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Item nonresponse on the Myeloproliferative Neoplasms Symptom Assessment Form (MPN-SAF): a comparison of missing data strategies

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Abstract

Administering questionnaires to patients is an efficient and effective method for assessing patients' symptoms. However, item nonresponse (skipped questions) potentially compromises the utility of these questionnaires. Using an international sample of 2,067 patients with myeloproliferative neoplasms, we evaluated the impact of item nonresponse on scoring of the Myeloproliferative Neoplasms Symptom Assessment Form Total Symptom Score (MPN-SAF TSS or MPN-10). We characterized item nonresponse on the MPN-10 and compared strategies for addressing item nonresponse (available-case analysis, proration, and multiple imputation) on the MPN-10 (multi-symptom assessment) and Brief Fatigue Inventory (BFI; single-symptom assessment). Characteristics of multi-symptom assessments would be expected to adversely affect proration, yet proration and multiple imputation provided very similar results for both the MPN-10 and BFI. This is likely because the MPN-10 item missing data rates were low, consistent with prior clinic- and internet-based studies. These results support the published scoring method for the MPN-10 (proration).

Introduction

Patients with myeloproliferative neoplasms (MPNs) experience a wide array of symptoms. Because the debilitating symptom profile is arguably the most recognizable feature of MPNs,[1] Mesa et al.[2] developed the Myelofibrosis Symptom Assessment Form (MFSAF) to enable patients with myelofibrosis (MF) to directly report their symptoms. The MFSAF was expanded and validated for use in patients with essential thrombocythemia (ET) and polycythemia vera (PV) to create the Myeloproliferative Neoplasms Symptom Assessment Form (MPN-SAF).[3] The MPN-SAF was later shortened to the 10-item Total Symptom Score (TSS) or MPN-10, which assesses the most prominent and clinically relevant symptoms among patients with MPNs—fatigue, concentration problems, early satiety, inactivity, night sweats, pruritus, bone pain, abdominal discomfort, weight loss, and fever.[4]

In this paper, we characterize item nonresponse (i.e., skipped questions) on the MPN-10 using an international sample of 2,067 patients with MPNs. Item nonresponse threatens both the internal and external validity of analytical results because patients who skip items may systematically differ from those who do not, and skipped items may systematically differ from completed items. We evaluate the impact of item nonresponse on scoring of the MPN-10 by applying various missing data strategies to the MPN-10. For comparison, we also apply these missing data strategies to the Brief Fatigue Inventory (BFI),[5] which is often co-administered with the MPN-SAF. Whereas the BFI consists of items measuring a single symptom, the MPN-10 consists of items measuring disparate symptoms. Multi-symptom assessments are an emerging focus of cancer therapeutic clinical trials given the Food and Drug Administration approval of ruxolitinib, which was partly based on patient-reported symptoms captured using a derivative version of the MPN-10.[6] Furthermore, multi-symptom assessments were the focus of an April 2017 meeting of the Patient-Reported Outcome Consortium formed by the Critical Path Institute.[7] To our knowledge, no published recommendations exist for addressing item nonresponse on multi-symptom assessments like the MPN-10.

Missing Data Strategies

When patients complete questionnaires, related items are summed or averaged to create scale scores. For example, the ten items on the MPN-10 form a scale score summarizing patients' symptom burden. Item nonresponse complicates the calculation of scale scores. Strategies for addressing item nonresponse include available-case analysis, proration, and multiple imputation, which we describe below.

Available-Case Analysis—Available-case analysis refers to excluding patients with missing scores on one or more items required for a particular analysis. That is, if a patient skips just one item, then his or her scale score is not computed. Even with modest missing data rates, available-case analysis can substantially reduce the sample size and, thus, power. For example, if 1.0% of scores were missing on each of the 18 BFI and MPN-10 items, available-case analysis could exclude up to 16.5% of patients (assuming each of these patients skipped one item).[8] Furthermore, excluding patients who skip items produces bias if patients who skip items systematically differ from those who do not.

Proration—Proration (sometimes called patient mean imputation) refers to averaging the available items for each patient. For example, if a patient answers six out of ten items, then his or her scale score is the average of the six responses. Typically, proration is only applied when patients complete at least half of the items.[9,10] That is, the scale score is computed if the patient answered at least half of the items but not if the patient answered less than half of the items. As shown in Table 1, proration is equivalent to imputing (i.e., replacing) each patient's missing scores on the skipped items with the mean of his or her observed scores on the completed items. Proration is often recommended by user manuals and key publications for questionnaires, including the BFI[5] and MPN-10.[4] However, methodologists have raised serious concerns about proration because different items may be contributing to the computed scale scores across patients.[11,12] For example, the MPN-10 scale score may be computed from the fatigue, early satiety, abdominal discomfort, inactivity, concentration

problems, and night sweats items for one patient and from the concentration problems, night sweats, itching, bone pain, fever, and weight loss items for another patient. Although these patients completed different sets of items, the patients' scale scores receive the same interpretation (i.e., symptom burden as assessed by the MPN-10). Proration is typically acceptable when the items have similar means and strong correlations with the other items on the scale (as would be expected for the BFI items, which all pertain to fatigue). However, proration is potentially problematic when the items have different means and weak correlations with the other items on the scale (as would be expected for the MPN-10 items, which pertain to disparate symptoms).[12]

Multiple Imputation—Multiple imputation involves creating multiple copies of the data set with different imputed scores (imputation phase), applying the desired analysis to each imputed data set (analysis phase), and pooling the estimates and standard errors across the imputed data sets to yield a single set of results (pooling phase; see Rubin[13] or Enders[14] for more technical details). To replace the missing scores with imputed scores, we use available information about patients' would-be responses to the skipped items. This information may include patients' responses to other items on the scale, patients' responses to other scales, clinician assessments, and medical records. As shown in Table 2, the observed scores remain the same across the imputed data sets, while the imputed scores change across the imputed data sets. These changes in the imputed scores quantify uncertainty due to the missing scores. That is, the more the imputed scores change across the imputed data sets, the more uncertain we are regarding how patients would have responded had they not skipped items. Unlike proration, multiple imputation properly accounts for this uncertainty due to the missing scores. Multiple imputation also uses the full sample size for all analyses and makes more plausible assumptions about the missing data relative to available-case analysis and proration. However, multiple imputation is more complex to implement than both available-case analysis and proration.

Given the advantages and disadvantages of these missing data strategies, we examined their appropriateness when applied to the MPN-10. We characterized item nonresponse on the MPN-10 and applied available-case analysis, proration, and multiple imputation to the MPN-10 (multi-symptom assessment) and BFI (single-symptom assessment) for comparison. Results of this study can inform best practice for addressing item nonresponse on the MPN-10.

Methods

Patients, Measures, and Procedures

Patients with MPNs were prospectively enrolled from various practice settings in Argentina, China, France, Germany, Italy, The Netherlands, Puerto Rico, Spain, Sweden, Switzerland, United Kingdom, United States, and Uruguay. Institutional review boards at all sites granted approval, and all patients provided informed consent prior to participation.

Patients completed the BFI and MPN-10. The BFI consists of three items measuring severity on a 0 (no fatigue) to 10 (as bad as you can imagine) scale and six items measuring interference with daily functioning on a 0 (does not interfere) to 10 (completely interferes)

scale. The published scoring method for the BFI instructs users to compute severity and interference scale scores for patients who completed at least half of the items by averaging the available items.[5] The MPN-10 consists of the BFI item capturing patients' worst level of fatigue plus nine MPN-SAF items—concentration problems, early satiety, inactivity, night sweats, pruritus, bone pain, abdominal discomfort, weight loss, and fever—rated on a 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be) scale. The published scoring method for the MPN-10 instructs users to compute the scale score for patients who completed six or more items by averaging the available items and multiplying by 10 to achieve a 0-to-100 scale.[4] Clinicians reported patients' fatigue, night sweats, pruritus, bone pain, weight loss, and fever on a 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be) scale. Patients with known MPN type (ET, PV, or MF) were included in this analysis. Because our focus was item nonresponse (i.e., patients completing some, but not all, of the items), we excluded patients who did not complete at least one item from each scale.

Statistical Analysis

Each item's missing data rate, mean, standard deviation, and correlations with the other items were computed for the full sample and by MPN type. Each scale's mean and correlations with the other scales were computed using available-case analysis, proration, and multiple imputation; 95% confidence intervals were also computed to assess the precision of each estimate. With available-case analysis, each scale score was computed for patients who completed all of the scale score's constituent items; patients missing a scale score required for a particular analysis were then excluded. With proration, each scale score was computed for patients who completed at least two of the three BFI severity items, at least three of the six BFI interference items, or at least six of the ten MPN-10 items; patients missing a scale score required for a particular analysis were then excluded. With multiple imputation, each scale score was computed following imputation of the missing items.[15]

Multiple imputation was conducted using the MI procedure in SAS 9.4. The imputation model included the 18 items from the BFI and MPN-10, MPN type, and six clinician-reported symptoms. MPN type and clinician-reported symptoms were included in the imputation model to provide information about patients' would-be responses to the skipped items. For example, patients with MF generally experience greater symptom burden relative to patients with ET or PV. Clinician-reported symptoms also generally correlate with patient-reported symptoms. In this sample, correlations between the clinician-reported symptoms and corresponding MPN-10 items ranged from .39 to .55, suggesting a moderate to strong association based on Cohen's conventions.[16] Using joint modeling, we generated 50 imputed data sets while setting the burn-in period (i.e., number of iterations prior to saving the first imputed data set) to 1,000 and the between-imputation interval (i.e., number of iterations separating two imputed data sets) to 250. Multiple imputation by chained equations yielded highly similar results (not shown). Pooled means and 95% confidence intervals were computed using the MIANALYZE procedure. Correlation coefficients were pooled across the imputed data sets while applying Fisher's r -to- z transformation.[17]

Results

Patient Demographic and Disease Characteristics

The sample consisted of 2,067 patients with MPNs (Argentina, 149; China, 601; France, 476; Germany, 94; Italy, 178; The Netherlands, 236; Puerto Rico, 10; Spain, 26; Sweden, 114; Switzerland, 19; United Kingdom, 54; United States, 102; Uruguay, 8) following exclusion of 8 patients who did not report their MPN type and 22 patients who did not complete at least one item from each scale. Of these 2,067 patients, 862 (41.7%) had ET, 726 (35.1%) had PV, and 479 (23.2%) had MF. Patients were on average 59.68 years old ($SD = 13.71$, range = 15 to 94) and 54.5% female. Lab abnormalities of anemia, leukopenia, and thrombocytopenia were more prevalent among patients with MF (62.2%) than among patients with ET (12.1%) or PV (12.2%). Most patients (84.2%) were currently receiving some form of treatment.

Item Characteristics

For the full sample, missing data rates ranged from 0.1% to 2.3% for the BFI items and from 1.2% to 4.0% for the MPN-10 items (Table 3). The most-skipped MPN-10 item pertained to inactivity, though this item's missing data rate was still low (4.0%). For the BFI, 1,928 (93.3%) of the 2,067 patients completed all nine items, 106 (5.1%) skipped one item, and 33 (1.6%) skipped two or more items. For the MPN-10, 1,820 (88.1%) of the 2,067 patients completed all ten items, 165 (8.0%) skipped one item, and 82 (4.0%) skipped two or more items (Table 4).

The BFI items had fairly uniform means (severity: range = 3.48 to 4.25, interference: range = 2.20 to 3.05), whereas the MPN-10 items had varying means (range = 0.45 to 4.25). The MPN-10 item pertaining to fatigue had the highest mean ($M = 4.25$), whereas the MPN-10 item pertaining to fever had the lowest mean ($M = 0.45$). Inter-item correlations were uniform and strong for the BFI items (severity: range = .82 to .88, interference: range = .61 to .83; Table 5) but were neither uniform in value nor strength for the MPN-10 items (range = .19 to .58; Table 5). As previously described, these characteristics of the MPN-10 would be expected to adversely affect proration.

Comparison of Missing Data Strategies

The scales' means and correlations were very similar across available-case analysis, proration, and multiple imputation (Table 6). The confidence intervals for the scales' means and correlations were also very similar across the missing data strategies (Table 6). That is, the results were largely unaffected by which strategy we used to address item nonresponse on the BFI and MPN-10. However, whereas multiple imputation relied on the same sample size across all analyses, available-case analysis and proration relied on different sample sizes for different analyses. Sample sizes ranged from 1,771 to 2,013 for available-case analysis (up to a 14.3% reduction in sample size) and from 2,043 to 2,066 for proration (up to a 1.2% reduction in sample size; Table 6).

Discussion

In this paper, we used an international sample of 2,067 patients with MPNs to characterize item nonresponse on the MPN-10 and compare strategies for addressing item nonresponse on the MPN-10. The results supported the published scoring method for the MPN-10 (proration). In this sample, the MPN-10 item missing data rates were low (1.2% to 4.0%), consistent with prior clinic- and internet-based studies where the MPN-10 item missing data rates never exceeded 3.4%. [18-20] Most patients completed all of the items (88.1%) or only skipped one item (8.0%). Patients did not seem to skip one item in particular. Because none of the MPN-10 items are particularly intrusive, we suspect that many patients who skipped items did so inadvertently. Nevertheless, item nonresponse should be considered when collecting and analyzing the MPN-10. First, item nonresponse should be prevented as much as possible through careful protocol development and staff training. Protocols should instruct staff to check paper forms for completeness, and online forms should prompt patients to complete or refuse items.

Second, researchers should justify their chosen missing data strategy. Often researchers contend with multiple sources of missing data, all of which should be considered. Focusing on item nonresponse, we compared available-case analysis, proration, and multiple imputation when applied to the BFI and MPN-10. In general, available-case analysis should be avoided. When patients with and without missing data systematically differ, available-case analysis produces bias and limits generalizability of the results. Even when patients with and without missing data do not systematically differ, available-case analysis reduces the sample size and, thus, power. Analyses that use all of the available information about patients' would-be responses to the skipped items (e.g., multiple imputation) reduce bias and power loss due to missing data. However, we acknowledge that procedural demands may prohibit such analyses. In theory, proration will produce bias unless the imputed items have the same properties as the remaining items on the scale, which seems unlikely to hold with the MPN-10. In practice, however, bias resulting from proration may be negligible, as seen with this sample. Proration and multiple imputation provided very similar results for both the BFI (single-symptom assessment) and MPN-10 (multi-symptom assessment), even though characteristics of the MPN-10 would be expected to adversely affect proration. This is likely because the item missing data rates were low, consistent with prior clinic- and internet-based studies. Based on these results, the published scoring method for the MPN-10 (proration) appears reasonable.

Finally, researchers can perform a sensitivity analysis if item nonresponse is a serious concern. A sensitivity analysis assesses the robustness of the results across various missing data strategies with different sets of assumptions about the skipped items. Similarity of the results across the missing data strategies supports the conclusions from the primary analysis. In this sample, the scales' means and correlations were very similar across the missing data strategies, though it is possible that greater differences would have been observed for other parameters of interest. Furthermore, the confidence intervals for the scales' means and correlations were very similar across the missing data strategies, though it is possible that greater differences would have been observed with a smaller sample size.

Our large international sample of patients with MPNs enabled us to evaluate the impact of item nonresponse on scoring of the MPN-10. However, additional research is needed to evaluate proration's performance under a variety of conditions and develop comprehensive guidelines for addressing item nonresponse on multi-symptom assessments. Such guidelines are essential as clinicians, researchers, funding agencies, and regulatory agencies increasingly acknowledge the importance of assessing symptom burden from the patient's perspective.

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Table 1.

Computing Scale Scores by Averaging the Available Items or Using Patient Mean Imputation

Patient	Method	Item 1	Item 2	Item 3	Item 4	Scale Score
001	Averaging Available Items	5	7	—	10	7.3
	Patient Mean Imputation	5	7	7.3	10	7.3
002	Averaging Available Items	4	—	3	—	3.5
	Patient Mean Imputation	4	3.5	3	3.5	3.5
003	Averaging Available Items	—	5	8	7	6.7
	Patient Mean Imputation	6.7	5	8	7	6.7
004	Averaging Available Items	2	0	—	—	1.0
	Patient Mean Imputation	2	0	1.0	1.0	1.0

Averaging the available items for each patient (proration) is equivalent to replacing each patient's missing scores with the mean of his or her observed scores (patient mean imputation). Missing scores are denoted by em dashes (—). Imputed scores are italicized and bolded.

Table 2.

Example Imputed Data Sets Following Multiple Imputation

Data Set	Patient	Item 1	Item 2	Item 3	Item 4
Observed Data Set Before Imputation	001	5	7	—	10
	002	4	—	3	—
	003	—	5	8	7
	004	2	0	—	—
Imputed Data Set 1	001	5	7	6.6	10
	002	4	3.6	3	5.1
	003	4.1	5	8	7
	004	2	0	1.3	1.9
Imputed Data Set 2	001	5	7	7.0	10
	002	4	1.4	3	2.6
	003	6.8	5	8	7
	004	2	0	0.8	1.6
Imputed Data Set 3	001	5	7	7.8	10
	002	4	2.9	3	4.6
	003	9.3	5	8	7
	004	2	0	3.5	1.3

Missing scores are denoted by em dashes (—). Imputed scores are italicized and bolded.

Table 3.

Missing Data Rate, Mean, and Standard Deviation for BFI and MPN-10 Items

Scale	Symptom	ET (N = 862)			PV (N = 726)			MF (N = 479)			Total (N = 2,067)		
		Missing Data Rate	Mean	SD	Missing Data Rate	Mean	SD	Missing Data Rate	Mean	SD	Missing Data Rate	Mean	SD
BFI Severity	Fatigue Right Now	0.1%	3.19	2.54	0.1%	3.49	2.63	0.0%	4.00	2.60	0.1%	3.48	2.61
	Usual Fatigue	0.3%	3.23	2.49	0.1%	3.56	2.55	0.2%	4.14	2.48	0.2%	3.56	2.53
	Worst Fatigue	1.7%	3.93	2.89	2.8%	4.22	2.93	2.7%	4.89	2.78	2.3%	4.25	2.90
	General Activity	1.6%	2.59	2.61	1.4%	3.11	2.71	0.6%	3.54	2.85	1.3%	2.99	2.73
BFI Interference	Mood	0.9%	2.60	2.72	1.0%	2.86	2.66	0.8%	3.18	2.65	0.9%	2.83	2.69
	Walking Ability	1.2%	2.41	2.78	1.1%	2.86	2.90	0.4%	3.58	3.10	1.0%	2.84	2.93
	Normal Work	2.0%	2.64	2.82	2.1%	3.03	2.84	0.6%	3.79	3.01	1.7%	3.05	2.91
	Relations with Other People	1.3%	1.92	2.54	1.0%	2.34	2.62	0.6%	2.48	2.60	1.0%	2.20	2.59
MPN-10	Enjoyment of Life	1.4%	2.19	2.75	1.8%	2.63	2.80	2.1%	3.06	2.87	1.7%	2.54	2.82
	Worst Fatigue	1.7%	3.93	2.89	2.8%	4.22	2.93	2.7%	4.89	2.78	2.3%	4.25	2.90
	Early Satiety	2.1%	2.06	2.64	1.7%	2.37	2.71	0.8%	3.21	2.97	1.6%	2.44	2.78
	Abdominal Discomfort	3.1%	1.57	2.27	2.6%	1.64	2.35	1.3%	2.61	2.84	2.5%	1.84	2.48
	Inactivity	4.1%	1.93	2.47	3.9%	2.40	2.76	4.0%	3.31	2.99	4.0%	2.41	2.75
	Concentration Problems	1.9%	2.23	2.70	2.6%	2.57	2.84	2.7%	2.79	2.88	2.3%	2.48	2.80
	Night Sweats	0.8%	1.85	2.70	1.4%	2.09	2.82	1.5%	2.84	3.15	1.2%	2.16	2.88
	Itching (Pruritus)	1.4%	1.69	2.56	1.4%	2.72	3.07	0.6%	2.10	2.86	1.2%	2.15	2.85
	Bone Pain	1.3%	1.71	2.59	2.3%	1.99	2.76	1.7%	2.20	2.90	1.7%	1.92	2.73
	Fever	2.8%	0.38	1.16	2.3%	0.43	1.25	2.1%	0.62	1.57	2.5%	0.45	1.30
	Weight Loss	1.2%	0.94	2.03	1.2%	1.16	2.24	2.5%	2.18	3.12	1.5%	1.30	2.44

Abbreviations: ET, essential thrombocythemia; PV, polycythemia vera; MF, myelofibrosis; BFI, Brief Fatigue Inventory; MPN-10, Myeloproliferative Neoplasms Symptom Assessment Form Total Symptom Score; N, sample size; SD, standard deviation.

Table 4.BFI and MPN-10 Items Completed ($N = 2,067$)

Scale	Items Completed	<i>N</i>	%
BFI Severity	3	2,013	97.4%
	2	53	2.6%
	1	1	0.1%
BFI Interference	6	1,970	95.3%
	5	70	3.4%
	4	9	0.4%
	3	9	0.4%
	2	3	0.2%
	1	6	0.3%
MPN-10	10	1,820	88.1%
	9	165	8.0%
	8	42	2.0%
	7	17	0.8%
	6	5	0.2%
	5	7	0.3%
	4	5	0.2%
	3	4	0.2%
	2	0	0.0%
	1	2	0.1%

Abbreviations: BFI, Brief Fatigue Inventory; MPN-10, Myeloproliferative Neoplasms Symptom Assessment Form Total Symptom Score; *N*, sample size.

Table 5.BFI and MPN-10 Inter-Item Correlations ($N = 2,067$)

BFI Item	BFI Inter-Item Correlations								
	1.	2.	3.	4.	5.	6.	7.	8.	
1. Fatigue Right Now									
2. Usual Fatigue	.88								
3. Worst Fatigue	.82	.88							
4. General Activity	.74	.75	.72						
5. Mood	.65	.65	.63	.73					
6. Walking Ability	.62	.64	.60	.72	.61				
7. Normal Work	.68	.71	.68	.83	.69	.80			
8. Relations with Other People	.60	.61	.58	.69	.73	.63	.70		
9. Enjoyment of Life	.61	.62	.60	.69	.73	.63	.69	.79	
MPN-10 Item	MPN-10 Inter-Item Correlations								
	1.	2.	3.	4.	5.	6.	7.	8.	9.
1. Worst Fatigue									
2. Early Satiety	.43								
3. Abdominal Discomfort	.38	.50							
4. Inactivity	.56	.47	.47						
5. Concentration Problems	.52	.38	.40	.58					
6. Night Sweats	.32	.31	.36	.33	.35				
7. Itching (Pruritus)	.33	.28	.29	.32	.35	.37			
8. Bone Pain	.37	.33	.38	.39	.42	.37	.35		
9. Fever	.22	.23	.25	.27	.24	.26	.20	.30	
10. Weight Loss	.28	.36	.28	.32	.25	.24	.19	.26	.27

Correlations among the three BFI severity items and the six BFI interference items are shaded. Abbreviations: BFI, Brief Fatigue Inventory; MPN-10, Myeloproliferative Neoplasms Symptom Assessment Form Total Symptom Score; N , sample size.

Table 6.

Comparison of Available-Case Analysis, Proration, and Multiple Imputation

Parameter	Available-Case Analysis	Proration	Multiple Imputation
BFI Severity			
<i>M</i> [95% CI]	3.76 [3.65, 3.87]	3.76 [3.65, 3.87]	3.77 [3.66, 3.88]
<i>N</i>	2,013	2,066	2,067
BFI Interference			
<i>M</i> [95% CI]	2.73 [2.62, 2.84]	2.74 [2.64, 2.85]	2.75 [2.64, 2.85]
<i>N</i>	1,970	2,058	2,067
MPN-10			
<i>M</i> [95% CI]	21.23 [20.46, 22.01]	21.40 [20.67, 22.13]	21.49 [20.77, 22.22]
<i>N</i>	1,820	2,049	2,067
BFI Severity, BFI Interference Association			
<i>r</i> [95% CI]	.78 [.77, .80]	.78 [.76, .80]	.78 [.77, .80]
<i>N</i>	1,928	2,058	2,067
BFI Severity, MPN-10 Association			
<i>r</i> [95% CI]	.74 [.72, .76]	.73 [.71, .75]	.73 [.71, .75]
<i>N</i>	1,815	2,049	2,067
BFI Interference, MPN-10 Association			
<i>r</i> [95% CI]	.77 [.75, .79]	.76 [.75, .78]	.77 [.75, .79]
<i>N</i>	1,771	2,043	2,067

Abbreviations: BFI, Brief Fatigue Inventory; MPN-10, Myeloproliferative Neoplasms Symptom Assessment Form Total Symptom Score; *N*, sample size; *M*, mean; *r*, product-moment correlation; CI, confidence interval.