Original Article

The Role of Sexuality Symptoms in Myeloproliferative Neoplasm Symptom Burden and Quality of Life: An Analysis by the MPN QOL International Study Group

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BACKGROUND: Patients with myeloproliferative neoplasms (MPNs) including polycythemia vera, essential thrombocythemia, and myelofibrosis, are faced with oppressive symptom profiles that compromise daily functioning and quality of life. Among these symptoms, sexuality-related symptoms have emerged as particularly prominent and largely unaddressed. In the current study, the authors evaluated how sexuality symptoms from MPN relate to other patient characteristics, disease features, treatments, and symptoms. **METHODS:** A total of 1971 patients with MPN (827 with essential thrombocythemia, 682 with polycythemia vera, 456 with myelofibrosis, and 6 classified as other) were prospectively evaluated and patient responses to the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ C30) were collected, along with information regarding individual disease characteristics and laboratory data. Sexuality scores were compared with an age-matched, healthy control population. **RESULTS:** Overall, patients with MPN were found to have greater sexual dysfunction compared with the healthy population (MPN-SAF score of 3.6 vs 2.0; $P<.001$), with 64% of patients with MPN describing some degree of sexual dysfunction and 43% experiencing severe symptoms. The presence of sexual symptoms correlated closely with all domains of patient functionality (physical, social, cognitive, emotional, and role functioning) and were associated with a reduced quality of life. Sexual problems also were found to be associated with other MPN symptoms, particularly depression and nocturnal and microvascular-related symptoms. Sexual dysfunction was more severe in patients aged >65 years and in those with cytopenias and transfusion requirements, and those receiving certain therapies such as immunomodulators or steroids. **Conclusions:** The results of the current study identify the topic of sexuality as a prominent issue for the MPN population, and this area would appear to benefit from additional investigation and management. ***Cancer*** **2016;122:1888-96.** *© 2016 American Cancer Society.*

KEYWORDS: hematological neoplasms, myeloproliferative neoplasms, quality of life, sexuality, symptoms.

INTRODUCTION

Myeloproliferative neoplasms (MPNs) including essential thrombocythemia (ET), polycythemia vera (PV), and myelofibrosis (MF), are recognized for their severe symptom burden profiles. Constitutive catabolic and proliferative dysregulation results in a variety of secondary pathological effects including profound cytopenias, fatigue, thrombosis, cachexia,

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splenomegaly, and resistant constitutional symptoms. In aggregate, these disease complications demonstrate direct correlations to premature mortality and impaired quality of life (QOL).[1-3]

A revealing, self-reported survey of patients with MPN published in 2007 revealed that MPN symptoms are not only prevalent, but also have a significant impact on QOL.[4] Patients demonstrating minimal "objective" manifestations of their disease still experience mild to severe fatigue and have a compromised ability to perform physical activities or be independent in daily tasks. Validation of the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) in 2011 revealed that of the 20 most prominent MPN symptoms, those regarding sexuality ranked as highly prevalent (57.9%) and contributed to compromised QOL (84.2%).

Concerns related to sexuality are indigenous to a variety of malignancies but are an important factor in patients with MPN not only for their prevalence and severity, but for the prolonged disease durations inherent to many of the MPN subtypes.[5-8] The origin of issues with "intimacy" are complex and may be influenced by biological features (elevated cytokine levels, hormonal levels), the impact of MPN symptoms (pruritus, fatigue), psychological issues (body image, mood), and treatment-related toxicity. To the best of our knowledge, within the MPN field, sexuality-related symptoms have received little attention, which is most likely a reflection of our restricted understanding of symptom origins and the paucity of therapeutic options. In the current study, we sought to further analyze the associations between MPN-related sexuality concerns and their corresponding MPN disease features, individual MPN symptom prevalence and severity, language, and overall QOL.

MATERIALS AND METHODS

Survey Development and Collection

Data were collected among an international cohort of patients with MPNs including PV, ET, and MF. Patients were recruited in the format that was previously published in the validation of the MPN-SAF.[9] In addition to the MPN-SAF, subjects also completed the Brief Fatigue Inventory and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) instruments. Data were collected in English, Dutch, French, Italian, Chinese, German, Swedish and Spanish. Questions related to MPN therapies included responses from patients with current or prior use. The control population was comprised of 401 healthy Swedish patients aged >55 years without the diagnosis of an MPN who anonymously completed the MPN-SAF. Control patients were recruited from among the friends and family of hematology patients, investigators, and family members or friends of investigators.

Symptom Evaluation

Surveyed symptoms on the MPN-SAF included the patient's perceptions of common MPN-related symptoms and overall QOL on a scale of 0 (absent) to 10 (worst imaginable). Assessed symptoms on the MPN-SAF included items related to sad mood, QOL, inactivity, concentration problems, dizziness, insomnia, night sweats, worst fatigue, early satiety, bone pain, numbness, cough, abdominal discomfort, itching, headache, weight loss, abdominal pain, and fever. Specifically, the MPN-SAF sexuality item asked about "problems with sexual desire or function." The total symptom score was computed based on 27 symptom items using the published scoring algorithm on a scale of 0 (all reported symptoms were absent) to 100 (all reported symptoms were the worst imaginable).

Prognostic Scoring

Prognostic scoring for PV survival was calculated using the Leukemia 2013 prognostic scoring model.[1] This scoring system includes the variables of age $\geq$67 years (5 points), age 57 to 66 years (2 points), white blood cell count $\geq 15 \times 10^9$/L (1 point), and prior thrombosis (1 point) to risk-stratify patients into high-risk ($\geq$3 points), intermediate-risk (1-2 points), and low-risk (0 points) groups. Prognostic scoring for ET was calculated using the International Prognostic Score for Essential Thrombocythemia.[2] This scoring system includes the variables of age $\geq$60 years (2 points), leukocyte count $\geq 11 \times 10^9$/L (1 point), and history of thrombosis (1 point) to risk-stratify patients into high-risk (3-4 points), intermediate-risk (1-2 points), or low-risk (0 points) groups. Prognostic scoring for MF survival was calculated using the Dynamic International Prognostic Scoring System.[3]

Statistical Analysis

Pairwise associations between the MPN-SAF sexuality item and continuous and categorical covariates were investigated using Pearson correlations and analysis of variance/Student *t* tests, respectively. Multivariate regression models were used to investigate the impact of groups of covariates on the sexuality item, with the final multivariate model selected using forward regression. Statistical

TABLE 1. Demographics of Patients With MPN

MPN Subtype	No. of Patients	%	MPN-SAF Sexuality Score	*P*
MPN subtype				<.0001
ET	827	42.0%	3.12	
PV	682	34.7%	3.61	
MF	456	23.2%	4.38	
MF subtype				.88
PMF	316	69.3%	4.41	
ET-MF	80	17.5%	4.19	
PV-MF	60	13.2%	4.48	
Age, y				.08
<60	947	48.0%	3.42	
≥60	1024	52.0%	3.71	
Sex				.13
Female	1060	53.2%	3.47	
Male	911	46.8%	3.72	
Anemia (hemoglobin <10 g/dL)				<.0001
Absent	1828	91.3%	3.38	
Present	143	8.8%	4.86	
Leukopenia (WBC <4.0 g/dL)				.035
Absent	1812	90.3%	3.44	
Present	159	9.7%	4.10	
Thrombocytopenia (<150 × 10^9/L)				.0004
Absent	1789	88.8%	3.39	
Present	182	11.2%	4.42	
Laboratory abnormality				<.0001
Absent	1618	78.4%	3.27	
Present	353	21.6%	4.34	
Prior thrombosis				.60
Absent	1572	79.3%	3.54	
Present	399	21.6%	3.65	
Prior hemorrhage				.39
Absent	1874	95.1%	3.57	
Present	97	4.9%	3.90	
RBC transfusion requirement				<.0001
Absent	1860	94.3%	3.49	
Present	111	5.7%	5.03	
Language				<.0001
Chinese	574	29.1%	4.60	
Dutch	236	12.0%	4.17	
English	150	7.6%	3.06	
French	444	22.5%	2.60	
German	103	5.2%	3.40	
Italian	170	8.6%	3.19	
Spanish	187	9.5%	3.51	
Swedish	107	5.4%	2.43	
MF (DIPSS)[a]				.098
Low risk	41	18.6%	3.05	
Intermediate-1/2 risk	173	78.6%	4.10	
High risk	6	2.7%		
PV (2013 Leukemia)[a]				.076
Low risk	114	21.9%	3.04	
Intermediate risk	160	30.8%	3.88	
High risk	246	47.3%	3.25	
ET (IPSET)[a]				.17
Low risk	264	37.1%	2.92	
Intermediate risk	323	45.4%	3.13	
High risk	125	17.6%	3.65	
MPN-SAF sexuality symptom score				
0	712	36.1%		
1	185	9.4%		
2	115	5.8%		
3	120	6.1%		
4	85	4.3%		
5	144	7.3%		
6	68	3.5%		
7	83	4.2%		
8	126	6.4%		
9	119	6.0%		
10	214	10.9%		

Abbreviations: DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; IPSET, International Prognostic Score for Essential Thrombocythemia; MF, myelofibrosis; MPN, myeloproliferative neoplasm; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; PMF, primary myelofibrosis; PV, polycythemia vera; RBC, red blood cell; WBC, white blood cell.

[a] Risk scoring was performed on patients as described in the "Methods" section.

significance was set at $P<.05$. Control data from the group of Swedish controls for the sexuality item score were compared with the MPN data set using the Student *t* test and analysis of variance. SAS statistical software (version 9.3; SAS Institute Inc, Cary, NC) was used for statistical analysis.

The current study was completed with approval from the Institutional Review Board of the Mayo Clinic and informed consent was provided by each participant.

RESULTS

Patient Demographics

A total of 1971 patients with MPN (827 with ET, 682 with PV, 456 with MF, and 6 with unknown status) completed the sexuality item (Table 1) and of these, 1259 patients (64%) described MPN-SAF sexuality scores >0. Participants were of typical age (median, 59.2 years) and sex (53.8% female), with >50% of patients from the Chinese (29.1%) or French (22.5%) language groups. Laboratory abnormalities including anemia (8.8%), leukopenia (9.7%), and thrombocytopenia (11.2%) were infrequent and the majority of patients did not have a history of requiring red blood cell transfusions (5.7%), prior thrombosis (21.6%), or hemorrhage (5.0%). The most common severity score provided by patients answering the MPN sexuality question was 0 of 10 (no symptoms; prevalence of 36.1%), followed by 10 of 10 (highly symptomatic; prevalence of 10.9%). The overall mean symptom score for sexuality was 3.6, which is a moderately high symptom burden (median, 2.0; standard deviation, 3.7 [range, 0-10]). It is interesting to note that 839 of the 1971 patients had severe sexuality-related symptoms (MPN-SAF item score ≥4). In contrast, the Swedish

TABLE 2. Final Multivariate Analysis of Sexuality Problems With Symptoms and Clinical Variables

	P
Age	<.0001
Chinese language	<.0001
Role functioning	<.0001
Numbness/tingling	<.0009
Insomnia	<.0001
Night sweats	<.0001
Overall quality of life	<.0001

control population (401 individuals with a mean age of 66.9 years) demonstrated a statistically significantly lower mean sexuality symptom score (2.0) when compared with the MPN cohort, independent of age distribution ($P<.001$).

Sexuality Correlations With Clinical Features

On univariate analysis, high scores on the MPN-SAF with regard to sexuality symptoms correlated with many clinical features (Table 1). Among the 3 disorders, patients with MF had the most problematic MPN-SAF sexuality scores (4.38) followed by patients with PV (3.61) and ET (3.12) ($P<.0001$). Sexuality symptom scores were more problematic in patients with laboratory abnormalities (4.34 vs 3.27; $P<.0001$) including anemia (4.86 vs 3.38; $P<.0001$), leukopenia (4.10 vs 3.44; $P = .035$), and thrombocytopenia (4.42 vs 3.39; $P = .0004$). Patients requiring red blood cell transfusions also had more problematic sexuality scores (5.03 vs 3.49; $P<.0001$). No differences were noted between MF subtype, age, sex, or MPN risk scores (Table 1). On a final multivariate analysis based on forward regression, age >60 years was the only variable listed above that was found to be associated with severe sexuality symptoms (Table 2).

Correlations With Language

The sexuality symptoms were evaluated based on language group. Of the 8 languages assessed (Chinese, Dutch, English, French, German, Italian, Spanish, and Swedish), the most problematic mean sexuality scores were noted among Chinese patients (4.6), followed by Dutch individuals (4.17) (Table 1). On multivariate analysis, presence of the Chinese language was found to be most closely associated with sexuality-related symptoms ($P<.0001$) (Table 2). When comparing MPN-SAF sexuality scores of Swedish patients with MPN (107 patients) with the Swedish controls, the scores did not statistically differ (2.4 vs 2.0; $P = .179$).

TABLE 3. Univariate Correlations Between Sexuality Problems and EORTC QLQ-C30 Subscale and Symptom Scale Items

	Pearson Correlation	*P*
EORTC QLQ-C30 subscale items		
Physical functioning	−0.31	<.001
Social functioning	−0.30	<.001
Role functioning	−0.29	<.001
Cognitive functioning	−0.27	<.001
Emotional functioning	−0.26	<.001
Global health status/QOL	−0.26	<.001
EORTC QLQ-C30 symptom scale items		
Fatigue	0.27	<.01
Insomnia	0.22	<.01
Dyspnea	0.21	<.01
Financial problems	0.19	<.01
Appetite loss	0.19	<.01
Pain	0.19	<.01
Constipation	0.13	<.01
Nausea/vomiting	0.14	<.01
Diarrhea	0.07	.002

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; QOL, quality of life.

Correlations With Functioning Scales and Other Symptoms

The sexuality item correlated closely with patient functionality and the presence of other symptoms (Table 3). On univariate analysis, patients who described sexuality symptoms also had impairments in physical functioning, social functioning, role functioning, cognitive functioning, emotional functioning, and overall global health status (all $P<.001$) (Table 3). Patients with problematic sexuality scores also were found to have an increased incidence of financial problems ($P<.01$). In comparing the sexuality symptom with other MPN symptoms on the MPN-SAF, univariate analysis demonstrated that all symptoms correlated significantly ($P<.001$) (Table 4). Items with the closest correlations included the MPN-SAF total symptom score (Pearson correlation, 0.39), sad mood (Pearson correlation, 0.38), inactivity (Pearson correlation, 0.34), concentration problems (Pearson correlation, 0.33), dizziness (Pearson correlation, 0.32), and insomnia (Pearson correlation, 0.31). Sexuality problems were least likely to correlate with fevers (Pearson correlation, 0.16) and abdominal pain (Pearson correlation, 0.18). On multivariate analysis, problematic sexuality scores correlated closely with impaired role functioning, numbness/tingling, insomnia, and night sweats (all $P<.0009$) (Table 2).

Correlations With QOL

The MPN-SAF sexuality item also was assessed for its correlations with QOL. Univariate correlations between

sexuality concerns and the MPN-SAF QOL score demonstrated strong associations between problematic sexuality scores and impaired QOL (Pearson correlation, 0.36; $P<.0001$) (Table 4). In addition, the EORTC QLQ-C30 QOL subscale item demonstrated correlations with the problematic sexuality scores (Pearson correlation, −0.26; $P<.001$) (Table 3). The final multivariate analysis confirmed that sexual symptoms were found to correlate with impaired QOL ($P<.0001$) (Table 2).

TABLE 4. Univariate and Multivariate Correlations Between Sexuality Problems and MPN-SAF Symptom Items

	Univariate Analysis		Multivariate Analysis
Variable	Pearson Correlation	*P*	*P*
TSS 10-item	0.39	<.001	-
Sad mood	0.38	<.001	.0007
Overall QOL	0.36	<.001	<.0001
Inactivity	0.34	<.001	.04
Concentration	0.33	<.001	.06
Dizziness	0.32	<.001	.003
Insomnia	0.31	<.001	.006
Night sweats	0.28	<.001	.001
Worst fatigue	0.25	<.001	.33
Early satiety	0.23	<.001	.42
Bone pain	0.23	<.001	.88
Numbness	0.24	<.001	.20
Cough	0.22	<.001	.035
Abdominal discomfort	0.22	<.001	.32
Itching	0.22	<.001	.73
Headache	0.21	<.001	.47
Weight loss	0.19	<.001	.09
Abdominal pain	0.18	<.001	.42
Fever	0.16	<.001	.80

Abbreviations: MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; QOL, quality of life; TSS, total symptom score.

Correlations With Current and Prior Therapies

The MPN-SAF sexuality item was evaluated based on current or prior therapy use (Fig. 1). Problematic MPN-SAF sexuality scores were observed in patients currently receiving interferon (4.06 vs 3.47; $P = .009$ [prevalence, 17.0%]), immunomodulators (thalidomide, lenalidomide, and pomalidomide: 5.31 vs 3.45; $P<.0001$ [prevalence, 6.5%]), and steroids (5.36 vs 3.49; $P<.0001$ [prevalence, 4.3%]) when compared with patients with MPN not receiving these therapies. Patients currently receiving cytoreduction therapy (hydroxyurea/hydroxycarbamide, busulfan, pipobroman, or melphalan), anagrelide, or warfarin did not demonstrate differences in their sexuality symptoms compared with patients not presently receiving these therapies (all $P>.05$; prevalence rates of 45.3%, 3.5%, and 2.6%, respectively). When compared according to prior use, MPN-SAF sexuality scores were found to be higher for patients who had previously received cytoreduction (3.96 vs 3.46; $P = .01$ [prevalence, 23.3%]), interferon (4.6 vs 3.42; $P<.0001$ [prevalence, 13.2%]), immunomodulators (5.25 vs 3.48; $P<.0001$ [prevalence, 5.3%]), and steroids (6.11 vs 3.49; $P<.0001$ [prevalence, 3.1%]). It is interesting to note that sexuality scores were improved in patients with a history of previous warfarin use (1.42 vs 3.59; $P = .43$). Patients with MPNs who had previously received anagrelide did not differ by sexuality scores. Janus kinase 2 (*JAK2*) inhibitors were not evaluated in the current study.

DISCUSSION

Our understanding of MPNs has unquestionably advanced within the past decade. The development of MPN-specific patient-reported outcome tools (Myelofibrosis Symptom Assessment Form [MF-SAF], Myeloproliferative Neoplasm Symptom Assessment Form [MPN-SAF] and

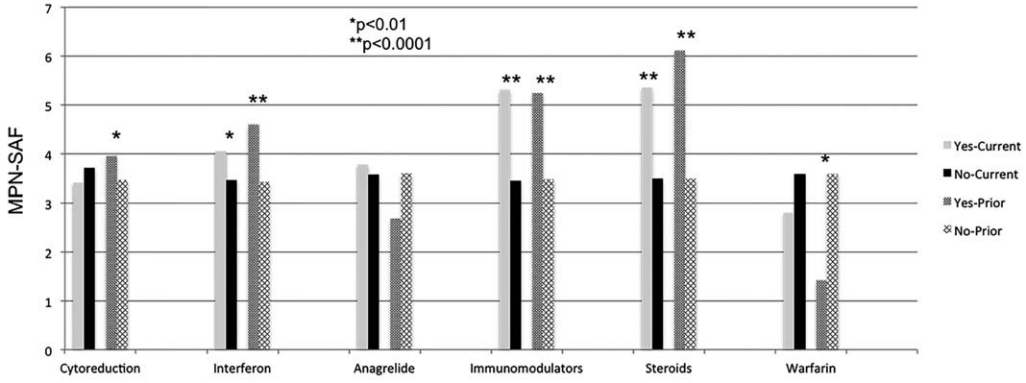

Figure 1. Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) sexuality score based on current and prior therapies. The vertical line represents averaged sexuality scores from the MPN-SAF based on prior or current therapies.

Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score [MPN-SAF TSS; MPN-10]) and risk scoring tools has allowed us to analyze how patient clinical and demographic features interrelate with symptoms to create the observed heterogeneous phenotypes. Sexuality-related symptoms have been particularly prominent among patients with MPN, and to a greater extent than that observed within the spectrum of other hematological malignancies. To our knowledge, no studies have specifically analyzed the correlations between sexuality-related symptoms and the MPN disease profile. In the current study, we aimed to further evaluate the correlations between sexuality concerns in patients with MPN and patient characteristics, disease features, symptom profiles, and overall QOL.

According to the World Health Organization, sexuality represents a central aspect of human existence and encompasses gender identity, gender roles, intimacy, pleasure, and reproduction. It must be interpreted further within an integrated framework of biological, psychological, social, economic, ethical, political, legal, historical, and religious contexts. Numerous sources may contribute to MPN-associated sexual dysfunction including pain, disfiguration, fatigue, depression/anxiety, hormonal disturbances, and a constitutive inflammatory state. It is well recognized that MPNs are inherently inflammatory conditions.[10-12] The presence of elevated inflammatory markers (interleukin [IL]-1, IL-6, IL-8, tumor necrosis factor-α, and C-reactive protein) is a veritable source of sexual dysfunction in other malignancies and noncancerous states demonstrating positive correlations with endothelial dysfunction through defects in nitric oxide activity, the propagation of microthrombotic events, and dysregulation of hormone pathways.[13-15]

Correlative analysis of the MPN-SAF sexuality item yielded several findings. On univariate analysis, correlations were noted between the sexuality symptom and all EORTC QLQ-C30 functioning scales including the physical, social, role, cognitive, and emotional scales, all EORTC QLQ-C30 symptom scales, and all other MPN-SAF symptoms. These findings demonstrate the expansive and complex interrelations between patient sexuality and its cognitive, emotional, and physical roots. As further observed within the final multivariate analysis, EORTC QLQ-C30 role functioning was particularly impacted along with overall reduced QOL. Previous studies of patients with cancer have identified that the diagnosis of malignancy is associated with changes in relationship status, frequency of sexual activity, performance of daily activities, time spent in the home, and relationship status with family and friends.[16-20] Within the MPN population, a patient's inability to fill previous gender-related responsibilities such as managing the household, earning the family income, or providing care to other family members can be a source of significant distress that likely imparts a secondary impact on sexual behavior.

The results of the current study also demonstrate the severity of sexual dysfunction in patients with MPN compared with healthy controls, and furthermore highlight the relationship between advancing patient age and worsening symptom burden. Contrary to prior assumptions, the historical supposition that advancing age and biological changes result in a decreased interest in sexual activities among patients with cancer remains an unsubstantiated claim.[7] For example, a study of 256 women responding to a self-reported questionnaire regarding issues of sexuality in the setting of a cervical cancer history found that >20% of patients who were still concerned about their sexuality were between the ages of 61 and 81 years.[21] It is important to recognize, however, that a patient's desire for cancer survival typically exceeds their desire to preserve sexuality.[22] Recognition by patients with MPN that their disorders may incur a significant risk of morbidity and/or mortality may result in a reprioritization of sexual activities as attention turns to survival. This trend has been observed in other malignancies and was demonstrated in an exploratory study of 400 Thai patients receiving radiotherapy for cervical cancer, in which patients were 22% less likely to believe that sexual intercourse was important to their married life after treatment.[23]

Our investigation also found correlations between MPN subtype and degree of sexual dysfunction. Congruent with previous studies, patients with MF were found to have the highest degree of symptomatology among MPN subtypes. It is of particular interest that distinct populations within the ET and PV subtypes also struggle with a high degree of sexual dysfunction, as noted previously within other MPN investigations.[24] It is also important to note that the sexuality score item did not differ by MPN risk, regardless of subtype. This suggests that sexuality remains a prominent issue, regardless of disease severity.

It was also determined that the MPN-SAF items regarding insomnia, depression, and anxiety correlated closely with the sexuality item. In patients without cancer, the prevalence of sexual dysfunction within the setting of depressive disorders has been reported to be as high as 77% and among patients with MPN, the prevalence of depression is higher than that of the average population.[25-27] Recognizing that the biological underpinnings associated with depression are complex and involve

similar regulatory pathways as those involved in sexual functions including the hypothalamic-pituitary-gonadal axis, the significant associations between these 2 symptoms within patients with MPN is not unexpected. A recent evaluation of 1788 patients with MPN attempted to determine the prevalence and risk factors for mental health disorders within this population. Overall, 23% of patients demonstrated a high probability of depression on the Patient Health Questionnaire 2 (PHQ-2).[27] In addition, patients with MPN endorsed having been seen for or diagnosed with depression (32.0%), anxiety (29.5%), stress (26.2%), and grief (15.0%). Up to 22.2% of patients with MPN had received treatment for their mental health disorder within the previous 6 months and 81.4% had received medication or counseling (40.3%). The issue of whether the treatment of depression impacts sexuality symptoms in the MPN population remains unknown.

We find it interesting that certain MPN therapies were associated with more problematic sexuality scores. Immunomodulators (thalidomide, lenalidomide, and pomalidomide) seemed to correlate quite strongly with sexual dysfunction. Although impotence has been reported in up to 8% of patients being treated with immunomodulators (thalidomide), this is unlikely to account for such a large discrepancy given the relative infrequency of occurrence, nor will it explain how symptoms transpire in females. Similarly, prior or current use of steroids was associated with a >30% increase in sexuality symptom scores. This finding is less surprising considering the plethora of documentation supporting the negative impact of steroids on serum hormone levels and their effects on the hypothalamic-pituitary axis.[28,29] The observation that patients had worse sexual dysfunction in the setting of prior but not current cytoreduction treatment may be explained if patients are in advanced stages of disease and cytoreduction is no longer used, perhaps as a result of intolerance or resistance.

The current study also suggests that patients with baseline thrombocytopenia and anemia tend to report more sexual symptoms. This correlates with the findings from a previous study in which patients with ET or PV with high sexual dysfunction demonstrated the highest percentage of laboratory abnormalities, including anemia.[24] To our knowledge, the mechanism accounting for these findings remains unclear but may be related to the elevated levels of inflammatory cytokines associated with MPNs, particularly those (ET and PV) in the process of transforming to MF, or in patients with MF whose baseline laboratory profiles are dominated by anemia. Alternatively, the presence of anemia also may subject patients to inhibitory levels of fatigue, subsequently compromising sexual function. As previously discussed, cytopenia-inducing pharmacological agents also may play a role.

It should be emphasized that there are numerous confines to the current study that limit the interpretation of the results. First, the MPN-SAF sexuality question did not specifically focus on any singular aspect of the term and as such remained open to broad patient interpretation as related to intimacy, fertility, menopause, erectile dysfunction, capacity for intercourse, contraception, or other symptoms. In addition, the current study did not specify whether thrombosis was arterial or venous in nature, a factor that could impact both manifestations and the degree of sexual dysfunction. It also is important to note that sexuality scores in the patients with MPN in the Swedish language group did not differ from the scores of Swedish control patients. It remains unclear whether this is related to Swedish patients naturally having fewer issues with sexuality or a statistical anomaly given the relatively low number of patients within the Swedish MPN patient population (107 patients). It also is important to recognize that although *P* values met statistical significance for MPN-SAF symptom items, EORTC QLQ-C30 symptoms, and EORTC QLQ-C30 functioning subscales, most Pearson correlations remained low (<0.4). It is interesting to note that the sexuality symptom did not correlate with age on univariate analysis but did correlate on multivariate analysis. This finding is likely explained by the numerous confounders that complicate data on univariate analysis that are subsequently controlled for on multivariate evaluation.

Sexuality-related symptoms are prevalent complaints that frequently escape the attention of health care professionals. The results of the current study confirm that this symptom has mental, physical, social, and spiritual roots and that a patient's inability to perform previous gender-related functions has the capacity to compromise their perceived QOL. The discovery that that this symptom occurs independent of patient age, sex, or disease risk speaks to the importance of eliminating provider bias and preconceived assumptions when addressing this symptom. It remains to be seen if activity-based and psychosocial interventions such as those used in the MPN Fatigue Project provide a symptomatic benefit via the alleviation of confounding symptoms and improvement of fatigue.[18] Although sexuality was not specifically examined in the Controlled Myelofibrosis Study with Oral Janus Associated Kinase (JAK) Inhibitor Treatment (COMFORT) studies using the JAK2 inhibitor ruxolitinib, substantial

symptomatic benefits were observed in patients with MF with regard to a variety of other inflammatory-related symptoms.[30,31] Recognizing that the pathophysiology of sexual dysfunction may be cytokine-driven, it is with great anticipation that we await future investigations of JAK2 inhibitors and other novel targeted agents whose mechanisms include inhibition of cytokine activity. Although many questions remain unanswered, this exploratory study clearly identifies potential areas for provider intervention. Invariably, open communication, patient education, and continued research will be recognized as constructive first steps in the management of this burdensome symptom.

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AUTHOR CONTRIBUTIONS

Holly L. Geyer: Conceptualization, methodology, investigation, resources, writing–original draft, writing–review and editing, and project administration. **Bjorn Andreasson**: Resources and writing–review and editing. **Heidi E. Kosiorek**: Methodology, formal analysis, investigation, resources, writing–original draft, writing–review and editing, and project administration. **Amylou C. Dueck**: Methodology, formal analysis, investigation, resources, writing–original draft, writing–review and editing, and project administration. **Robyn M. Scherber**: Methodology, investigation, resources, writing–original draft, writing–review and editing, and project administration. **Kari Martin**: Resources and writing–review and editing. **Kristina Butler**: Resources and writing–review and editing. **Claire N. Harrison**: Investigation, resources, and writing–review and editing. **Deepti Radia**: Investigation, resources, and writing–review and editing. **Francisco Cervantes**: Investigation, resources, and writing–review and editing. **Jean-Jacques Kiladjian**: Investigation, resources, and writing–review and editing. **Andreas Reiter**: Investigation, resources, and writing–review and editing. **Gunnar Birgegard**: Investigation, resources, and writing–review and editing. **Francesco Passamonti**: Investigation, resources, and writing–review and editing. **Zhenya Senyak**: Investigation, resources, and writing–review and editing. **Alessandro M. Vannucchi**: Investigation, resources, and writing–review and editing. **Chiara Paoli**: Investigation, resources, and writing–review and editing. **Zhijian Xiao**: Investigation, resources, and writing–review and editing. **Jan Samuelsson**: Investigation, resources, and writing–review and editing. **Ruben A. Mesa**: Conceptualization, methodology, formal analysis, investigation, resources, writing–original draft, writing–review and editing, and supervision.

REFERENCES

1. Tefferi A, Rumi E, Finazzi G, et al. Survival and prognosis among 1545 patients with contemporary polycythemia vera: an international study. *Leukemia.* 2013;27:1874-1881.
2. Passamonti F, Thiele J, Girodon F, et al. A prognostic model to predict survival in 867 World Health Organization-defined essential thrombocythemia at diagnosis: a study by the International Working Group on Myelofibrosis Research and Treatment. *Blood.* 2012;120: 1197-1201.
3. Passamonti F, Cervantes F, Vannucchi AM, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). *Blood.* 2010;115:1703-1708.
4. Mesa RA, Niblack J, Wadleigh M, et al. The burden of fatigue and quality of life in myeloproliferative disorders (MPDs): an international Internet-based survey of 1179 MPD patients. *Cancer.* 2007; 109:68-76.
5. Theobald DE. Cancer pain, fatigue, distress, and insomnia in cancer patients. *Clin Cornerstone.* 2004;6(suppl 1D):S15-S21.
6. Ananth H, Jones L, King M, Tookman A. The impact of cancer on sexual function: a controlled study. *Palliat Med.* 2003;17:202-205.
7. Hordern A. Intimacy and sexuality after cancer: a critical review of the literature. *Cancer Nurs.* 2008;31:E9-E17.
8. Mercadante S, Vitrano V, Catania V. Sexual issues in early and late stage cancer: a review. *Support Care Cancer.* 2010;18:659-665.
9. Scherber R, Dueck AC, Johansson P, et al. The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF): international prospective validation and reliability trial in 402 patients. *Blood.* 2011;118:401-408.
10. Tefferi A, Vaidya R, Caramazza D, Finke C, Lasho T, Pardanani A. Circulating interleukin (IL)-8, IL-2R, IL-12, and IL-15 levels are independently prognostic in primary myelofibrosis: a comprehensive cytokine profiling study. *J Clin Oncol.* 2011;29:1356-1363.
11. Dueck AC, Cleeland CS, Dantzer R, et al. Cytokine profile changes in 309 myelofibrosis patients: comparison of JAK1/JAK2 inhibitor therapy vs. placebo-correlative analysis from the COMFORT-I trial. Blood. 2013;122:4074.
12. Squires M, Harrison CN, Barosi G, et al. The relationship between cytokine levels and symptoms in patients (Pts) with myelofibrosis (MF) from COMFORT-II, a phase 3 study of ruxolitinib (RUX) vs best available therapy (BAT). *Blood.* 2013;122:4070.
13. Giugliano F, Esposito K, Di Palo C, et al. Erectile dysfunction associates with endothelial dysfunction and raised proinflammatory cytokine levels in obese men. *J Endocrinol Invest.* 2004;27:665-669.
14. Sullivan ME, Thompson CS, Dashwood MR, et al. Nitric oxide and penile erection: is erectile dysfunction another manifestation of vascular disease? *Cardiovasc Res.* 1999;43:658-665.
15. Vlachopoulos C, Aznaouridis K, Ioakeimidis N, et al. Unfavourable endothelial and inflammatory state in erectile dysfunction patients with or without coronary artery disease. *Eur Heart J.* 2006;27:2640-2648.
16. Jirojwong S, Thassri J, Skolnik M. Perception of illness and the use of health care givers among cervical cancer patients at Songkla Nagarind Hospital. A study in southern Thailand. *Cancer Nurs.* 1994;17:395-402.
17. Flay LD, Matthews JH. The effects of radiotherapy and surgery on the sexual function of women treated for cervical cancer. *Int J Radiat Oncol Biol Phys.* 1995;31:399-404.

18. Scherber RM, Senyak Z, McCallister A, et al. The MPN Fatigue Project: stage 1 results of the MPN Forum Internet-Based Survey among 879 MPN patients. *Blood.* 2013;122:1595.
19. Kiserud CE, Schover LR, Dahl AA, et al. Do male lymphoma survivors have impaired sexual function? *J Clin Oncol.* 2009;27:6019-6026.
20. Behringer K, Muller H, Gorgen H, et al. Sexual quality of life in Hodgkin lymphoma: a longitudinal analysis by the German Hodgkin Study Group. *Br J Cancer.* 2013;108:49-57.
21. Bergmark K, Avall-Lundqvist E, Dickman PW, Henningsohn L, Steineck G. Vaginal changes and sexuality in women with a history of cervical cancer. *N Engl J Med.* 1999;340:1383-1389.
22. Little M, Jordens C, Paul K, Sayers E. Survivors and their intimates. In: Surviving Survival: Life After Cancer. Marrickville, NSW, Australia: Choice Books; 2001:125-136.
23. Kritcharoen S, Suwan K, Jirojwong S. Perceptions of gender roles, gender power relationships, and sexuality in Thai women following diagnosis and treatment for cervical cancer. *Oncol Nurs Forum.* 2005;32:682-688.
24. Geyer HL, Dueck AC, Emanuel RM, et al. The Myelofibrosis Symptom Burden (MF-SB): an international phenotypic cluster analysis of 329 patients [abstract]. *Blood ASH Annual Meeting Abstracts.* 2012;120:1731.
25. Casper RC, Redmond DE Jr, Katz MM, Schaffer CB, Davis JM, Koslow SH. Somatic symptoms in primary affective disorder. Presence and relationship to the classification of depression. *Arch Gen Psychiatry.* 1985;42:1098-1104.
26. Angst J. Sexual problems in healthy and depressed persons. *Int Clin Psychopharmacol.* 1998;13(suppl 6):S1-S4.
27. Scherber RM, Senyak Z, Dueck AC, et al. High prevalence of mood disorders in MPNs and their possible role in MPN related fatigue. *Blood.* 2014;124:3173-3173.
28. MacAdams MR, White RH, Chipps BE. Reduction of serum testosterone levels during chronic glucocorticoid therapy. *Ann Intern Med.* 1986;104:648-651.
29. Morrison D, Capewell S, Reynolds SP, et al. Testosterone levels during systemic and inhaled corticosteroid therapy. *Respir Med.* 1994; 88:659-663.
30. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med.* 2012; 366:799-807.
31. Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med.* 2012;366:787-798.