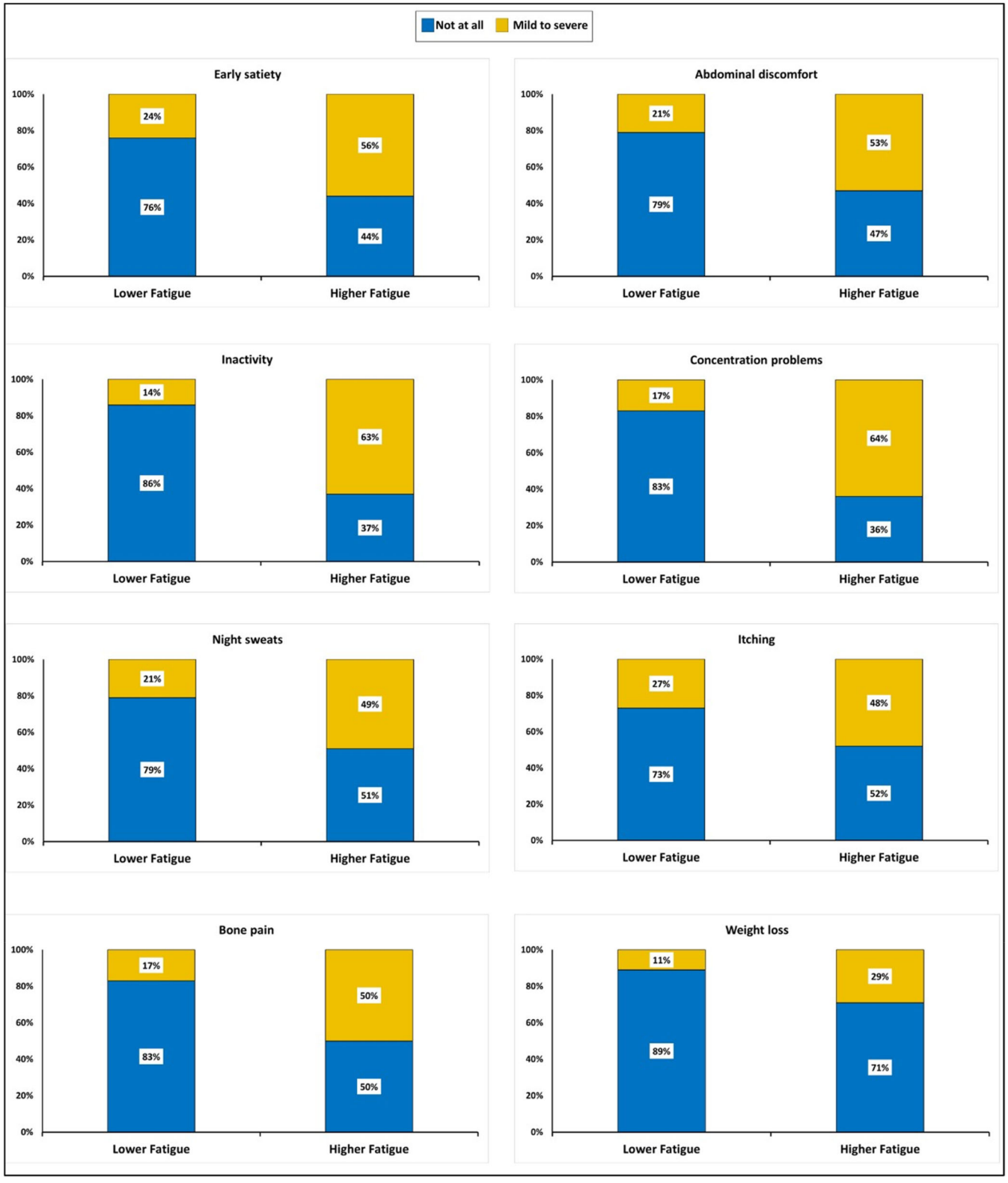


FIGURE 3 **Disease-specific symptoms by fatigue severity.** Lower fatigue and higher fatigue correspond, respectively, to scores above and below the median of the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue) questionnaire. In this questionnaire, the higher the score, the lower the level of fatigue. "Not at all" is defined as score 0, whereas "Mild to severe" is defined as score ≥ 1 on the Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS). Fatigue from the MPN-SAF TSS was not included, as the analysis was already stratified according to fatigue levels assessed by the FACIT-Fatigue scale. This analysis did not consider fever, given its low prevalence and consequently minimal impact to the severe category, rendering the graphical representation uninformative.

were available. Agreement between patients and physicians was modest, with Cohen's coefficients of concordance (*k*) ranging from 0.28 to 0.52 (Table S6), indicating only fair to moderate concordance across symptoms. Underreporting, defined as cases in which the physician did not record a symptom that the patient reported with any grade, was frequent with all symptoms underreported in more than 30% of the comparisons. With regard to early satiety, abdominal discomfort, and weight loss, underreporting was 56.5%, 55.7% and 55.3%, respectively (Figure 4). Analysis of physician underestimation of severe grade symptoms ranged from 52.2% for inactivity to 86.2% for abdominal discomfort (Figure 5). We note that the median time from the first encounter between the patient and the treating physician was 2.2 months (IQR: 0.0–5.1).

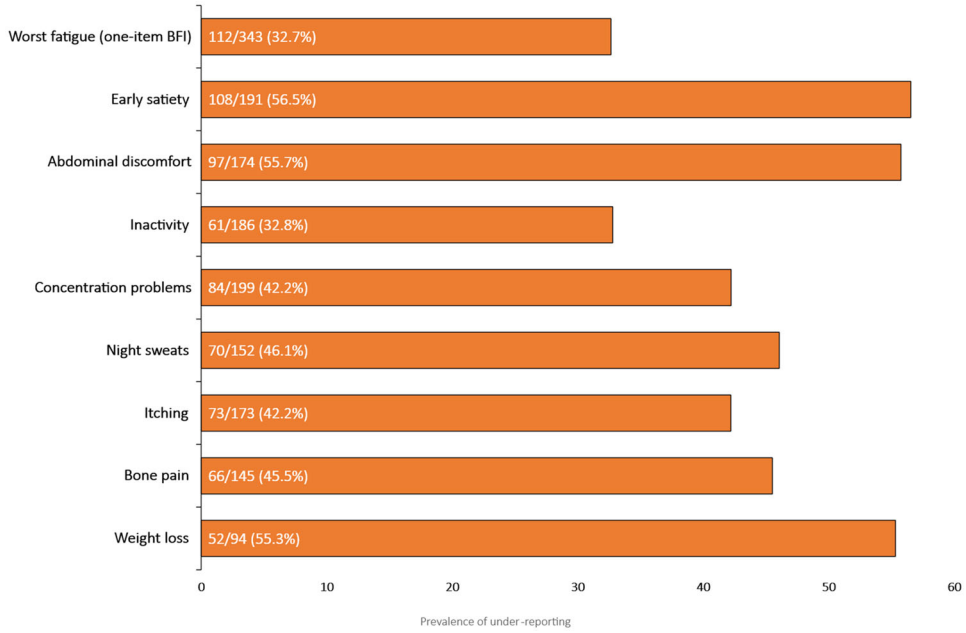


FIGURE 4 **Physician underreporting of symptoms (any grade).** Bars represent the proportion of patient-reported symptoms not recognized by physicians, calculated as [*c*/(*b* + *c*)] of data reported in Table S6. This analysis did not consider fever, given its low prevalence and consequently minimal impact. BFI, Brief Fatigue Inventory.

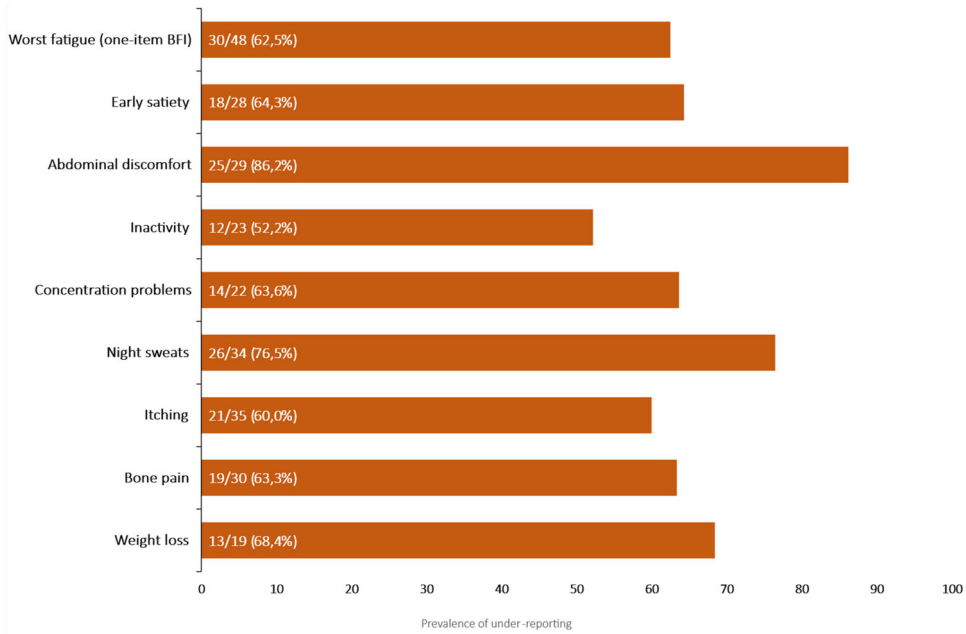


FIGURE 5 **Physician underestimation of severe symptoms.** Symptoms were classified as severe when patients reported a score ≥ 7. Underreporting was defined as cases in which the physician's score was ≤6 while the patient's score was ≥7 for the same symptom. BFI, Brief Fatigue Inventory.

DISCUSSION

This study reports one of the most extensive real-world datasets on HRQoL and symptom profiles of patients with MPNs by diagnostic group in Italy. HRQoL assessment and comparison with the general population revealed a substantial functional and symptom burden among patients with MPN. EORTC QLQ-C30 scores indicated a multisystemic impairment, with notable deficits in physical, cognitive, and particularly role functioning. Few studies have systematically compared HRQoL between MPN patients and general population controls, and heterogeneity in assessment tools and treatment status complicates comparisons. Anderson et al.[31] employed the MPN-SAF in a UK-based cohort of 106 MPN patients and 124 population controls, reporting significantly greater symptom burden across all items except for the "relations with others" domain. In contrast, Scherber et al.[32] applying the EORTC QLQ-C30, found only minimal differences in HRQoL between ET and PV patients compared to the general population. Similarly, a large Danish population-based study of 2228 MPN patients also used the EORTC QLQ-C30 and reported lower HRQoL scores in MPN patients compared to controls; however, absolute differences were modest, and the variation across diagnostic subgroups was limited.[33] These findings have led to the hypothesis that the attenuated symptom burden observed in treated cohorts compared to the general population may reflect therapeutic effects. However, this is challenged by a Swedish study of 179 newly diagnosed, treatment-naïve MPN patients assessed with the EORTC QLQ-C30, which reported HRQoL profiles comparable to previously treated cohorts.[34] In line with this observation, our cohort showed more pronounced HRQoL impairments despite being composed mainly of treated patients, with clinically meaningful reductions across several functional and symptom domains.

Our analysis revealed a surprisingly complex symptom profile in MPN patients. HRQoL impairment was most pronounced in MF and PV patients, affecting both the extent and severity of impairment. Nonetheless, ET deserves specific attention. Often considered a relatively indolent MPN and typically managed with a limited range of therapies such as hydroxyurea or, in select cases, interferon, ET is far from asymptomatic. Several studies have reported its substantial clinical impact, and both international and US-based MPN Landmark surveys have documented a significant impact on work productivity among ET patients.[35-37] In our cohort, symptoms were reported by 85% of ET patients, with 22% presenting with an MPN-SAF TSS score greater than 20. Functional impairment was particularly evident in domains such as role and cognitive functioning, even when compared to the general population, underscoring the concrete and multifaceted impact of the disease on daily life, extending well beyond the hematologic consequences of thrombocytosis alone.

Comparative analyses of international cohorts further contextualize our findings, highlighting possible differences in healthcare systems. In a recent Canadian study of 784 MPN patients assessed with the MPN-SAF TSS, MF patients exhibited higher average TSS scores than those in our cohort (18 vs. 14.9), with 54% presenting a TSS score greater than 20, compared to 24% in our study.[37] Fatigue emerged as a central symptom in both analyses, consistent with existing literature.[2,32,38] The MPN Landmark survey reported fatigue prevalence of 80% in MF, 73% in PV, and 71% in ET, with mean severity scores of 6.68, 6.53, and 6.44, respectively.[36] In our study, fatigue prevalence was similar being 81% in MF, 77% in PV, and 75% in ET.

In the Canadian cohort, fatigue severity scores were lower, with mean values of 4.4, 3.8, and 3.5 for MF, PV, and ET, respectively.[37] Compared to these findings, our analysis revealed consistently lower mean scores across all measures, both overall and within disease subgroups. We also observed that fatigue is associated with a broader and more complex symptom profile compared to patients without fatigue. These findings are consistent with a large analysis of 1788 MPN patients, in which MPN-SAF scores correlated with both the prevalence and severity of fatigue.[38] As suggested by Mesa et al.[2] it is also plausible that fatigue is exacerbated by self-perpetuating vicious cycles. In support of this, our cohort demonstrated a high frequency of inactivity across the MPN population. Contrary to our expectations and in contrast to the Mayo Clinic study, anemia did not show a strong association with fatigue levels in our cohort. This discrepancy may be due to the lower proportion of anemic patients in our cohort compared to the 48% reported in the Mayo Clinic survey.[38] However, by integrating fatigue perception, symptom burden, and HRQoL impact, the combined use of the three questionnaires offers a multidimensional characterization of fatigue in patients with MPNs.

Another key aspect of our study is the comparison between patient- and physician-reported symptom assessments. Consistent with MERGE[39] and MPN Landmark[40] studies, physicians frequently underestimated the overall symptom burden. In our study, important symptoms such as abdominal discomfort and early satiety were underreported by the treating hematologist in more than 50% of the comparisons. Moreover, our analysis focused specifically on severe symptoms indicated that these were also frequently underestimated by hematologists. For example, this was the case in 86.2% of the comparisons concerning abdominal discomfort. Notably, in our cohort, physicians already knew their patients having met them before in previous clinical visits. In our study, fatigue also emerged as the most frequently reported symptom by both patients and physicians. This aligns with a recent analysis by Manz et al.[41] reporting longitudinal data from 3979 patients enrolled in the German Study Group for MPN Bioregistry (GSG-MPN). Similar discrepancies were noted by Harrison et al.[42] in a study comparing perspectives from 133 physicians and 274 patients with PV. Several factors may underlie these divergences. As demonstrated by the results of the Landmark 2.0 study,[42] clinicians may focus primarily on objective disease parameters and prognostic indicators, inadvertently overlooking the subjective burden of symptoms reported by patients. Additionally, the structure of outpatient visits may not consistently allow for comprehensive symptom assessment. Some patients may also underreport symptoms they perceive as expected or not clinically relevant, further compounding underrecognition. These findings reinforce the need for systematic implementation of standardized PRO measures in routine clinical practice. Their incorporation may help improve symptom detection, mitigate the discordance between physician and patient assessments, and support a more comprehensive, patient-centered approach to disease management.[43]

Our study has limitations. For example, the cross-sectional analysis does not allow us to make causal inferences. Moreover, most patients were receiving treatment at the time of assessment, which may have altered symptom prevalence and severity, thereby limiting our ability to assess baseline burden. Nevertheless, this limitation is partly mitigated by the inclusion of patients within one year of diagnosis. This study also has key strengths. The multidimensional approach of this analysis, combining various validated PRO measures, provides a comprehensive overview of a wide range of health domains including symptoms, physical, cognitive, and social aspects. The direct comparison with general population norms highlights the distinctive burden of MPNs, especially regarding role functioning. Also, the inclusion of both patient- and physician-reported symptoms allows for the exploration of perception gaps, which may inform better patient-centered care.

In conclusion, this study points to the multifaceted burden of MPNs, which extends beyond hematologic parameters and thrombotic risk, affecting every dimension of patients' lives, from physical and

emotional spheres to social engagement and professional identity. While the profound impact of MF and PV on HRQoL is well established, our findings emphasize that ET, often underestimated, imposes a significant and underrecognized symptomatic and functional burden. With regard to patients with MF, future analyses could also further explore possible differences between pre-PMF and fibrotic PMF patients.

Our findings reinforce the value of integrating PROs into routine practice to facilitate treatment decisions by better aligning care with patients' lived experiences.

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AUTHOR CONTRIBUTIONS

Giovanni Caocci: Investigation; methodology; writing—review and editing; conceptualization; data curation; writing—original draft; supervision; resources; project administration; funding acquisition. **Alessandro Costa**: Investigation; methodology; writing—review and editing; conceptualization; data curation; writing—original draft. **Francesca Palandri**: Conceptualization; investigation; writing—original draft; methodology; writing—review and editing; data curation. **Paola Guglielmelli**: Investigation; methodology; writing—review and editing. **Andrea Patriarca**: Investigation; methodology; writing—review and editing. **Alessandra Iurlo**: Investigation; methodology; writing—review and editing. **Alessia Tieghi**: Investigation; methodology; writing—review and editing. **Elisabetta Abruzzese**: Investigation; methodology; writing—review and editing. **Thomas Baldi**: Data curation; formal analysis; software; writing—review and editing. **Elena Rossi**: Investigation; methodology; writing—review and editing. **Eloise Beggiato**: Investigation; methodology; writing—review and editing. **Monia Marchetti**: Investigation; methodology; writing—review and editing. **Carmen Fava**: Investigation; methodology; writing—review and editing. **Simona Tomassetti**: Investigation; methodology; writing—review and editing. **Elisa Rumi**: Investigation; methodology; writing—review and editing. **Claudio Fozza**: Investigation; methodology; writing—review and editing. **Mario Luppi**: Investigation; methodology; writing—review and editing. **Fabrizio Pane**: Investigation; writing—review and editing; methodology. **Sara Bigliardi**: Investigation; methodology; writing—review and editing. **Massimo Breccia**: Investigation; methodology; writing—review and editing. **Elena Maria Elli**: Investigation; methodology; writing—review and editing. **Francesca Tartaglia**: Project administration; data curation; writing—review and editing. **Olga Mulas**: Investigation; methodology; writing—review and editing. **Paola Fazi**: Investigation; methodology; writing—review and editing. **Marco Vignetti**: Investigation; methodology; writing—review and editing. **Alessandro Maria Vannucchi**: Investigation; methodology; writing—review and editing; conceptualization. **Fabio Efficace**: Investigation; methodology; writing—review and editing; conceptualization; funding acquisition; writing—original draft; project administration; data curation; supervision; resources.

CONFLICT OF INTEREST STATEMENT

Fabio Efficace: Consultancy or advisory role for AbbVie, Incyte, Novartis, and Jazz Pharmaceuticals; research grant (institution) from Daiichi Sankyo, all outside the submitted work.

Giovanni Caocci: Advisory board for Novartis.

Alessandra Iurlo: Speaker honoraria from AOP Health, BMS, GSK, Incyte, Novartis, and Pfizer.

Andrea Patriarca: Honoraria (SOBI, Sanofi, Pfizer, Incyte, Alexion, Takeda, Novartis, BMS, and Recordati); Other financial relationships (Alexion Hospitality at ASH 2022, SOBI Hospitality at ASH 2023); Sanofi Hospitality at EHA 2022, Sanofi Hospitality at EHA 2021.

Carmen Fava: Speaker honoraria Gentili, GSK, Incyte, Novartis, and Pfizer.

Francesca Palandri: Consultancy and honoraria from Novartis, GSK, BMS, Incyte, Sanofi, Takeda, SOBI, and AOP.

Massimo Breccia: Honoraria by Novartis, Incyte, Pfizer, BMS, AOP, AbbVie, GSK, Servier, and Otsuka.

Monia Marchetti: Honoraria by Novartis, MSD, BeiGene, Roche, Menarini, AOP, GSK, and Otsuka.

Mario Luppi: Advisory board and meeting with honoraria for AbbVie, Incyte, Novartis, Jazz Pharmaceuticals, Grifols, Sanofi, Istituto Gentili, Roche, AstraZeneca, and Otsuka.

Paola Guglielmelli: Speaker bureau (Novartis, GSK, Incyte, and AOP); advisory board (Novartis, GSK, Incyte, and Takeda).

Marco Vignetti: Reports honoraria from AbbVie and Novartis; all outside the submitted work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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