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ORIGINAL REPORT

Myeloproliferative Neoplasm (MPN) Symptom Assessment Form Total Symptom Score: Prospective International Assessment of an Abbreviated Symptom Burden Scoring System Among Patients With MPNs

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ABSTRACT

Purpose
Myeloproliferative neoplasm (MPN) symptoms are troublesome to patients, and alleviation of this burden represents a paramount treatment objective in the development of MPN-directed therapies. We aimed to assess the utility of an abbreviated symptom score for the most pertinent and representative MPN symptoms for subsequent serial use in assessing response to therapy.

Patients and Methods
The Myeloproliferative Neoplasm Symptom Assessment Form total symptom score (MPN-SAF TSS) was calculated as the mean score for 10 items from two previously validated scoring systems. Questions focus on fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers.

Results
MPN-SAF TSS was calculable for 1,408 of 1,433 patients with MPNs who had a mean score of 21.2 (standard deviation [SD], 16.3). MPN-SAF TSS results significantly differed among MPN disease subtypes ($P < .001$), with a mean of 18.7 (SD, 15.3), 21.8 (SD, 16.3), and 25.3 (SD, 17.2) for patients with essential thrombocythemia, polycythemia vera, and myelofibrosis, respectively. The MPN-SAF TSS strongly correlated with overall quality of life (QOL; $r = 0.59$; $P < .001$) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) functional scales (all $P < .001$ and absolute $r \geq 0.50$ except social functioning $r = 0.48$). No significant trends were present when comparing therapy subgroups. The MPN-SAF TSS had excellent internal consistency (Cronbach's $\alpha = .83$). Factor analysis identified a single underlying construct, indicating that the MPN-SAF TSS is an appropriate, unified scoring method.

Conclusion
The MPN-SAF TSS is a concise, valid, and accurate assessment of MPN symptom burden with demonstrated clinical utility in the largest prospective MPN symptom study to date. This new prospective scoring method may be used to assess MPN symptom burden in both clinical practice and trial settings.

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INTRODUCTION

Myeloproliferative neoplasms (MPNs) represent a unique, heterogeneous grouping of clonal or oligoclonal hemopathies characterized by the proliferation and accumulation of mature myeloid cells. Categorized by the WHO in 2008, MPN subgroups currently encompass essential thrombocythemia (ET), polycythemia vera (PV), and myelofibrosis (MF). Notably, MF may arise either as primary or antecedent to ET and PV. The clinical presentation of MPNs is dependent on the MPN subtype. Initial symptoms may include erythrocytosis, leukocytosis, thrombocytosis, and variable degrees of cytopenias. Over time, patients may advance to massive splenomegaly, extramedullary hematopoiesis, cachexia,

vascular complications, constitutional symptoms, and risk for transformation to acute myeloid leukemia. Mortality rates are characteristically dependent on the subtype of MPN, ranging from a normal life expectancy in ET to 5 to 7 years in MF.

Historically, treatment options have been limited and have been primarily focused on symptom palliation and prevention of end-organ dysfunction. The 2005 groundbreaking discovery of the *JAK2 V617F* mutation in multipotent MPN progenitor cells presented a new therapeutic venue for treatment. JAK2 inhibitors rapidly came under focus for clinical development. Several JAK2 inhibitors have since emerged that boast effectiveness in reducing spleen size and constitutional symptoms[1] while improving anemia,[2] exercise tolerance, and weight gain.[2] Ruxolitinib, the first JAK2 inhibitor to obtain approval by the US Food and Drug Administration, was released in November 2011. With the rapid expansion of JAK2-directed therapies, it became obvious that a formal symptom evaluation tool was necessary to provide an accurate assessment of disease burden while allowing nonrandomized comparisons between therapeutic agents.

Our group had previously conducted a survey among 1,179 patients with MPN, the results of which suggested that MPN symptoms significantly compromise social functioning, physical activity, independence with daily tasks, and global quality of life (QOL).[3] From this work, the Myelofibrosis Symptom Assessment Form (MF-SAF) was derived,[4] an instrument measuring disease impact among patients with MF. This form was later expanded into the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF),[5] a 17-item instrument monitoring the most debilitating symptoms among patients with MPNs. This instrument has since been validated in English, Italian, Swedish, German, French, Spanish, and Dutch. This survey was ultimately co-administered with the 10-item Brief Fatigue Inventory (BFI).[6]

Evaluation of the MPN-SAF in clinical practice suggested that international implementation would necessitate modification of the instrument to include an abbreviated version that focused on the most representative and clinically relevant MPN symptoms. The purpose of this study was to construct the MPN-SAF total symptom score (TSS) by applying the 10 items deemed most clinically important and characteristic of MPN symptoms. It is our aim that this revised tool be used to provide an expedient, accurate assessment of MPN symptom burden and guide subsequent therapy decisions.

PATIENTS AND METHODS

Initial MPN-SAF Survey Administration

By using the previously validated BFI and MPN-SAF, we sought to reduce survey length and improve ease of administration by creating an abbreviated instrument consisting of the most pertinent and representative MPN symptoms. As detailed in previous publications, translations of the MPN-SAF were created by using the patient-reported outcome translation method.[7] Using our existing database of 1,433 patients with MPNs, we analyzed patient responses and condensed the survey to include the 10 items that most closely correlated with symptom burden.

International collaborators prospectively administered the survey for self-completion to patients during an initial clinic visit. Patients were accrued prospectively from a variety of practice settings, including private practice, academic centers, and government-funded medical centers in Argentina, France, Germany, Italy, the Netherlands, Puerto Rico, Spain, Sweden, United Kingdom, Uruguay, and the United States from November 2009 to January 2011. Approval for this research was given by all institutional review boards at all participating locations before the patients provided informed consent and before the survey was implemented.

Patients were queried on symptom manifestations by using the BFI,[6] MPN-SAF,[4] and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30).[8] Physicians independently provided information on patient-specific disease features, demographics, treatments, complications, and perceptions of six disease-related symptoms. Specifically, physicians were queried on patient's severity of night sweats, fevers, fatigue, weight loss, bone pain, and pruritus on a scale of 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be). Language validation and survey creation are detailed in previous publications.[5] Participants completed all survey items in the native language of their respective country.

MPN-SAF TSS Construction

The TSS items chosen were the nine most clinically relevant symptoms from the 17-item MPN-SAF. MPN-SAF TSS items included "worst fatigue" from the BFI plus nine items from the MPN-SAF—concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fever—scored on a 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be) linear analog self-assessment scale (Data Supplement). QOL scores were defined as "clinically deficient" if scores were rated as at least 4 of 10 on a 0-to-10 scoring system. In addition, MPN-SAF TSS items were designated as "moderate" if symptoms were rated as $\geq$ 4 of 10 or $\leq$ 6 of 10 and as "severe" if symptoms were rated as $\geq$ 7 of 10. For patients who completed at least six of these 10 items on the BFI and MPN-SAF, the MPN TSS was computed as the average of the observed items multiplied by 10 to achieve a 0-to-100 scale. The MPN-SAF TSS thus had a possible range of 0 to 100.

Data Analysis

MPN-SAF TSS results were compared between MPN disease groups by using analysis of variance (ANOVA) F-tests to compare means and χ^2 tests to compare incidences (score $>$ 0). For assessing known groups validity, the MPN-SAF TSS was compared between known groups (MPN disease type, clinically deficient patient-reported QOL, and number of common MPN symptoms endorsed by the physician [to be considered "endorsed," the physician was required to rate the symptom $\geq$ 2 of 6]) by using ANOVA F-tests. For assessing convergent validity, Pearson correlations were computed between the MPN-SAF TSS and alternate measures of disease burden (EORTC QLQ-C30 functional and symptom scales, patient-reported overall QOL, and physicians' symptom ratings), and absolute correlations more than 0.5 were considered as at least a moderate level of correlation. Internal consistency was evaluated by calculating Cronbach's α, which was considered as indicating good internal consistency with a value more than .7. Construct validity was evaluated by using principal axis factoring analysis. Eigenvalues more than 1 were considered as meaningful factors. *P* values less than .05 were considered statistically significant throughout. Statistical software used for these analyses included SAS, version 9 (SAS Institute, Cary, NC).

RESULTS

Patient Demographic and Disease Characteristics

In all, 1,433 patients with MPN were prospectively enrolled (Argentina, 22; France, 482; Germany, 59; Italy, 186; the Netherlands, 236; United Kingdom, 57; United States [including Puerto Rico], 112; Spain, 157; Sweden, 114; and Uruguay, 8). Data included 594 patients with ET, 538 with PV, and 293 with MF (61% primary MF; 23% post-ET MF; 15% post-PV MF; eight missing MPN data).

Patients were of age (mean, 62 years; range, 20 to 94 years) and sex (54% female) common to the disease (Table 1). Laboratory abnormalities of anemia, thrombocytopenia, and leukopenia were most prominent in patients with MF. Patients were an average of 6.7 years

Table 1. Demographic, Laboratory, and Historical Characteristics of Patients by MPN Type

Characteristic	No. of Patients	ET (n = 594)			PV (n = 538)			MF (n = 293)		
		%	Mean	SD	%	Mean	SD	%	Mean	SD
No. of patients with known MPN type	1,425									
Age, years			60.7	14.5		62.8	13.1		63.5	11.5
Range			20-94			22-91			26-89	
Female sex		64			46			47		
Language										
Italian	186	47			37			16		
English	157	29			26			45		
Swedish	114	46			46			7		
French	477	48			37			16		
Spanish	196	48			30			22		
German	59	24			39			37		
Dutch	236	31			50			19		
Laboratory abnormalities										
Anemia		7.4			3.4			49		
Leukopenia		3.9			3.9			9.8		
Thrombocytopenia		3.1			7.7			26		
Circulating blasts		0.6			1.1			20		
Any laboratory abnormality		13			12			59		
Prior thrombohemorrhagic events or spleen-related symptoms										
Average spleen size, cm (below costal margin)			0.8	3.0		2.5	5.1		7.4	7.2
Prior splenectomy		1.1			0.7			3.9		
Thrombosis		21			30			14		
Hemorrhage		3.5			7.7			7.1		
Requiring red cell transfusions		1.4			1.3			23		

Abbreviations: ET, essential thrombocythemia; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PV, polycythemia vera; SD, standard deviation.

(range, 0 to 43 years) out from diagnosis of MPN at survey completion. Sixty-eight percent of patients were currently receiving cytoreductive therapy, most commonly hydroxyurea.

MPN-SAF TSS Burden of MPN Symptoms

The MPN TSS was calculable for 1,408 patients (98%) with 1,214 completing all 10 items. Consistent with prior studies, the majority of patients (> 50%) were symptomatic (score > 0) in each MPN-SAF TSS item except for items of bone pain (49%), weight loss (31%), and fever (18%; Table 2). Fatigue carried the highest symptom intensity (mean, 4.4; standard deviation [SD], 2.8), followed by problems with concentration (mean, 2.5; SD, 2.8) and early satiety (mean, 2.5; SD, 2.7). More than one third of patients (35%) endorsed having a clinically deficient QOL (≥ four of 10), with patients who had MF

Table 2. Patient's Assessment of Symptom Severity and Symptom Incidence by Disease Type (n = 1,425 with known MPN type)

Symptom	ET (n = 594)			PV (n = 538)			MF (n = 293)			Total (n = 1,425)		
	Mean	SD	Incidence (%)*	Mean	SD	Incidence (%)*	Mean	SD	Incidence (%)*	Mean	SD	Incidence (%)*
Worst fatigue (one-item BFI)	4.1	2.8	87	4.4	2.9	88	5.0	2.6	96	4.4†	2.8	89†
Early satiety	2.2	2.7	59	2.5	2.7	64	3.2	2.8	77	2.5†	2.7	64†
Abdominal discomfort	1.7	2.3	50	1.6	2.3	51	2.5	2.7	66	1.8†	2.4	54†
Inactivity	1.9	2.5	56	2.4	2.7	61	3.1	2.8	74	2.4†	2.7	62†
Concentration problems	2.3	2.7	59	2.7	2.9	65	2.6	2.8	69	2.5†	2.8	63†
Night sweats	2.0	2.8	50	2.1	2.8	52	2.6	2.9	62	2.1†	2.8	53†
Itching	1.7	2.6	46	2.8	3.2	62	2.0	2.9	50	2.2†	2.9	53†
Bone pain	1.7	2.7	46	2.0	2.7	50	2.2	2.9	52	1.9†	2.8	49
Fever	0.3	1.1	17	0.4	1.1	18	0.5	1.3	22	0.4	1.2	18
Weight loss	0.8	2.0	24	1.0	2.1	31	1.7	2.7	42	1.1†	2.2	31†
MPN-SAF TSS	18.7	15.3	—	21.8	16.3	—	25.3	17.2	—	21.2†	16.3	—

NOTE. Symptom severity was rated on a 0 (absent/as good as it can be) to 10 (worst-imaginable/as bad as it can be) scale. Myeloproliferative Neoplasm Symptom Assessment Form total symptom score (MPN-SAF TSS) has a possible range of 0 to 100 with 100 representing the highest level of symptom severity.

Abbreviations: BFI, Brief Fatigue Inventory; ET, essential thrombocythemia; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PV, polycythemia vera; SD, standard deviation.

*Score > 0.

†Comparisons of prevalence were evaluated by using χ^2 tests. Comparisons of severity were evaluated by using analysis of variance F tests. $P < .05$ across groups.

endorsing the greatest frequency of clinically deficient QOL (42%) compared with patients who had ET or PV (30% and 38%, respectively). More than half the patients rated their worst fatigue in the previous 24 hours as moderate to severe (≥ four of 10; 60%). Overall mean MPN-SAF TSS was 21.2 (SD, 16.3). Range of MPN-SAF TSSs was 0 to 85 (Fig 1).

Known Groups Validity

MPN-SAF TSS significantly differed among MPN disease subtypes ($P < .001$) with means of 18.7 (SD, 15.3), 21.8 (SD, 16.3), and 25.3 (SD, 17.2) for patients with ET, PV, and MF, respectively. Statistically significant differences in MPN-SAF TSS results were also observed between patients with clinically deficient (≥ four of 10; n = 480) versus nonclinically deficient QOL scores (< four of 10; n = 894; mean 33.2 *v* 14.7; $P < .001$). When compared with physicians' perceptions of patient symptoms, MPN-SAF TSS was significantly higher in patients whose physicians rated two or more of six common MPN-related symptoms as present (28.1; n = 400) versus fewer than two symptoms (15.5; n = 726; $P < .001$). No significant trends were observed when comparing MPN-SAF TSSs between current medical therapy groups within each disease type.

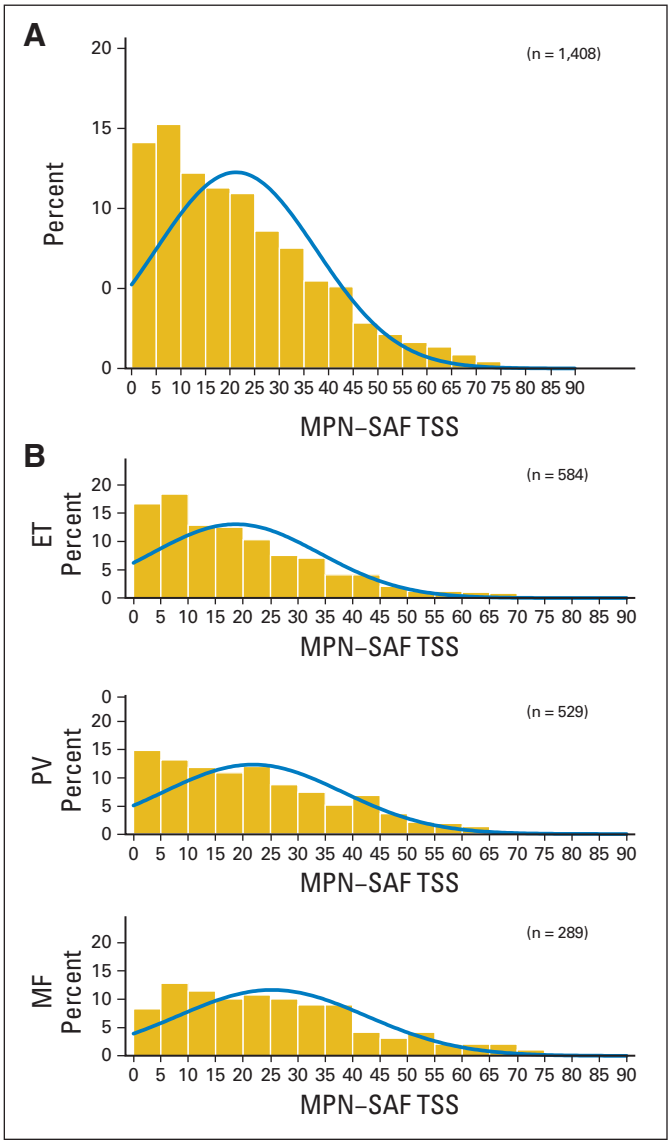

Fig 1. Myeloproliferative Neoplasm Symptom Assessment Form total symptom scores (MPN-SAF TSS) represented by a histogram and overlaid normal distribution (mean and standard deviation based on sample estimates). (A) Total symptom burden for all MPN-SAF TSS respondents completing at least five of 10 survey items (n = 1,408). (B) Total symptom burden by MPN type. ET, essential thrombocythemia; MF, myelofibrosis; PV, polycythemia vera.

Convergent Validity

The MPN-SAF TSS strongly correlated with patient-reported overall QOL ($r = 0.59$; $P < .001$). Strong correlations existed between the MPN-SAF TSS and EORTC QLQ-C30 functional scales (all $P < .001$ and absolute $r \geq 0.50$ except social functioning [$r = 0.48$]; Table 3). In addition, strong correlations were observed between the MPN-SAF TSS and EORTC QLQ-C30 fatigue and pain symptom scales ($r > 0.5$; $P < .001$).

Internal Consistency and Construct Validity

The MPN-SAF TSS had excellent internal consistency (Cronbach's $\alpha = .83$). Factor analysis identified a single underlying construct among the 10 MPN-SAF TSS items (only a single eigenvalue being > 1). Factor loadings ranged from 0.43 for fever and weight loss to 0.71 for inactivity. The single factor suggests that the arithmetic mean of the 10 items is an appropriate global MPN-SAF TSS.

Table 3. Pearson Correlations Between Selected MPN-SAF TSS Items and Alternative Measures of MPN Disease Burden (n = 1,408)

Item	Measurement Instrument	Associated Measure	Pearson Correlation*
Worst fatigue (1-item BFI)	QLQ-C30 Symptom Scale	Fatigue	0.66
	Overall QOL	Overall QOL	0.53
	Physicians' perceptions	Fatigue	0.51
Inactivity	QLQ-C30 Functional Scale	Physical	0.58
		Role	0.60
		Social	0.52
	QLQ-C30 Symptom Scale	Fatigue	0.59
Concentration	QLQ-C30 Functional Scale	Cognitive	0.63
	QLQ-C30 Symptom Scale	Fatigue	0.52
	Overall QOL	Overall QOL	0.53
Itching	Physicians' perceptions	Itching	0.54
Bone pain	QLQ-C30 Symptom Scale	Pain	0.53
Weight loss	Physicians' perceptions	Weight loss	0.54
MPN-SAF TSS†	QLQ-C30 Functional Scale	Physical	0.57
		Role	0.51
		Emotional	0.51
		Global health/QOL	0.51
	QLQ-C30 Symptom Scale	Fatigue	0.65
		Pain	0.56
	Physicians' perceptions	Average physician's perception	0.51
	Overall QOL	Overall QOL	0.59

Abbreviations: BFI, Brief Fatigue Inventory; MPN, myeloproliferative neoplasm; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form total symptom score; QLQ-C30, [European Organisation for Research and Treatment of Cancer] Quality of Life Questionnaire C30; QOL, quality of life.

*For all items, $P < .001$. Absolute value of Pearson correlation is reported.

†MPN-SAF TSS is the average score of worst fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fever.

DISCUSSION

The MPN-SAF TSS is a valid and concise assessment of symptom burden among patients with MPN in a variety of clinical settings. The MPN-SAF TSS demonstrated excellent psychometric properties, including convergent validity, construct validity, differences between known groups, and internal consistency. Being an abbreviated version of the MPN-SAF,[5] the TSS captures the breadth and intricacies of the overall symptom burden while enhancing the research utility of the original survey. The MPN-SAF TSS also demonstrated extensive global utility in assessing symptom burden in a broad range of private and public medical care settings, including recent use in the COMFORT I study [Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment Comparing Ruxolitinib to Placebo].[9] This study incorporated a diverse cohort of patients with ET, PV, and MF, representative of all stages of severity, including a small cohort of patients with PV and ET who had obvious disease progression.

The MPN-SAF TSS also represents the largest evaluation of symptoms among an international, multilinguistic cohort of MPN patients to date. This shortened scoring system will allow for serial assessments capable of depicting a chronologic impression of symptom burden. In addition, the clinical utility of the MPN-SAF may be expanded when it is supplemented with physicians' perceptions of symptoms and other methods of symptom assessment such as the EORTC QLQ-C30.[8]

We envision the MPN-SAF TSS as a useful tool in the clinical practice setting when directing symptom therapy and monitoring disease evolution. Although longitudinal evaluation of the MPN-SAF TSS has not yet been validated, we believe serial assessments of symptom burden may provide a sensitive clinical indicator of disease progression. Thus far, our results suggest that the application of conventional medical therapy (including hydroxyurea) does not correlate with alterations in symptom burden. The promising disease-modifying effects of JAK2 inhibitors provide a unique opportunity to use the MPN-SAF TSS in quantifying symptom reduction. Anticipated studies include application of the MPN-SAF TSS in evaluating the symptoms of bone marrow transplantation recipients, JAK2 inhibitor recipients, and patients receiving other novel experimental therapies.

In conclusion, the MPN-SAF TSS appears to be an efficient, sensitive, and reliable tool for assessing symptom burden in MPN subpopulations. This instrument carries the potential to evaluate response to treatment and track disease progression. With utility extending to both trial and clinical practice settings, we believe the MPN-SAF TSS will prove to be an indispensable resource as we enter this new era of gene-targeted therapies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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