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Running Head: Gender Differences in MPN

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Abstract

The myeloproliferative neoplasms including polycythemia vera, essential thrombocythemia and myelofibrosis, are distinguished by their debilitating symptom profiles, life-threatening complications and profound impact on quality of life. The role gender plays in myeloproliferative neoplasm symptomatology remains under-investigated. In this study, we evaluated how gender relates to patient characteristics, disease complications and overall symptom expression. A total of 2006 patients (polycythemia vera=711, essential thrombocythemia=830, myelofibrosis=460, unknown=5) were prospectively evaluated with patients completing the MPN-SAF and Brief Fatigue Inventory Patient Reported Outcome tools. Information on individual patient characteristics, disease complications and laboratory data was collected. Consistent with known literature, most female patients were more likely to have essential thrombocythemia (48.6% vs. 33.0%; p<0.001) and most male patients were more likely to have polycythemia vera (41.8% vs. 30.3%; p<0.001). Males demonstrated higher rates of thrombocytopenia (13.9% vs. 8.2%; p<0.001) and had higher red-blood cell transfusion requirements (7.3% vs. 4.9%; p=0.02) with lower mean disease durations (6.4 vs. 7.2 years, p=0.03). Despite no statistical differences in risk scores, receipt of most therapies or prior complications (hemorrhage, thrombosis), females had more severe and more frequent symptoms for most individual symptoms, along with overall total symptom score (22.8 vs. 20.3; p<0.001). Females demonstrated particularly burdensome scores for abdominal-related symptoms (abdominal pain/discomfort) and microvascular

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symptoms (headache, fatigue, insomnia, concentration difficulties, dizziness; all p<0.01). Despite vocalizing more severe symptom burdens, females documented similar quality of life scores to males. The results of this study suggest that gender contributes to myeloproliferative neoplasm heterogeneity by influencing phenotypic profiles and symptom expression.

Introduction

        The Myeloproliferative neoplasms (MPNs) have an acquired reputation for molecular complexity, clinical heterogeneity and profound impact on length and quality of life. Polycythemia vera (PV), essential thrombocythemia (ET) and myelofibrosis (MF) are debilitating MPNs associated with arterial and venous thrombosis, cytopenias, marked splenomegaly, persistent constitutional symptoms and predilection for transformation to acute myelogenous leukemia (AML) or MF (in ET and PV).

        Understanding how gender impacts MPN development, disease manifestation and progression has been a topic of emerging interest. As exemplified by increased prevalence of females in ET and males in PV, it has long been recognized that males and females may be impacted discordantly. However, advancing literature supports the potential for gender to influence genotypic expression and potentially clonal expansion. A recent investigation evaluating gene expression in circulating CD34+ cells from 19 *JAK2*V617F positive PV patients identified reduced gene expression in females (235 genes) as compared to males (571), while activating more than three times as many molecular pathways.[1] Females have also been shown to have dramatically lower *JAK2*V617F allele burdens.[2,3] More recent data has uncovered the existence of female-dominant MPN clusters (both PV and ET) typified by a high prevalence of laboratory abnormalities and sexuality-related complaints.[4]

Despite these new insights, little is known about how gender relates to symptomatic profiles. The timely development of MPN-specific Patient Reported Outcome (PRO) tools has allowed us to objectively quantify the MPN symptom burden and evaluate its impact on quality of life. The Myelofibrosis Symptom Assessment Form (MF-SAF), Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) and MPN-10 have been applied in both clinical and trial settings, yielding significant insight into how observed clinical and symptomatic heterogeneity may, in fact, follow predictable patterns and/or harbor otherwise unrecognized associations. In this study, we examine associations between gender and patient symptomatology, along with disease features, laboratory abnormalities and overall quality of life.

Methods

Survey Development and Collection:

This study was approved by the Mayo Clinic Institutional Review Board (IRB). Data was collected among an international cohort of patients with MPNs including ET, PV and MF. All patients were recruited via mechanisms described previously during the validation of the MPN-SAF.[5] A description of MPN SAF PRO development and validation may be found in Appendix 1. The process for language translation may also be found in Appendix 1 and is based on standard PRO translational methods.[6] In addition to the MPN-SAF, subjects also completed the Brief Fatigue Inventory (BFI)[7]. Data was collected in the English, Dutch, Italian, French, German, Chinese, Swedish and Spanish languages.

Gender was recorded based on patient self-reporting under the question of 'sex' with respondent options of 'male' or 'female'. Evaluation of cultural/regional variations in symptom expression involved comparison of Chinese patients with 'Western' patients which were composed of predominantly Caucasian individuals from western Europe and the United States of America.

Symptom Evaluation:

Symptoms listed on the MPN-SAF included the patient's perceptions of common MPN-related symptoms and overall quality of life (QOL) on a 0 (absent) to 10 (worst imaginable) scale. Assessed symptoms included items related to sad mood, quality of life, inactivity, concentration problems, abdominal pain/discomfort, dizziness, insomnia, night sweats, worst fatigue, early satiety, bone pain, numbness, cough, itching, headache, fever and weight loss. Total symptom score (TSS) was computed based on 10 symptom items. For individuals completing at least 6 of the 10 MPN-SAF TSS items, the survey was scored by multiplying the average score across items by 10 to achieve a 0 to 100 scaled score.

Prognostic Scoring:

Prognostic scoring for ET was calculated using the International Prognostic Scoring for Essential Thrombocythemia (IPSET).[8] This scoring system includes the variables of leukocyte count >/= 11 x 10(9)/L (1 point), age>/=60 (2 points), and history of thrombosis (1 point) to risk stratify patients to

low risk (0 points), intermediate risk (1-2 points) or high risk (3-4 points). Prognostic scoring for PV survival was calculated using the Leukemia 2013 prognostic scoring model.[9] This scoring system includes the variables of age >/=67 (5 points), age 57-66 (2 points), prior thrombosis (1 point) and WBC >/=15 x 10(9)/L (1 point) to risk stratify patients into low-risk (0 points), intermediate risk (1-2 points) and high risk (>/=3 points). Prognostic scoring for MF survival was calculated using the Dynamic International Prognostic Scoring System (DIPSS).[10] This scoring model includes the variables of hemoglobin <10 g/dL (2 points), age >/=65 (1 point), white blood cell count >/= 25 x 10(9)/L (1 point), the presence of constitutional symptoms (1 point) and >/=1 percent blasts (1 point) to risk stratify patients into low risk (0 points), intermediate-1 risk (1-2 points), intermediate-2 risk (3-4 points) and high risk (>4 points).

Statistical Analysis:

All patient symptom comparisons were adjusted for MPN type and age. Continuous variables were compared using analysis of variance and dichotomous data were compared using chi-square test. Statistical significance was set at $p < 0.05$. SAS version 9.3 (Cary, NC) was used for analysis.

Results

Patient Demographics

A total of 2006 (male; n=917 / female; n=1089) MPN patients completed the MPN-SAF and BFI (Table 1). MPN subtypes included polycythemia vera

(n=711), essential thrombocythemia (n=830) and myelofibrosis [n=460; PMF (68.3%); post-ET MF (18%); post-PV MF (13.7%)]. Patients were of expected age (mean 59.9 years, range 15-94) for the disorders and composed primarily of Chinese (27.1%) and French (23%) language groups. When separated by risk categories, most MF patients met DIPSS intermediate-1 risk (54.5%) followed by intermediate-2 risk (24.3%), low risk (18.3%) and high risk (3%). Most ET patients met intermediate risk (46.7%), followed by low risk (36.0%) and high risk (17.3%). For PV, most patients were in the high risk category (49.5%) followed by intermediate risk (29.7%) and low risk (20.7%). Mean hemoglobin (13.4, SD 3.17), white blood cell count (WBC, 8.9, SD 7.15), and platelet count (429.5, SD 269.72) were evaluated, along with laboratory abnormalities including anemia (8.5%), thrombocytopenia (10.7%) and leukopenia (10.0%). Prior thrombosis (21.2%) and prior hemorrhage (5.4%) were relatively uncommon and most patients (94.0%) had no red blood cell transfusion requirements.

Clinical Factors

When comparing clinical factors between genders, female patients were found to be slightly younger (59.3 vs. 60.7 years, p=0.02) with more patients under age 60 at the time of data collection (48.9% vs. 43.4%, p=0.01; Table 1). The prevalence of MPN subtypes also differed by gender (p=0.01) with most females having a diagnosis of ET (48.6%), followed by PV (30.3%) and MF (21.2%) and most male patients having a history of PV (41.8%) followed by ET (33.0%) and MF (25.2%). Gender distribution also differed by MPN subtype with

PMF more prevalent in males (74.8% vs. 61.7%; p=0.01), and post-ET MF more common in females (21.7% vs. 14.3%; p=0.01). Mean hemoglobin (13.8 vs. 13.0 g/dL, p<0.001) and white blood cell counts (9.5 vs. 8.5 x 10(9)/L, p=0.004) were higher in males whereas females demonstrated higher platelet counts (454.1 vs. 399.5 x 10(9)/L, p<0.001). Thrombocytopenia was most common in males (13.9% vs. 8.2%, p<0.001) and no differences were noted in prevalence of anemia or leukopenia (p>0.05). Males were also more likely to have a history of red blood cell transfusion requirements (7.3% vs. 4.9%, p=0.02). Risk scores, language prevalence, history of prior thrombosis or hemorrhage did not differ by gender (all p>0.05). Prior thrombosis was further stratified by gender and MPN type. No differences were noted in ET (male 23.5% vs. female 19.3%, p=0.156), PV (male 26.7% vs. 29.8%, p=0.339) or MF (male 12.8% vs. female 9.7%, p=0.298). Few differences were noted between genders when compared by prior therapies with the exception of higher rates of phlebotomy/venesection and givinostat/vorinostat use in males (both p<0.05; Figure 1).

MPN Symptoms by Gender

After adjusting for MPN subtype and age, overall total symptom scores (MPN TSS) were higher for females than males (22.8 [SD=17.0] vs. 20.3 [SD=16.3], p<0.001; Figure 2). Females also had higher individual symptoms scores for all individual MPN symptoms that met statistical significance (Figure 3). This included fatigue (4.5 vs. 4.0, p<0.001), early satiety (2.6 vs. 2.3, p=0.02), abdominal pain (1.6 vs. 1.2, p=0.001), abdominal discomfort (2.1 vs. 1.6,

p<0.001), headache (2.2 vs. 1.6, p<0.001), concentration difficulties (2.7 vs. 2.3, p=0.01), dizziness (2.5 vs. 2.0, p<0.001), numbness (2.6 vs. 2.2, p=0.001), insomnia (3.4 vs. 2.4, p<0.001), sad mood (2.6 vs. 2.3, p=0.01), night sweats (2.4 vs. 2.0, p=0.002) and bone pain (2.3 vs. 1.6, p<0.001). Items that did not differ between gender included inactivity, sexuality concerns, cough, pruritus, fevers, weight loss and overall quality of life. Fatigue was the most severe symptom for both genders. Symptom prevalence differed for many of the MPN individual questions (Figure 4). With the exception of weight loss (males 37.4% vs. females 31.7%, p=0.008), women demonstrated higher prevalence of all symptoms for all items demonstrating statistical differences from males. These symptoms included abdominal pain (46.0% vs. 40.8%, p=0.02), abdominal discomfort (55.2% vs. 50.7%, p=0.046), headache (58.1% vs. 49.1%, p<0.001), dizziness (61.0% vs. 56.6%, p=0.046), numbness (64.1% vs. 58.1%, p=0.007), insomnia (70.5% vs. 59.9%, p<0.001), night sweats (55.6% vs. 49.8%, p=0.01) and bone pain (53.2% vs. 43.4%, p<0.001).

MPN Symptoms by Region/Culture

The influence of region/culture was also explored amongst male and female patients by comparing the Chinese cohort (n=544) with the remaining Western cohort (European and United States of America; n=1462). Overall, female Chinese patients expressed more severe symptoms related to headaches (2.5 vs. 2.0, p=0.01), dizziness (3.1 vs. 2.2, p<0.0001), sexuality difficulties (4.6 vs. 2.9, p<0.0001), fevers (0.6 vs. 0.4, p=0.005) and weight loss (1.6 s. 1.1,

p=0.001) with higher Total Symptom Scores (22.2 vs. 19.5, p=0.023) and worse overall QOL (3.1 vs. 2.8, p=0.048; Figure 5). Highest scores for Chinese females were noted for sexuality related complaints (4.6/10) and insomnia (3.3/10). In contrast, Western females described worse fatigue (4.7 vs. 4.0, p=0.0003) and abdominal pain (1.7 vs. 1.1, p=0.0004). Highest scores for Western females were noted for fatigue (4.7/10) and insomnia (3.4/10).

Similar to Chinese females, Chinese males also expressed more severe symptoms related to headaches (1.9 vs. 1.4, p=0.001), dizziness (2.6 vs. 1.8, p<0.0001), sexuality problems (4.5 vs. 3.4, p=0.0001), fevers (0.7 vs. 0.4, p=0.0002) and weight loss (2.2 vs. 1.1, p<0.0001; Figure 6) than Western counterparts. Highest scores for Chinese males were noted for sexuality concerns (4.5/10) and fatigue (3.9/10). Similarly, highest scores for Western males were noted for fatigue (4.1/10) and sexuality concerns (3.4/10).

Discussion

The diversity of myeloproliferative neoplasms has made full characterization of their symptom profiles challenging. Polycythemia vera, essential thrombocythemia and myelofibrosis may concurrently impair length of survival, quality of life, and invariably efforts to manage both. For decades, MPN gender differences have been observationally documented but remained of low investigational priority given the paucity of exploratory tools. Objective examination of symptom heterogeneity has emerged an option via the

development of MPN-specific PRO tools (MF-SAF, MPN-SAF and MPN-10), enhanced precision of risk scoring algorithms and advancements in genomic sequencing.[5,11,12] Applying many of these novel instruments, this study represents the first large-scale investigation into the correlates between gender, clinical features and patient symptomatology.

This investigation yielded number of important findings. The first is the observance that female patients were more likely to have ET (48.6%) and male patients were more likely to have PV (30.3%). Consistent with previous findings, literature has historically supported a prevalence of females in ET and prevalence of males in PV.[13-17] Gender discrepancies within the hematological malignancies are not unique to MPNs. Other disorders such as acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL) and multiple myeloma (MM), have all demonstrated similar discordances in gender prevalence.[18,19] Though the etiology driving this observation remains unclear, sex chromosome complement/aberrations/aneuploidy, sex-steroid influence, immune-competence, and gene expression may be potential contributors.[20-23] Evaluation of these prospective sources was beyond the scope of this investigation but are worthy of exploring in future studies.

This study also found males and females to have similar rates of thrombosis. Previous investigations have shown that thrombotic risk typically differs by sex amongst the MPN subtypes.[2,24-26] Within the ECLAP study,

female PV patients were more likely to suffer thrombotic complications (11% vs 8%), particularly within the splanchnic system.[27] Similarly, a recent international collaborative study of 891 ET patients identified that on multivariable analysis, only male gender was predictive of venous thrombosis.[28] Gender also appears to influence the location of vascular events. A recent investigation identified that women were more likely to experience macrothrombosis within the abdominal venous system (hepatic, portal, mesenteric or splenic veins) whereas males were more likely to experience deep venous system events including extremity thrombosis and pulmonary emboli.[16]

Though gender influence on thrombosis pathogenesis remains unclear, mounting evidence suggests that both the type and ratio of circulating sex-steroids plays an important role in the thrombotic cascade. In an investigation involving exogenous sex-steroid administration, ET patients exposed to hormone replacement therapy (HRT; estrogen only) had similar rates of arterial and venous thrombosis when compared to ET patients not on therapy.[29] Importantly, this finding conflicts with studies of healthy populations where females using HRT have been observed to be at greater thrombotic risk. However, ET patients utilizing oral contraceptive therapy (OCP, estrogen and progesterone combined) had increased rates of venous thrombosis, and specifically, a 5-fold increased risk of splanchnic venous thrombosis (15% vs. 3%). From a hormonal standpoint, it remains unclear why male ET patients face higher thrombotic risk than females and serves to show that pathogenesis is likely multifactorial. In our population

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specifically, it remains unclear why males and females demonstrated similar rates of thrombosis, independent of subtype. It should be noted that this investigation also did not specify the location or type of thrombosis (arterial vs. venous) which may have further shed light into this discrepancy.

We find it interesting that despite not differing by total number of thrombotic events, our female population still described more abdominal pain. Given that this study utilized reported events only (and did not prospectively investigate for thrombosis), it is possible that unrecognized macrothrombosis was present in the abdominal cavity of female patients, accounting for symptomatology. Alternatively, the source may relate to discrepancies in splenic size which were not investigated in this study or symptom expression differences which are discussed below.

The observation that males and females reported different symptom burdens remains a major finding. Overwhelmingly, females described symptoms with greater frequency and severity than males. In particular, abdominal complaints (abdominal pain, discomfort) and microvascular symptoms (headache, fatigue, insomnia, concentration difficulties, dizziness) dominated the female symptom burden. Factors that might have accounted for higher symptom scores (such as anemia, high-risk disease status or increased counts of hemorrhagic/thrombotic complications) were not observed at higher rates in females. In fact, males were more likely to have increased transfusion

requirements (despite describing less fatigue) and thrombocytopenia. The source of these observations is uncertain. It is well recognized that the prevalence of abdominal pain is higher among females.[30] Irritable bowel syndrome (IBS), a chronic syndrome of abdominal symptoms characterized by pain, discomfort and alterations in bowel habits, has been reported to exist in a female-to-male ratio of 3:1 and remains a common source of abdominal complaints in younger populations [31] However, the prevalence of IBS declines in individuals over 60 and given the average age of MPN females, IBS is unlikely to serve as a primary symptom driver. As we consider patient symptomatology, it is plausible that in addition to facing higher macrovascular risks, females also incur more microvascular events. Microthrombosis contributes to microvascular symptoms (lightheadedness, dizziness, vertigo, concentration problems, numbness/tingling and sexual dysfunction) by compromising endothelial function and inducing local hypoxia.[32] In this study, females clearly described microvascular symptoms more frequently and with more severity than males. Mechanisms that may account for discrepant risks of microvascular dysfunction are worthy of further exploration and may parallel those driving macrothrombosis. Underreporting of microvascular symptoms by males is also a potential source and discussed further below. Congruent with previous investigations, males and females described similar degrees of sexual dysfunction and fatigue remained the most symptomatic facet of the disease burden.

Patient ethnicity and culture also appear to contribute to symptom burden. Variations in symptom expression were noted when Western and Eastern patients were compared. Independent of gender, Chinese patients described more microvascular symptoms (headaches, dizziness) and more concerns related to sexuality. In contrast, fatigue was the most prominent symptom for Western male and female patients. Eastern and Western MPN variations underscored by the presence of fundamental biological and clinical differences have been increasingly discussed within the literature.[33,34] For example, Eastern myelofibrosis patients are more likely to be younger and less likely to struggle with constitutional symptoms or splenomegaly. Survival differences between the two cohorts has also been observed, with median survival slightly improved in those of Chinese ethnicity. Given the subjectivity inherent to symptom reporting, it remains unclear whether the differences in MPN-SAF scoring between races were related to norms of cultural expression (exp. willingness to verbalize sexuality complaints) or the natural outworkings of true genotypic and phenotypic variances between races.

The potential that our observations relate to reporting discrepancies is also an important discussion. Within the literature, females tend to describe more numerous and more intense symptoms than males, independent of location or organ system. In a study of 13,538 non-patient community residents, participants evaluated the lifetime prevalence of non-menstrual complaints and 20 of the 22 most common symptoms were vocalized more frequently by

females.[35] Similarly, experimental studies involving induction of pain have shown females to have a lower threshold of pain tolerance and report more symptoms than males.[36] Driving these findings may be biological differences in somatic and visceral sensation, sex-influenced descriptiveness in symptom labeling and reporting, social acceptance of symptom revelation, sex-variances in the prevalence of depression and anxiety and gender biases inherent to the research process. Some studies have suggested that females engender greater bodily vigilance, potentially as an innate contrivance to optimize fertility.[37,38] Other studies advocate that social cues have impressed upon males the importance of limiting expression of discomfort/illness, upholding a stoic appearance and underemphasizing complaints.[39]

Independent of the source, we find it intriguing that MPN females scored the same quality of life despite more frequent and severe symptomatology. The literature supports health-related quality of life as typically being rated lower among females. This has traditionally been attributed to the higher prevalence of disability and chronic conditions in this population.[40] However, in this study comorbidities were similar between the two sexes. It is plausible that MPN females have socially adapted to compensate for their intensified symptomatic burdens. Alternatively, female patients may simply be more disposed to vocalize their complaints. We also note that females described higher symptom burdens but maintained similar risk scores to men. This information corroborates previous

findings of the MPN Symptom Burden study that identified MPN symptoms are not surrogates for disease severity.[4]

It is important to recognize that there are a number of limitations to this exploratory investigation. The first is that the term 'gender' is being used synonymously with genotypically-defined 'sex'. As stated, the surveys allowed patients to self-report their sex as either 'male' or 'female'. Though it may be assumed that the recorded value referred to genotypic makeup, it is possible that some patients recorded their 'gender identity' instead, which may not be synonymous with chromosomal makeup. Should this have occurred, we believe number of cases small and likely consistent with the prevalence of discordant associations in the community. We furthermore lack information on the exact location of these events (peripheral vs. central). We also note that males also had increased transfusion requirements despite similar rates of anemia. We suspect that this likely related to the averaging of pre- and post-transfusion hemoglobin checks within males, resulting in a falsely high hemoglobin level. It is worthy to note that the majority of patients within this MPN population were of low to intermediate risk which potentially skews symptom burden towards lower values. Though evaluation of symptom burden between genders by risk category was beyond the scope of this study, future investigations could further explore this to see if symptom progression differs between the sexes. It is important to note that the imposed 'self-reporting' format also has inherent flaws. However, we believe the use of validated MPN-specific PRO tools greatly

improves the cogency of the results. In addition, medical team members were primarily responsible for all data collection not related to symptom expression, conceivably limiting errors in the recording process. It is regrettable that driver mutations was not available for analysis as this may have offered insightful information.

The convergence of technological innovations with novel symptom assessment tools has revolutionized the treatment landscape for MPNs. As evidenced, few fields of study can boast of the rapidity and cooperative manner via which pioneering research has translated into improved patient outcomes. In this study, we've determined that gender integrally relates to disease features and symptom burden. Results further underscore the importance of considering each sex individually as treatment regimens are built. Understanding that males may be less likely to vocalize their MPN symptoms should influence clinicians to explore potentially under-expressed complaints. Similarly, acknowledging that females may face greater symptom burdens should motivate providers to consider novel therapies and explore trial options. This exploratory study affirms the importance including gender as a contributor to heterogeneity and point of investigation in future studies.

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Table 1. MPN Patient Demographics by Gender

	Females (N=1089)	Males (N=917)	Total (N=2006)	P Value
Mean Age	59.3 (14.36)	60.7 (12.64)	59.9 (13.61)	0.02
Age <60	532 (48.9%)	397 (43.4%)	929 (46.4%)	0.01
MPN Subtype (n, %)				<0.001
ET	528 (48.6%)	302 (33.0%)	830 (41.5%)	
PV	329 (30.3%)	382 (41.8%)	711 (35.5%)	
MF	230 (21.2%)	230 (25.2%)	460 (23.0%)	
MF (n, %)				0.01
PMF	142 (61.7%)	172 (74.8%)	314 (68.3%)	
ET-MF	50 (21.7%)	33 (14.3%)	83 (18%)	
PV-MF	38 (16.5%)	25 (10.9%)	63 (13.7%)	
Mean MPN Duration (years, SD)	7.2 (7.0)	6.4 (6.5)	6.8 (6.9)	0.03
Language (n, %)				0.19
Chinese	292 (26.8%)	252 (27.5%)	544 (27.1%)	
Dutch	118 (10.8%)	118 (12.9%)	236 (11.8%)	
English	75 (6.9%)	82 (8.9%)	157 (7.8%)	
French	257 (23.6%)	205 (22.4%)	462 (23%)	
German	72 (6.6%)	41 (4.5%)	113 (5.6%)	
Italian	103 (9.5%)	83 (9.1%)	186 (9.3%)	
Spanish	112 (10.3%)	82 (8.9%)	194 (9.7%)	
Swedish	60 (5.5%)	54 (5.9%)	114 (5.7%)	
MF DIPSS Risk (n, %)				0.55
Low	24 (20.7%)	19 (16.0%)	43 (18.3%)	
Int-1	64 (55.2%)	64 (53.8%)	128 (54.5%)	
Int-2	24 (20.7%)	33 (27.7%)	57 (24.3%)	
High	4 (3.4%)	3 (2.5%)	7 (3%)	
ET IPSET Risk (n, %)				0.11
Low	176 (37.8%)	86 (32.7%)	262 (36%)	
Int	218 (46.9%)	122 (46.4%)	340 (46.7%)	
High	71 (15.3%)	55 (20.9%)	126 (17.3%)	
PV Risk (n, %)				0.30

Low	49 (19.1%)	66 (22.1%)	115 (20.7%)	
Int	71 (27.7%)	94 (31.4%)	165 (29.7%)	
High	136 (53.1%)	139 (46.5%)	275 (49.5%)	
Anemia (<10 g/dL; n, %)	78 (8.4%)	66 (8.7%)	144 (8.5%)	0.84
Leukopenia (<4.0 x 10(9)/L)	91 (9.9%)	77 (8.7%)	168 (10.0%)	0.83
Thrombocytopenia (<150 x 10(9)/L; n, %)	76 (8.2%)	105 (13.9%)	181 (10.7%)	<0.001
Mean hemoglobin (SD)	13.0 (3.36)	13.8 (2.86)	13.4 (3.17)	<0.001
Mean WBC (SD)	8.5 (6.09)	9.5 (8.24)	8.9 (7.15)	0.004
Mean Platelet Count (SD)	454.1 (269.42)	399.5 (267.21)	429.5 (269.72)	<0.001
Lab Abnormality (n, %)	206 (22.2%)	200 (26.3%)	406 (24%)	0.049
Prior Thrombosis (n, %)	217 (20.4%)	200 (22.2%)	417 (21.2%)	0.34
Prior Hemorrhage	55 (5.1%)	52 (5.7%)	107 (5.4%)	0.53
RBC Transfusion Requirements	53 (4.9%)	67 (7.3%)	120 (6.0%)	0.02

Legend

Figure 1. Percentage of MPN patients who have received prior therapies (x axis) compared by gender.
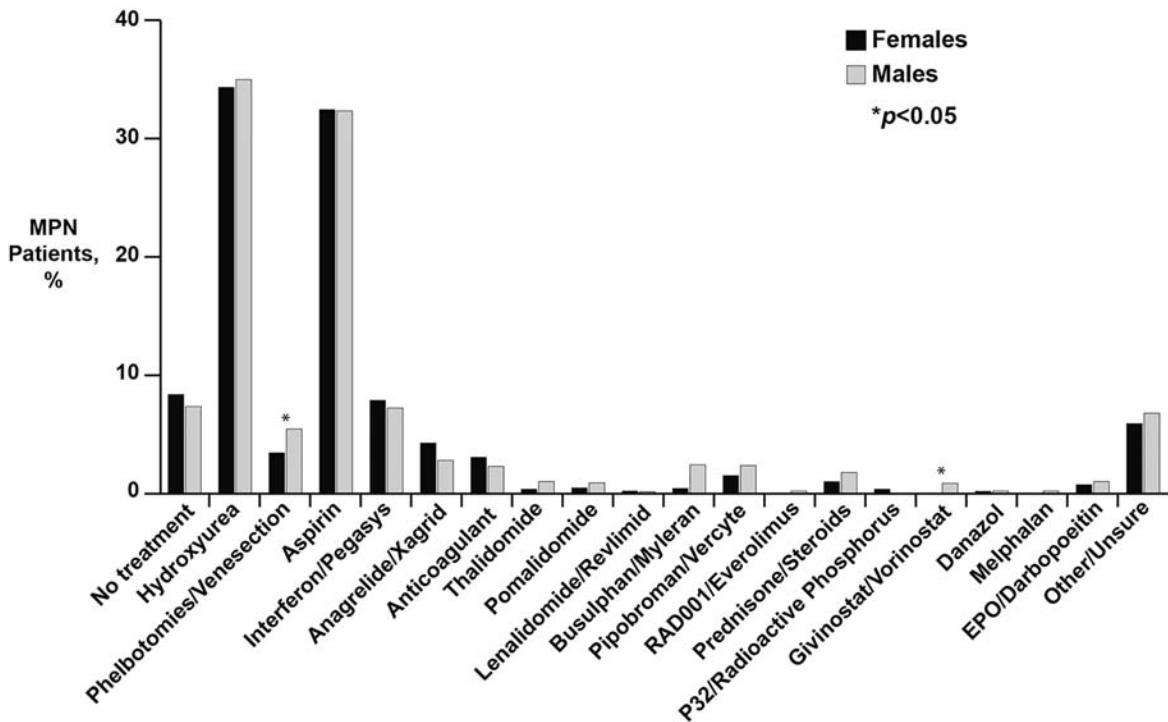
Figure 2.   Evaluation of total number of patients in each gender (y axis) when compared by total MPN-SAF TSS value (x axis).
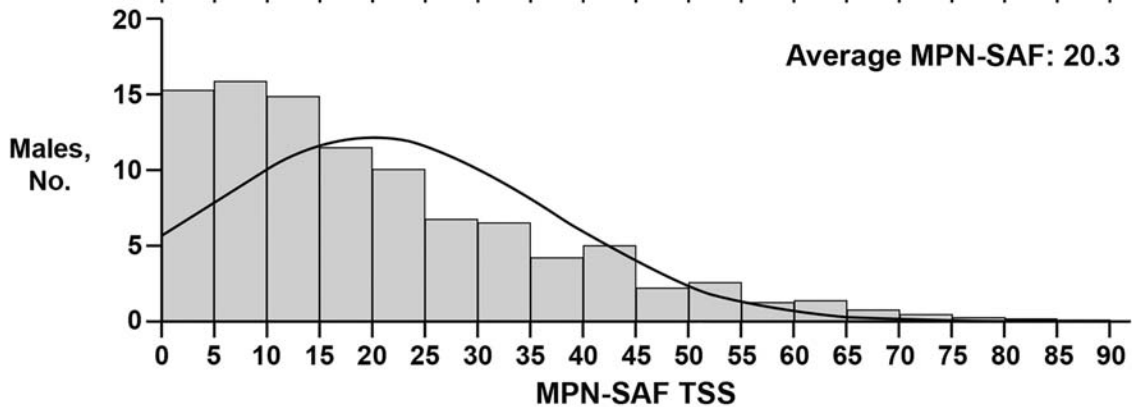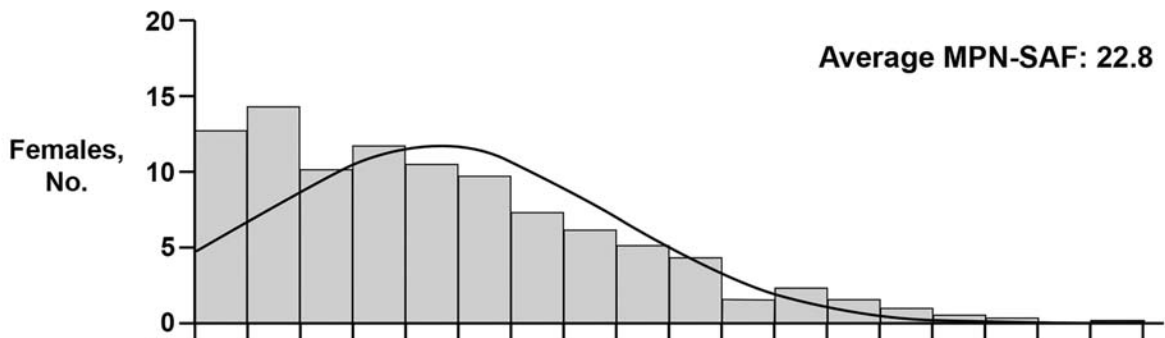
Figure 3. Comparison of Total MPN SAF (y axis) for individual items (x axis) between male and female genders.
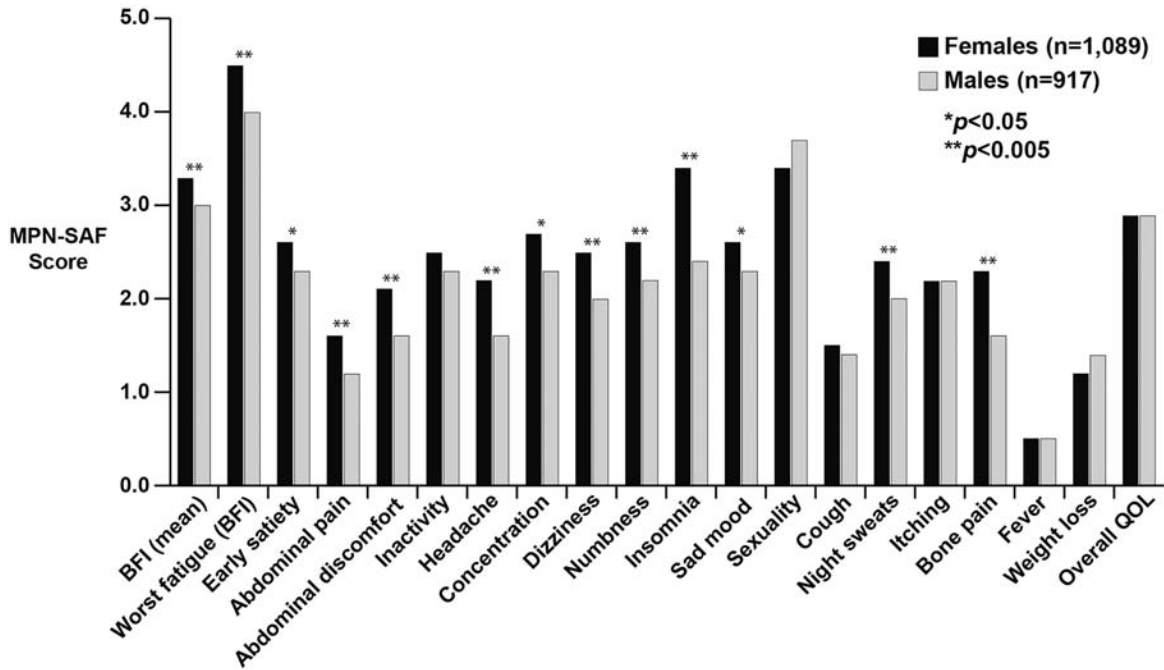
Figure 4. Comparison of MPN SAF symptom prevalence (y axis) for individual items (x axis) by gender.
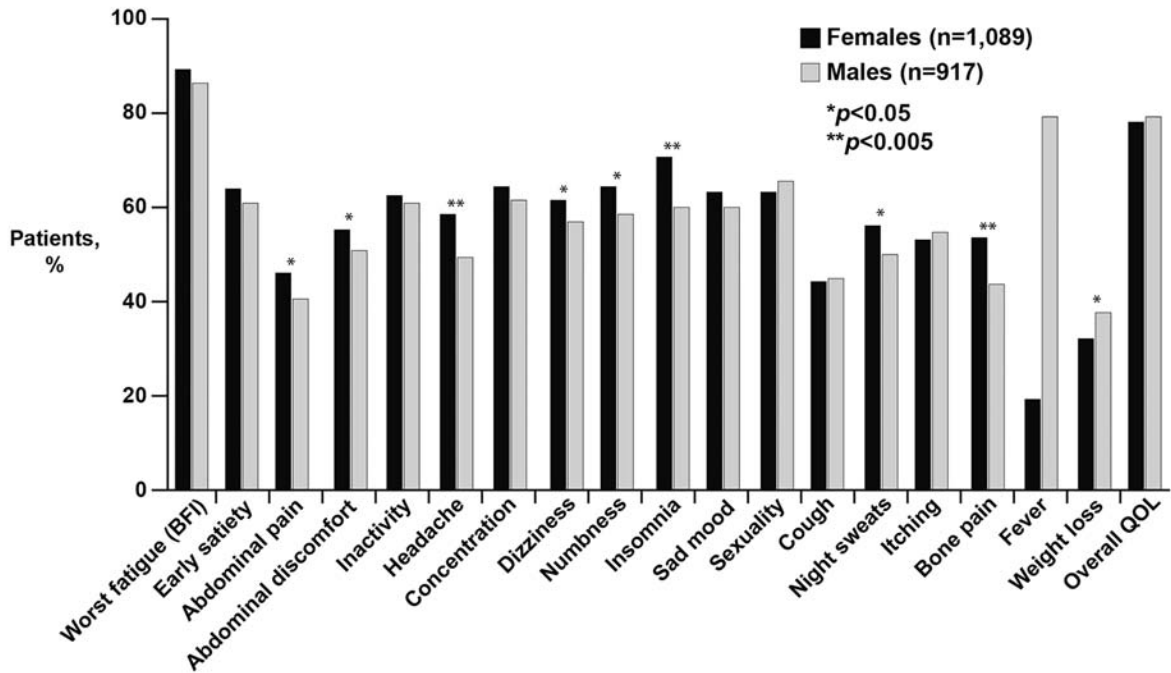
Figure 5. Comparison Chinese and Western female patient scores for individual MPN-SAF items.

Figure 6. Comparison Chinese and Western male patient scores for individual MPN-SAF items

Average MPN-SAF: 22.8

Average MPN-SAF: 20.3

Figure legend:
- **Females (n=1,089)**
- **Males (n=917)**

*p<0.05
**p<0.005

MPN-SAF Score

X-axis categories: BFI (mean), Worst fatigue (BFI), Early satiety, Abdominal pain, Abdominal discomfort, Inactivity, Headache, Concentration, Dizziness, Numbness, Insomnia, Sad mood, Sexuality, Cough, Night sweats, Itching, Bone pain, Fever, Weight loss, Overall QOL

Legend:
- ■ Females (n=1,089)
- □ Males (n=917)

*p<0.05
**p<0.005

Y-axis: Patients, %

X-axis categories: Worst fatigue (BFI), Early satiety, Abdominal pain, Abdominal discomfort, Inactivity, Headache, Concentration, Dizziness, Numbness, Insomnia, Sad mood, Sexuality, Cough, Night sweats, Itching, Bone pain, Fever, Weight loss, Overall QOL
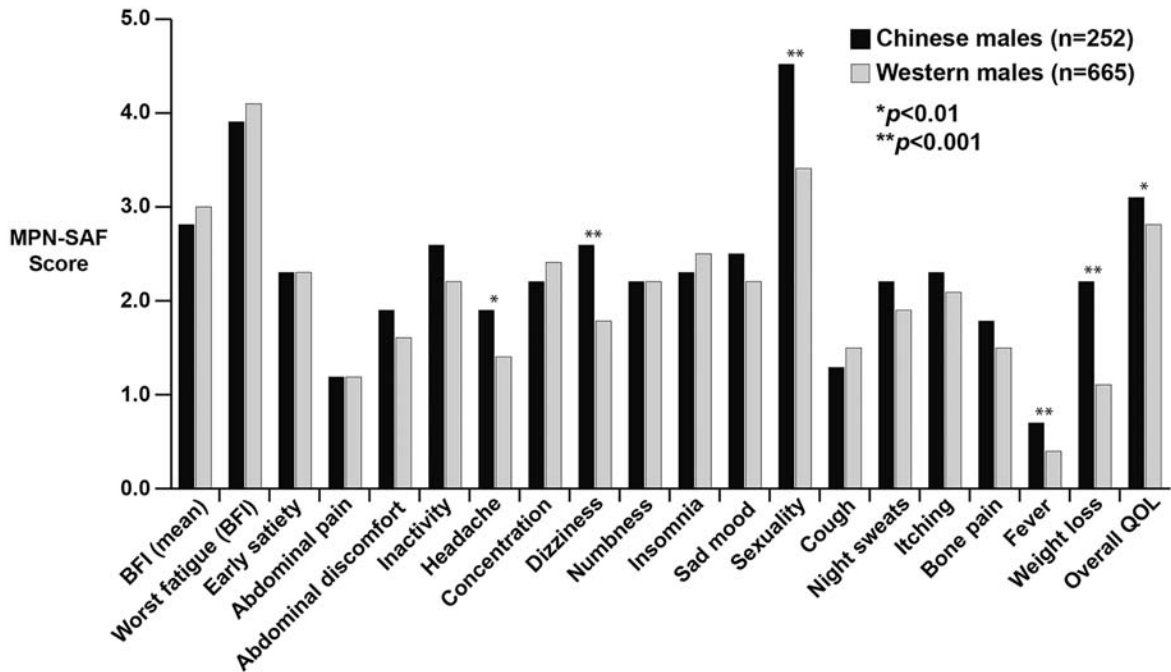
Appendix 1: MPN-SAF PRO Development and Validation

The MPN-SAF included existing questions from the Myelofibrosis Symptom Assessment Form (MF-SAF; fatigue, early satiety, abdominal pain, abdominal discomfort, inactivity, cough, night sweats, pruritus, bone pain, fever, weight loss and quality of life) and was expanded to include 'problems with concentration', 'difficulty sleeping', 'numbness/tingling', 'depression or sad mood' and 'problems with sexual desire or function'. All questions were scored on a scale from 0 (as good as it can be/absent) to 10 (as bad as it can be/worst-imaginable). The survey was drafted in English format and translated into other languages via an established Patient Reported Outcome translation method. Translation for each language involved three independent survey translations created by translators fluid in both English and the respective language requiring translation. A fourth translator then compares the three translator manuscripts to develop a consensus translation.

Upon completion of the survey, patients were recruited from academic, government-funded and private practice international medical centers. Patients were requested to self-complete the MPN-SAF during an office visit. Patients were also provided the opportunities to include additional symptoms omitted from the survey via open-ended questions.

Physicians who were blinded to patient responses were required to rank patient symptoms on the same 0-10 scale as well as document patient disease status including laboratory data, treatment history and prognostic scores. Anova F tests or 2-sample t tests were used to assess continuous variables whereas x^2 tests were used to compare categorical variables. The relationships between variables was assessed using Pearson correlations. Patient scores between language groups were adjusted by disease type using general linear models and intraclass correlation coefficient (ICC) was analyzed on the basis of a 2-way ANOVA model.

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