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Prevalence of Physical Problems Detected by the Distress Thermometer and Problem List in Patients with Myeloproliferative Disorders

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Abstract

Background—Patients with myeloproliferative neoplasms (MPNs) can have severe physical symptom burden over an extended disease trajectory that contributes to decreased quality of life. Few studies, however, have characterized for which MPN patients physical symptoms are most frequently considered a problem. As such, this study describes MPN patients' physical symptoms and their relationship with patient characteristics.

Methods—Patients (*N*=117) with MPNs completed questionnaires in a dedicated academic medical center MPN clinic. Patients reported demographics (age, race/ethnicity, gender, marital status, employment status) and disease characteristics (MPN type, time with MPN). Patients reported whether they were bothered by any of 22 Physical Problem List variables from the Distress Thermometer and Problem List (DT&PL).

Results—The median number of physical problems endorsed by patients was 2 (*M*=2.26, SD=3.18) with a range from 0 to 20. Two-fifths endorsed no physical problems, one-fifth endorsed one problem, and two-fifths endorsed 2 or more problems. Fatigue (35.5%), sleep (27.1%), pain (21.5%), dry skin/pruritus (18.7%), and memory/concentration (16.8%) were the most commonly reported. Non-Caucasian participants reported more problems with sleep (p=.050), pain (p=.016), and tingling (p=.026). Polycythemia vera (PV) patients reported more issues with tingling (p=.046) and sexual problems (p=.032).

Conclusion—It is more likely among patients with MPN to report physical symptom bother than to report no bother with multiple physical problems on the DT&PL. Patients of minority race/

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ethnicity and those with PV, however, showed heightened prevalence of physical problems, characteristics which may be used to triage patients for more intensive symptom management.

Introduction

Myeloproliferative neoplasms (MPNs) are a unique form of hematologic malignancy that are characterized by an elevated rate of physical symptom burden along a progressive and chronic disease trajectory.[1] Patients with MPNs often report high physical symptom burden that has been shown to adversely affect their quality of life and psychological outcomes.[2,3] Although it is known that patients with MPNs report frequent fatigue, early satiety, or pruritus depending on their MPN type and severity, little research has sought to identify which physical problems are most commonly reported among which patients with MPNs using the Distress Thermometer and Problem List (DT&PL). The DT&PL is endorsed by the National Comprehensive Cancer Network (NCCN) for the identification of distress in patients with cancer as a practical means to triage patients to appropriate resources,[4] and it offers convenience and proven acceptability in busy oncology clinics.[5] The accompanying Problem List provides a comprehensive reference of common physical symptoms in cancer patients. Better understanding of patients for whom symptoms are bothersome will be critical to targeting those patients most at risk for adverse outcomes related to physical problems for advanced symptom management interventions. Also, physician reporting of symptoms has been shown to be less reliable than patient reported symptoms.[6] As such, this study is the first to characterize patient-reported physical problems using the DT&PL with demographic and medical characteristics among patients with MPNs.

The MPNs represent a continuum of disease: essential thrombocythemia (ET), polycythemia vera (PV), and myelofibrosis (MF) that all display variable but significant symptom burden. Across subtypes, MPN patients experience a unique constellation of physical symptoms such as pruritus, night sweats, bone and splenic pain, fatigue, and fevers. Symptom burden can be similar in severity to the experience of those patients with metastatic cancer or AML, but with a much longer period of overall survival,[7] although symptom profiles and disease trajectories exist on a severity spectrum.

Physical symptom burden perceived by the individual is captured by the Physical Problems category of the Distress Thermometer & Problem List (DT&PL), a helpful tool that is the most accepted and frequently implemented measure of distress used internationally[8] and meets national distress screening mandates.[8,9] The Problem List accompaniment includes a list of 22 physical symptoms that patients endorse whether or not a symptom has been a problem over the past week (yes/no). Capturing patients' subjective report of their physical symptom burden is important, given that doctors frequently underestimate patients' bother from physical symptoms, which may lead to inappropriate treatments and delayed referrals to palliative care.[10,11] Patients' self-reporting of their symptom burden is strongly associated with their quality of life.[12] Ours is the first study to use the DT&PL to characterize subjective physical symptom burden among a large, diverse sample of patients with MPN.

Our study fills an important gap in the current literature, namely, that there is little known regarding physical problems on the DT&PL or their associations with patient demographics

and disease characteristics among those with MPN. First, we characterize physical symptom burden self-reported by patients with MPN. Next, we examine associations between endorsing the most frequent physical symptom burdens and patient characteristics.

Methods and Materials

The Mount Sinai Hospital Institutional Review Board approved this study in July 2014. Surveys were collected from participants from May 2015 to October 2015. All participants provided written informed consent to participate.

Participants

Men and women with documented MPNs were screened based on inclusion criteria consisting of a confirmed tissue diagnosis of an MPN, as reported by the treating physician. Exclusion criteria consisted of another cancer diagnosis as identified by the patient. Recruitment occurred over four months in a dedicated MPN clinic. New and established patients were recruited to participate in the survey.

Procedure

Participants were asked to participate by either a clinic receptionist or treating staff (i.e., nurse practitioner, hematologist). They were told that the survey was anonymous, as part of a research initiative, and that it did not relate to their ongoing care. Available psychological services were listed in the survey and patients were asked to bring up any concerns with clinic staff. A board-certified psychiatrist oversaw the study and was available for consultation. Participants completed surveys while waiting in the clinic office space prior to or after their appointments and returned them directly to clinic staff.

Measures

Patient demographic and medical characteristics—Patients reported demographic information including age, race/ethnicity, gender, and marital and employment status, as well as medical information including disease type (ET, PV, MF, ‘other MPN’ [e.g., hypereosinophilic syndrome, PDGFRA-positive MPN, systemic mastocytosis, or chronic neutrophilic leukemia]) and length of time with disease (under 1 year, 1-3 years, 3-5 years, 5-10 years, over 10 years).

Physical problems—Patients endorsed whether a physical symptom had been a problem for them over the past week using the Physical Problem List on the DT&PL. The Physical Problem List contains 22 separate items (see Table 2 for items). The DT&PL has been used widely by cancer institutions to meet the Commission on Cancer distress-screening mandate for accreditation in 2015.[9]

Statistical Analysis

The primary outcome of this study was to determine the prevalence of 22 Physical Problem List variables. Associations with demographics (age, race/ethnicity, gender, marital and employment status) and disease characteristics (MPN type, time with MPN) were examined if at least 10% of patients endorsed that particular physical symptom (to ensure adequate

power). Independent t-tests were used to assess the bivariate associations between patient age and endorsement of physical problems. Chi-square tests were used to assess the bivariate associations between categorical patient characteristics and endorsement of physical problems. For significant chi-square tests with disease characteristic variables, follow-up pairwise comparisons were conducted to compare proportions of physical problem endorsement among variable levels. Keppel's modified Bonferroni correction as used to control for Type I error at the .05 level across follow-up comparisons.[13] Statistical procedures were performed using the SPSS version 22 software (SPSS, Chicago, IL 2013) and statistical tests were two-tailed with a 5% significance level.

Results

Characteristics of the 117 patients with confirmed MPN who completed the survey (78% response rate) are listed in Table 1. The average age was 57.7 years (SD 14.8) and 69 respondants (60.5%) were female. Thirty-four respondants (31.2%) had PV, 31 (28.4%) had ET, 31 (28.4%) had MF, and 13 (11.9%) had another type of MPN. The sample comprised approximately half patients with an MPN for fewer than 5 years versus patients with the disease for 5 years or more. The majority of participants were caucasion (76.1%), partnered (65.2%), and working (55.8%).

The median number of Physical Problem List variables endorsed by patients was 2 (M=2.26, SD=3.18) with a range from 0 to 20 (see Table 2). Two-fifths endorsed no physical problems, one-fifth endorsed one problem, and two-fifths endorsed 2 or more problems. The five most commonly reported physical problems were fatigue (35.5%), sleep (27.1%), pain (21.5%), skin dry/itchy (i.e., pruritis, 18.7%), and tingling (17.8%). Problems with bathing (1.9%), fevers (1.9%), and substance abuse (1.9%) were not commonly reported.

Results of bivariate comparison tests examining the associations between patient characteristics and endorsement of physical problems are listed in Table 3. Non-Caucasian participants reported more problems with sleep (p=.050), pain (p=.016), and tingling (p=.026). Compared with Caucasian participants, the probability of reporting a problem was 1.8 times higher for sleep (.458/.261), 2.3 times higher for pain (.435/.186), and 2.6 times higher for tingling (.296/.116) for non-Caucasian participants. Patients who were married had less difficulty with fatigue (p=.008). The probability of reporting a problem with fatigue was 2 times (.576/.293) higher for unmarried participants than married ones.

Patients differed in reports of tingling (p=.046) and sexual problems (p=.032) across MPN disease type. For tingling, follow-up planned comparisons using Keppel's modified Bonferroni correction (α_{pc}=.044) revealed that the only significant pairwise difference was between ET and other MPN ($\chi^2(1, n=45)=8.809$, p=.003). The probability of reporting a problem with tingling was 11 times (.357/.032) higher for those with MPNs other than ET. For sexual problems, follow-up planned comparisons using Keppel's modified Bonferroni correction (α_{pc}=.044) revealed that the only significant pairwise difference was between PV and ET ($\chi^2(1, n=54)=6.533$, p=.011). The probability of reporting sexual problems was 8 times (.296/.037) higher for those with PV than those with ET. Age, gender, employment

status, and time with MPN were not significantly associated with endorsing Physical Problem List variables, although trends ($p<.10$) emerged that warrant further study.

Discussion

This study is the first to characterize patient-reported physical symptom burden using the DT&PL among a large, diverse sample of patients with MPN. The DT&PL is a short and convenient measure that is already most commonly used to screen for distress internationally and may provide a convenient way to also screen physical symptom burden in patients with MPNs. Equal proportions of the sample reported no physical problems and two or more physical problems, with fatigue and sleep disturbance reported by over one-quarter of the sample. Several patient demographic and medical characteristics were associated with likelihood of endorsing a physical problem. Findings suggest that particular patient characteristics may be used to target symptom management interventions to patients at highest risk for adverse outcomes related to these problems.

The symptom prevalence documented in the current study fits with prior studies of MPNs. The most commonly endorsed physical symptom among patients was fatigue, consistent with prior research.[7,14] Fatigue may be mediated by increased cytokine release in patients with MPNs since this is a clonal disease leading to excessive production of protein mediators.[15,16] Interestingly, having a spouse or partner appeared to be protective against fatigue. Romantic partners can exert a positive effect on one's lifestyle that may lessen fatigue, such as promoting healthy lifestyle behaviors,[17] consistent social routines,[18] and behavioral activation during the day.[18,19]

Non-Caucasian MPN patients more commonly reported physical issues of tingling (e.g., peripheral neuropathy), sleep, and pain compared to Caucasian patients. This may represent under-treatment of these symptoms among non-Caucasian patients, an ethnically distinct symptom producing mechanism inherent to MPNs, or cultural differences in symptom reporting. However, reporting more problems with tingling, sleep, and pain among non-Caucasians is consistent with other studies that show greater symptom burden among African American and Hispanic ethnicities and under-treatment of those symptoms in various subsets of cancer.[20,21] Additionally, there may be more barriers to managing cancer-related pain in the advanced cancer setting consistent with known disparities in pain management, which may also be seen in the MPN setting.[22]

Patients with MPN diagnoses other than the three major subtypes reported more neuropathy than those with ET, while patients with PV reported more sexual problems compared to those with ET. This is consistent with the underlying vascular pathophysiology that leads to sexual impotence in men.[23] Therefore, clinicians should be particularly vigilant of symptoms of neuropathy and sexual dysfunction as reported on the DT&PL in patients with PV. These symptoms are known to be common in patients with PV.[24,25] Pruritus was not found to be exclusively associated with PV. Since PV is associated with pruritus and erythromelalgia, this was an unexpected finding that may have been mitigated by length of time with MPN and/or adequate treatments.[26] Another explanation may be due to the wording of the DT&PL, which asks whether a patient has been *bothered by* a physical

symptom, rather than simply *experienced* the symptom. Lack of differences may therefore represent a lack of distress or effective coping with skin itching among those with PV, even if they more commonly experience this side effect. Further research to test these hypotheses is warranted.

The primary limitation to this study is the use of a non-validated tool (DT&PL) specifically for measuring physical symptom burden, as opposed to measures such as the Myeloproliferative Neoplasm Symptom Assessment Form (MPN- SAF)[7], or the Functional Assessment of Cancer Therapy-Anemia (FACT-An)[27], which have been validated as patient-reported outcome measures.[7,27] However, results of physical symptom burden were comparable in our study using the DT&PL compared to prior studies that used longer quality of life measures.[2,7] This suggests the utility of using the DT&PL, which is widely used, has confirmed clinic acceptability, and is rapidly completed by patients,[5,8] although further study should test this hypothesis and establish validity in the MPN population. As data are cross-sectional, future research should seek to examine associations between patient characteristics and the development of physical symptom burden from MPN longitudinally. Furthermore, as several of the commonly reported symptoms (e.g., fatigue, sleep, pain, memory/concentration problems) may also be related to psychological symptoms elevated in MPNs, future research should examine the interrelations between MPNs' physical and psychological symptom burdens.[3]

In summary, this study provides evidence for an association between certain physical symptoms problems and MPN disease type and patient demographics using the DT&PL. Two-fifths of patients reported two or more physical symptoms that were problematic, and thus not adequately controlled. Patients who were non-Caucasian and unmarried were more likely to report certain problems relative to Caucasian and married patients, while those with ET were less likely to report certain problems relative to those with PV or another MPN than the three major subtypes. The DT&PL, widely implemented as a distress-screening instrument, may also be helpful in delineating problematic physical symptomatology in patients with MPNs. The development of targeted, effective symptom management strategies for MPN patients at highest risk for adverse outcomes from physical problems associated with the disease and treatment will be critical to sustaining the quality of life among this vulnerable population of chronically ill patients.

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Table 1
MPN Sample Demographics and Characteristics (*N*=117)

	Mean	SD
Age	57.7	14.8
	N	*%*
Race/Ethnicity		
Caucasian	86	76.1
Non-Caucasian	27	23.9
Gender		
Female	69	60.5
Male	45	39.5
Married		
Yes	73	65.2
No	39	34.8
Employed		
Yes	63	55.8
No	50	44.2
Disease Type		
PV	34	31.2
ET	31	28.4
MF	31	28.4
Other	13	11.9
Time with MPN		
<1 year	8	7.5
1-3 years	21	19.8
3-5 years	25	23.6
5-10 years	21	19.8
>10 years	31	29.2

Note: where sum ≠ 117, patients did not report data. Abbreviations: ET, Essential Thrombocythemia; MF, Myelofibrosis; MPN, Myeloproliferative Neoplasm; PV, Polycythemia Vera.

Table 2

Frequency of Physical Problems Endorsed

Physical Problem List Variables	*N*	*%*
Fatigue	38	35.5
Sleep	29	27.1
Pain	23	21.5
Skin dry/itchy	20	18.7
Tingling	19	17.8
Memory/Concentration	18	16.8
Feeling swollen	12	11.2
Breathing	11	10.3
Sexual	11	10.3
Mouth Sores	10	9.3
Appearance	9	8.4
Constipation	9	8.4
Diarrhea	9	8.4
Getting around	9	8.4
Nose dry	9	8.4
Eating	7	6.5
Indigestion	6	5.6
Nausea	5	4.7
Change in urination	4	3.7
Bathing	2	1.9
Fevers	2	1.9
Substance abuse	2	1.9

Table 3

Associations of MPN Demographics with Physical Problem List Variables

	Fatigue			Sleep			Pain			Skin Dry/Itchy			Tingling			Memory/Concentration			Feeling Swollen			Breathing			Sexual		
	Yes	**No**		**Yes**	**No**		**Yes**	**No**		**Yes**	**No**		**Yes**	**No**		**Yes**	**No**		**Yes**	**No**		**Yes**	**No**		**Yes**	**No**	
	M(SD)	***M(SD)***	***t***	***M(SD)***	***M(SD)***	***t***	***M(SD)***	***M(SD)***	***t***	***M(SD)***	***M(SD)***	***t***	***M(SD)***	***M(SD)***	***t***	***M(SD)***	***M(SD)***	***t***	***M(SD)***	***M(SD)***	***t***	***M(SD)***	***M(SD)***	***t***	***M(SD)***	***M(SD)***	***t***
Age	**56.9 (13.9)**	**57.8 (15.8)**	**0.228**	**57.4 (14.0)**	**57.4 (15.4)**	**1.265**	**61.6 (15.8)**	**56.4 (14.2)**	**1.265**	**58.65 (17.0)**	**57.47 (14.4)**	**-0.323**	**56.7 (16.0)**	**57.9 (14.6)**	**0.302**	**53.56 (17.59)**	**58.45 (14.18)**	**1.291**	**54.83 (17.15)**	**58.01 (14.55)**	**0.702**	**49.6 (17.0)**	**58.5 (14.4)**	**1.941†**	**51.33 (19.1)**	**58.18 (14.6)**	**1.056**
	n	*n*	χ^2	*n*	*n*	χ^2	*n*	*n*	χ^2	*n*	*n*	χ^2	*n*	*n*	χ^2	*n*	*n*	χ^2	*n*	*n*	χ^2	*n*	*n*	χ^2	*n*	*n*	χ^2
Race/ Ethnicity			1.227			3.777*			5.769*			0.101			4.972*			1.049			0.077			0.077			1.450
Caucasian	26	44		18	51		13	57		15	71		10	76		12	74		8	78		8	78		8	62	
Non-Caucasian	12	12		11	12		10	13		4	23		8	19		6	21		3	24		3	24		4	16	
Gender			0.010			2.810†			0.030			0.911			3.238†			0.221			0.027			0.759			3.735†
Female	22	33		21	34		13	41		14	55		8	61		10	59		7	62		8	61		4	49	
Male	16	23		8	29		10	29		6	39		11	34		8	37		5	40		3	42		8	29	
Married			7.028**			0.858			3.280†			0.366			1.817			0.230			2.902†			1.815			1.079
Yes	17	41		16	43		11	49		11	60		9	62		10	61		5	66		5	66		5	52	
No	19	14		11	19		11	20		8	32		9	31		7	33		7	33		5	34		5	26	
Employed			0.605			3.587†			2.276			0.043			0.090			0.287			0.524			0.524			0.564
Yes	20	34		12	41		10	43		11	52		10	53		9	54		5	58		5	58		8	42	
No	18	22		16	23		13	27		8	42		9	41		9	41		6	44		6	44		4	35	
Disease Type			2.469			1.117			4.823			4.674			7.984*			3.134			6.138			2.521			8.811*
PV	12	15		8	18		5	22		9	25		6	28		7	27		2	32		3	31		8	19	
ET	8	19		10	17		4	23		3	28		1	30		2	29		2	29		2	29		1	26	
MF	10	14		6	18		8	16		4	27		6	25		6	25		4	27		3	28		2	22	
Other	7	6		5	8		5	7		4	10		5	9		3	11		4	10		3	11		1	9	
Time with MPN			0.530			5.789			2.436			3.325			0.969			3.423			2.395			2.513			1.143
<1 year	2	4		1	5		1	5		0	8		2	6		0	8		1	7		1	7		0	5	
1-3 years	8	11		4	15		4	15		4	17		3	18		2	19		2	19		2	19		3	16	
3-5 years	7	14		4	15		5	15		5	20		3	22		5	20		3	22		2	23		3	18	
5-10 years	10	11		10	11		3	16		6	15		4	17		6	16		1	20		3	18		2	18	
>10 years	9	12		9	13		8	15		5	26		5	26		5	26		4	27		2	29		3	17	

Abbreviations: ET, Essential Thrombocythemia; MF, myelofibrosis; MPN, Myeloproliferative Neoplasm; PV, Polycythemia Vera; SD, standard deviation; T, t-test statistic; χ^2 chi squared test statistic.

† p<.1, * p<.05, ** p<.01, *** p<.001