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Symptom burden profile in myelofibrosis patients with thrombocytopenia: Lessons and unmet needs

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Abstract

Myelofibrosis is a myeloproliferative neoplasm associated with progressive cytopenias and high symptom burden. MF patients with thrombocytopenia have poor prognosis but the presence of thrombocytopenia frequently precludes the use of JAK2 inhibitors. In this study, we assessed quality of life and symptom burden in 418 MF patients with (n = 89) and without (n = 329) thrombocytopenia using prospective data from the MPN-QOL study group database, including the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) and Total Symptom Score (MPN10). Thrombocytopenia, defined as platelet count $< 100 \times 10^9/L$ (moderate $51\text{--}100 \times 10^9/L$; severe $50 \times 10^9/L$), was associated with anemia (76% vs. 45%, $p < 0.001$), leukopenia (29% vs. 11%, $p < 0.001$), and need for red blood cell transfusion (35% vs. 19%, $p = 0.002$). Thrombocytopenic patients had more fatigue, early satiety, inactivity, dizziness, sad mood, cough, night sweats, itching, fever, and weight loss; total symptom scores were also higher (33 vs. 24, $p < 0.001$). Patients with severe thrombocytopenia were more likely to have anemia (86% vs. 67%, $p = 0.04$), leukopenia (40% vs. 20%, $p = 0.04$), and transfusion requirements (51% vs. 20%, $p = 0.002$) but few differences in symptoms when compared to patients with moderate thrombocytopenia. These results suggest that MF patients with thrombocytopenia experience greater symptomatic burden than MF patients without thrombocytopenia and may benefit from additional therapies.

Keywords

Myeloproliferative neoplasm; Myelofibrosis; Thrombocytopenia; Quality of life; Symptomatology

1. Introduction

Myelofibrosis (MF) is a clonally derived Philadelphia chromosome negative myeloproliferative neoplasm (MPN) associated with progressive cytopenias and potential to transform into acute myelogenous leukemia (AML). MPNs are often associated with dysregulated signaling of the Janus kinase-signal transducers and activators of transcription (JAK-STAT) pathway. The most common somatic mutation, JAK2 V617F, occurs in 50–60% of patients with MF [1–3].

MF patients exhibit a high degree of symptomatology with potentially dramatic impacts on quality of life (QOL). Common symptoms include abdominal pain, bone pain, fatigue,

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pruritus, night sweats, fever, and weight loss [4]. Cytopenic derangements are common and closely linked to disease progression. In particular, thrombocytopenia is a proven negative prognostic indicator and predictor of transformation to AML [5]. MF patients with platelets under $50 \times 10^9/L$ have more frequent anemia and leukopenia and higher rates of both hemorrhagic and thrombotic complications compared to MF patients with higher platelet counts [6].

Treatment options are limited for patients with thrombocytopenia. Ruxolitinib, a JAK1/JAK2 inhibitor, was shown in the phase III COMFORT-I [7] and COMFORT-II [8] trials to have significant symptomatic benefit in intermediate-2 or high risk MF patients with platelets of at least $100 \times 10^9/L$. However, the drug may paradoxically contribute to thrombocytopenia and is presently only indicated in patients with platelets of at least $50 \times 10^9/L$.

To date, no investigation has evaluated the correlations between patient symptomatology and platelet count. In this study, we aimed to characterize the symptom burden in MF patients with and without thrombocytopenia using prospectively collected quality of life data. We also assessed differences in clinical characteristics and symptomatology among patients with varying degrees of thrombocytopenia.

2. Methods

2.1. Patient selection

This study was approved by the Institutional Review Board (IRB) of the Mayo Clinic. Data were prospectively collected from an international pool of MPN patients recruited from academic, private practice, and government-funded centers. A total of 418 patients were included in the study; all had a diagnosis of MF. Patients completed the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF), Brief Fatigue Inventory (BFI), and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) via self-reporting. All surveys were completed in the patients' native language (English, German, Dutch, French, Spanish, Italian, Chinese, and Swedish) and translated to English using standard PRO translational methods. Clinical information was also gathered at the time of survey collection and included laboratory information, treatment history, prognostic scoring, and physical examination results as assessed by clinicians.

In this study, thrombocytopenia was defined as a platelet count less than $100 \times 10^9/L$, anemia was defined as hemoglobin less than 11 g/dL, and leukopenia was defined as a white blood cell (WBC) count less than $3.5 \times 10^9/L$. Moderate thrombocytopenia was defined as a platelet count of $51\text{--}100 \times 10^9/L$, and severe thrombocytopenia was defined as a platelet count less than or equal to $50 \times 10^9/L$. A broader categorization of patients with "lab abnormality" included any patient who met criteria for anemia, leukopenia, or thrombocytopenia.

2.2. Symptom evaluation

Symptom evaluation was performed using the previously validated MPN-SAF [9]. All participants were required to complete at least six of the ten MPN-SAF symptom questions to meet study inclusion criteria. Symptoms were scored on a scale from 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be), and items specifically assessed quality of life (QOL), early satiety, abdominal pain or discomfort, inactivity, headache, difficulty with concentration, dizziness, numbness, insomnia, sad mood, difficulty with sexual desire or function, cough, night sweats, itching, bone pain, fever, and weight loss. Total symptom score (TSS) was calculated by multiplying the average score across items by ten to achieve a 0–100 scaled score. The MD Anderson BFI was used to assess worst fatigue rating [10]. Splenomegaly was assessed by clinicians based on physical examination and reported as an estimated value in centimeters.

2.3. Prognostic scoring

The Dynamic International Prognostic Scoring System (DIPSS) was used to calculate MF prognostic scores [11]. Patients were stratified into low risk (0 points), intermediate-1 risk (1–2 points), intermediate-2 risk (3–4 points), and high risk (> 4 points) using the following scoring variables: circulating blasts greater than or equal to 1% (1 point), constitutional symptoms (1 point), age greater than 65 years (1 point), WBC count greater than or equal to $25 \times 10^9/L$ (1 point), and hemoglobin less than 11 g/dL (2 points).

2.4. Statistical analysis

Demographics, clinical variables, and symptom scores were compared between subgroups of MF patients with and without thrombocytopenia using analysis of variance (ANOVA) F-tests for continuous variables or Chi-squared tests for discrete data. Comparisons between patients with severe and moderate thrombocytopenia were done similarly. Statistical significance was set at $p < 0.05$. All statistical analyses were conducted using SAS software version 9.4 (SAS Inc., Cary, NC).

3. Results

3.1. Demographic and clinical characteristics

A total of 418 MF patients with ($n = 89$) and without ($n = 329$) thrombocytopenia completed the MPN-SAF and BFI. Patients with thrombocytopenia were further classified as having moderate ($n = 46$) or severe ($n = 43$) thrombocytopenia. Demographic and clinical characteristics are shown in Tables 1 and 2. Mean age overall was 60.2 (SD = 12.3) years and 47.4% of patients were male. Most patients had a diagnosis of primary myelofibrosis (69.4%) and met intermediate-1 DIPSS risk criteria (54.9%). Anemia (51.6%) and laboratory abnormalities (62.4%) were common. However, most patients had no history of prior thrombosis (11.3%), prior hemorrhage (5.1%), or RBC transfusion requirements (22.5%).

Total Symptom Scores (TSS) stratified by presence or absence of clinical and lab abnormalities are shown in Table 3. Patients with anemia ($p < 0.001$), any lab abnormality ($p < 0.001$), those requiring RBC transfusion ($p = 0.003$), and those with higher DIPSS risk

scores ($p < 0.001$) reported significantly higher TSS. There was no significant association between leukopenia and overall symptom burden as reported by TSS, though a trend toward high TSS in patients with leukopenia was observed.

Overall, the highest symptom scores in this cohort were reported for worst fatigue (4.8/10), sexuality (4.3/10), overall compromise in QOL (3.4/10), and inactivity (3.2/10). In contrast, lowest scores were reported for fever (0.6/10), cough (1.6/10), abdominal pain (1.7/10), and headache (1.7/10).

3.2. Impact on symptoms and phenotype: thrombocytopenia vs. no thrombocytopenia

Patient demographics, clinical features, prognostic scores, and MPN-SAF and BFI results including symptom scores (Fig. 1) and prevalence (Fig. 2) were compared among MF patients with and without thrombocytopenia. Overall, patients with thrombocytopenia were slightly younger (57.4 vs. 61.0 years, $p = 0.01$), had longer disease duration (11.9 vs. 8.8 years, $p = 0.05$), had more RBC transfusion requirements (34.8% vs. 19.1%, $p = 0.002$), were more likely to have PMF (82% vs. 66%, $p = 0.01$), and had more laboratory abnormalities including anemia (76.4% vs. 44.8%, $p < 0.001$) and leukopenia (29.2% vs. 10.6%, $p < 0.001$). Patients with thrombocytopenia did not differ from patients without thrombocytopenia by DIPSS risk score, gender, history of prior thrombosis, or prior hemorrhage (Table 1).

Patients with thrombocytopenia experienced significantly worse symptom burden in comparison to patients without thrombocytopenia with higher symptoms scores for worst fatigue (5.6 vs. 4.6, $p = 0.002$), inactivity (4.4 vs. 2.9, $p < 0.001$), impaired overall QOL (4.3 vs. 3.1, $p < 0.001$), dizziness (3.2 vs. 2.4, $p = 0.046$), sad mood (3.8 vs. 2.5, $p < 0.001$), cough (2.2 vs. 1.4, $p = 0.003$), night sweats (3.4 vs. 2.6, $p = 0.02$), itching (2.9 vs. 1.8, $p = 0.001$), fever (0.9 vs. 0.5, $p = 0.04$), weight loss (3.3 vs. 1.9, $p < 0.001$), and early satiety (3.8 vs. 2.9, $p = 0.01$); see Fig. 1. Overall TSS was also significantly higher (32.8 vs. 24.1, $p < 0.001$) in patients with thrombocytopenia. There were no differences in abdominal discomfort, abdominal pain, bone pain, headache, poor concentration, sexual dysfunction, numbness, or insomnia. With regard to prevalence of symptoms, weight loss (72.1% vs. 41.3%, $p < 0.001$) and decline in overall QOL (90.8% vs. 81.9%, $p = 0.045$) were seen with significantly higher frequency in the thrombocytopenic group compared to MF patients without thrombocytopenia; see Fig. 2.

3.3. Impact on symptoms and phenotype: moderate vs. severe thrombocytopenia

Patient demographics, clinical features, prognostic scores, and MPN-SAF and BFI results were compared between MF patients with moderate (platelets $51\text{--}100 \times 10^9/\text{L}$) and severe (platelets $< 50 \times 10^9/\text{L}$) thrombocytopenia. As seen in Table 2, patients with severe thrombocytopenia were more likely to have anemia (86.0% vs. 67.4%, $p = 0.04$), leukopenia (39.5% vs. 19.6%, $p = 0.04$), and require RBC transfusions (51.2% vs. 19.6%, $p = 0.002$). Patients did not differ by MF subtype, age, gender, history of prior thrombosis, prior hemorrhage, DIPSS risk scores, or mean MPN duration. No differences were noted in individual or total symptom scores between groups (Figs. 3 and 4) with one exception;

patients with severe thrombocytopenia experienced less frequent sad mood (60.5% vs. 82.2%, $p = 0.02$).

4. Discussion

As a group, myelofibrosis patients experience a high symptom burden affecting quality of life. In this analysis, we demonstrate that MF patients with thrombocytopenia exhibit an even greater symptom burden, as well as distinct clinical characteristics, when compared to MF patients without thrombocytopenia. Several important symptoms were both more prevalent and more severe in MF patients with thrombocytopenia including fatigue, inactivity, early satiety, and impaired quality of life. In accordance with this, the total symptom score was also significantly higher. Notably, there do appear to be some symptom clusters for which there are no major differences between MF patients with and without thrombocytopenia. These include symptoms related to abdominal complaints (pain, discomfort), neurological issues (headache, poor concentration, numbness, insomnia), or extramedullary hematopoiesis (bone pain, abdominal pain).

Interestingly, data from this study do not demonstrate a significant association between DIPSS risk category and either presence or degree of thrombocytopenia, despite the fact that thrombocytopenia is a known risk factor for disease advancement. In fact, the DIPSS Plus score, an updated version of the DIPSS scoring system, includes platelet count in its calculation [5]. While we did observe a trend toward patients with lower platelet counts having higher DIPSS scores, this did not reach statistical significance. This may be because other clinical factors included in the DIPSS score such as age did not differ significantly between study groups, thus diluting the effect of thrombocytopenia or other laboratory abnormalities. The fact that thrombocytopenic patients experience a high degree of symptoms despite them not being in a higher risk category suggests that clinical risk score is not necessarily an accurate surrogate for symptom burden or quality of life for MF patients. This aligns with previously published data suggesting that high symptom burden can be seen even in patients with lower clinical risk scores due to significant heterogeneity of symptomatology within MF and other MPN subtypes [12].

In this study, patients with thrombocytopenia were no more likely to have a history of thrombosis or hemorrhage than patients without thrombocytopenia. This is supported by other literature suggesting that low platelet counts in this population do not necessarily correlate with risk for bleeding complications [13]. Additionally, some data have shown that MF patients with lower platelet counts at diagnosis actually have a higher risk for arterial, venous, and total thrombotic events [14,15]. This likely because thrombocytopenia is associated with more advanced disease and higher degrees of inflammation and is therefore seen in association with thrombosis. In addition, cytoreductive therapy to control thrombocytosis does not necessarily result in decreased risk for thrombosis [16].

Of note, in this study abdominal pain and discomfort were two of the few symptoms that were not rated as more severe in thrombocytopenic patients with MF as compared to patients with normal platelet counts. This is somewhat surprising, as thrombocytopenic MF patients frequently experience splenomegaly due to both extramedullary hematopoiesis and splenic

platelet sequestration. This in turn can cause abdominal symptomatology that negatively impacts QOL. The fact that these symptoms were not reported to a high degree in this study population suggests that bone marrow failure more than splenic sequestration may be the underlying cause of thrombocytopenia in this patient group. In addition, the lack of symptom differences between the moderate and severe thrombocytopenia groups indicates that symptom burden may not be related directly to low platelet counts, but rather to the underlying bone marrow failure and its sequelae that are seen in the more advanced disease states characteristic of these patients. In short, the utility of platelet count as a clinical indicator of disease status and burden is at least in part related to its role as a marker of adequate bone marrow function for MF patients.

While treatment options for MF patients with thrombocytopenia have been limited due to risk of exacerbating cytopenias, more recent data indicate that judicious use of ruxolitinib in this group can be both safe and clinically effective. An interim analysis of the phase III COMFORT-I and -II trials evaluating the subset of MF patients with platelet counts of $50\text{--}100 \times 10^9/\text{L}$ found that more than half of patients achieved stable dosing and demonstrated an average 24% reduction in spleen volume and 44% reduction in TSS [17]. Similarly, the first post-market analysis of ruxolitinib showed that patients with platelets under $100 \times 10^9/\text{L}$ experienced improvement in symptom burden and a decrease in splenomegaly with only minimal decline in platelet count and no serious bleeding complications [18]. Successful use of ruxolitinib, even in patients with severe thrombocytopenia, has also been reported with minimal adverse effects [19].

Pacritinib, an inhibitor of both JAK2 and Fms-related tyrosine kinase 3 (FLT3), has also been tested in phase III trials that included patients with baseline cytopenias. The PERSIST-1 trial demonstrated that pacritinib reduces MF symptom burden even amongst patients with baseline thrombocytopenia [20]. The PERSIST-2 trial specifically evaluated pacritinib in MF patients with platelets less than $100 \times 10^9/\text{L}$, including those who previously received ruxolitinib, and found it be more effective than best available therapy at inducing spleen volume reduction and decreasing TSS [21].

Given the high symptomatic burden in this population, these data support a paradigm where MF patients with thrombocytopenia can be reasonably considered for targeted therapies. While there is some risk of lowering platelet count further or exacerbating concomitant cytopenias in this setting, there is now evidence that with close monitoring these patients can be safely treated in many cases. In conclusion, the results of this study demonstrate that MF patients with thrombocytopenia face a significant symptom burden and are likely to benefit from close surveillance of their symptomatology while receiving consideration for additional therapies.

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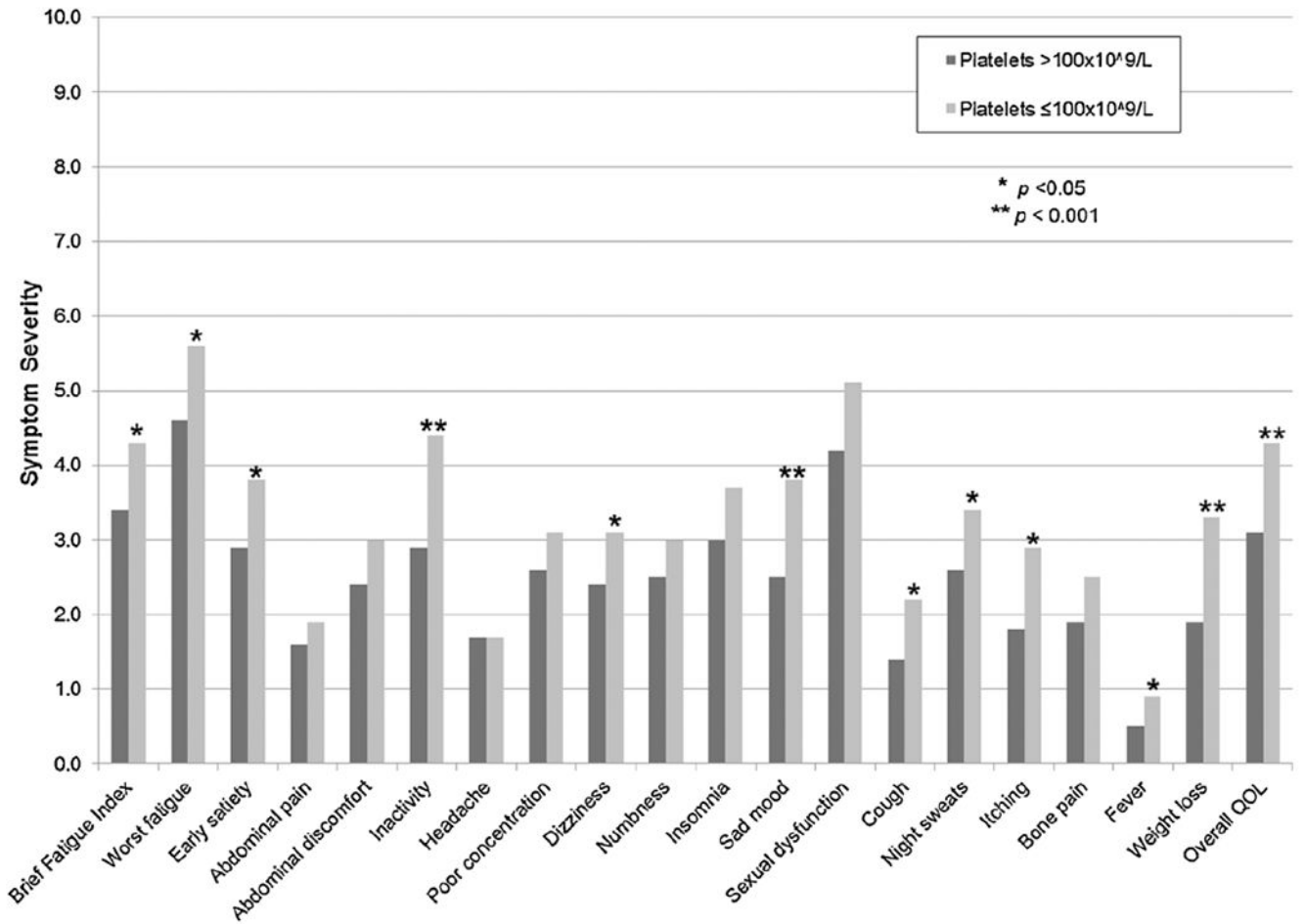


Fig. 1. Thrombocytopenia versus no thrombocytopenia by individual MPN-SAF score.

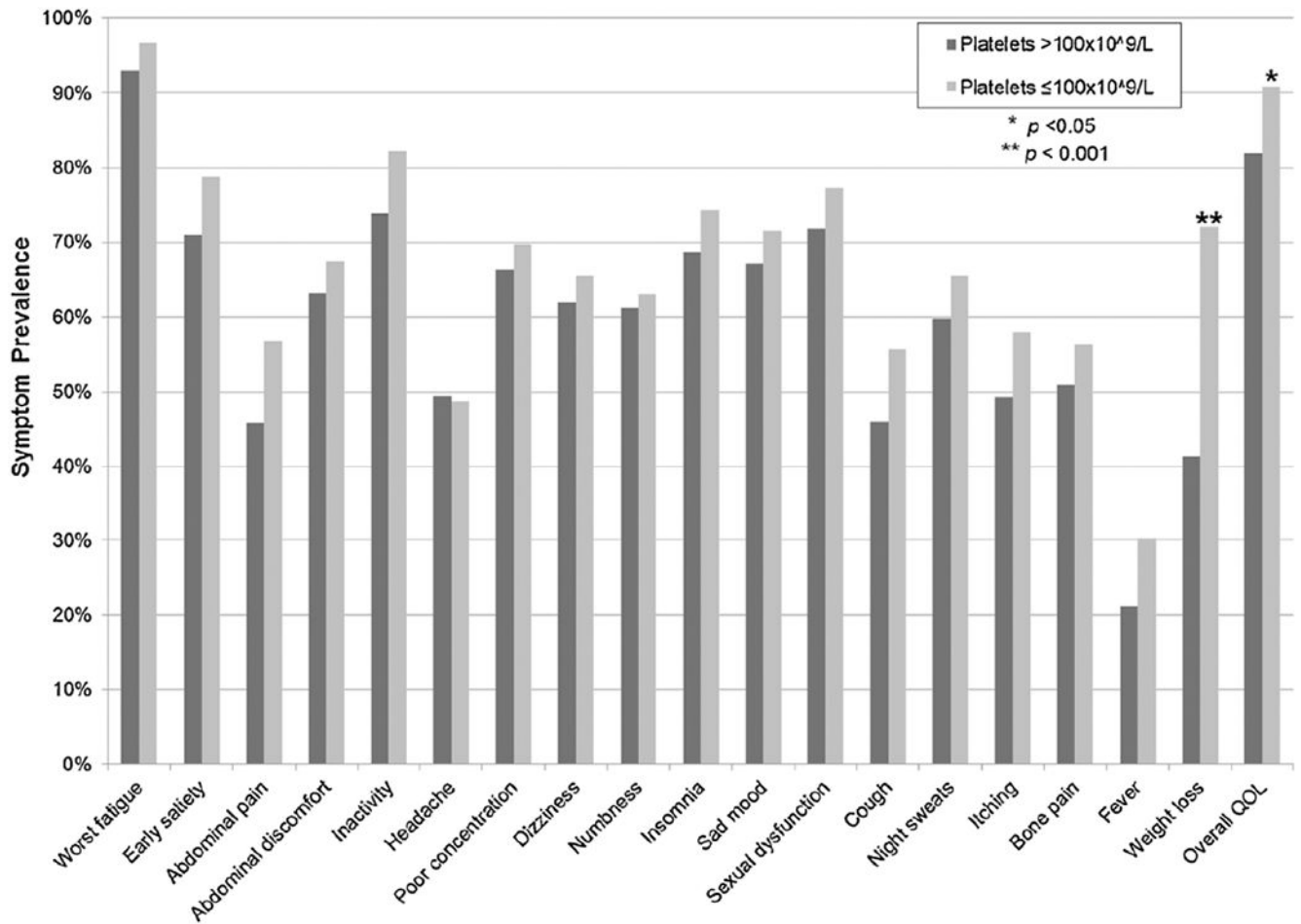


Fig. 2. Thrombocytopenia versus no thrombocytopenia by individual MPN-SAF symptom prevalence.

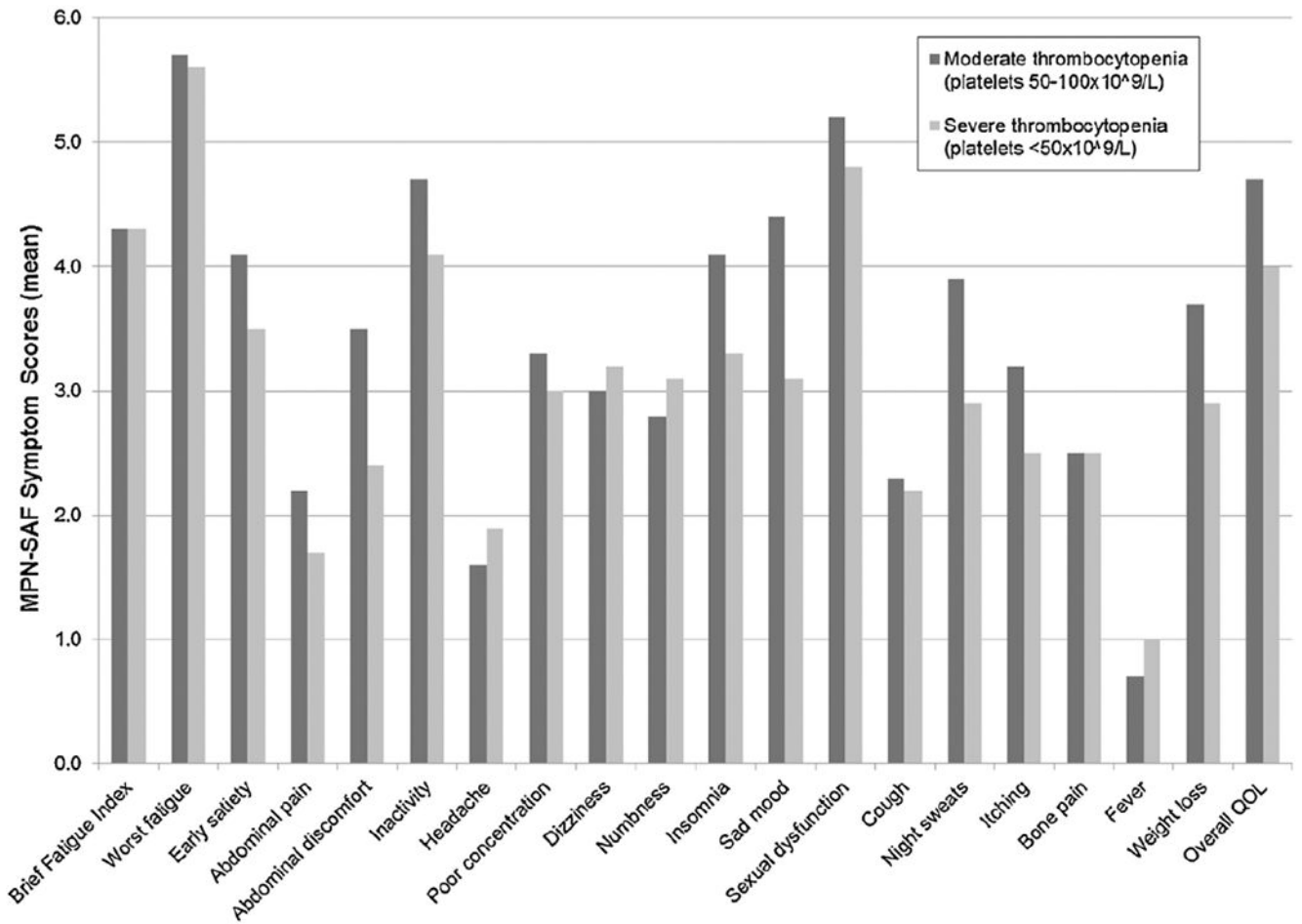


Fig. 3.
Moderate versus severe thrombocytopenia by individual MPN-SAF Score.

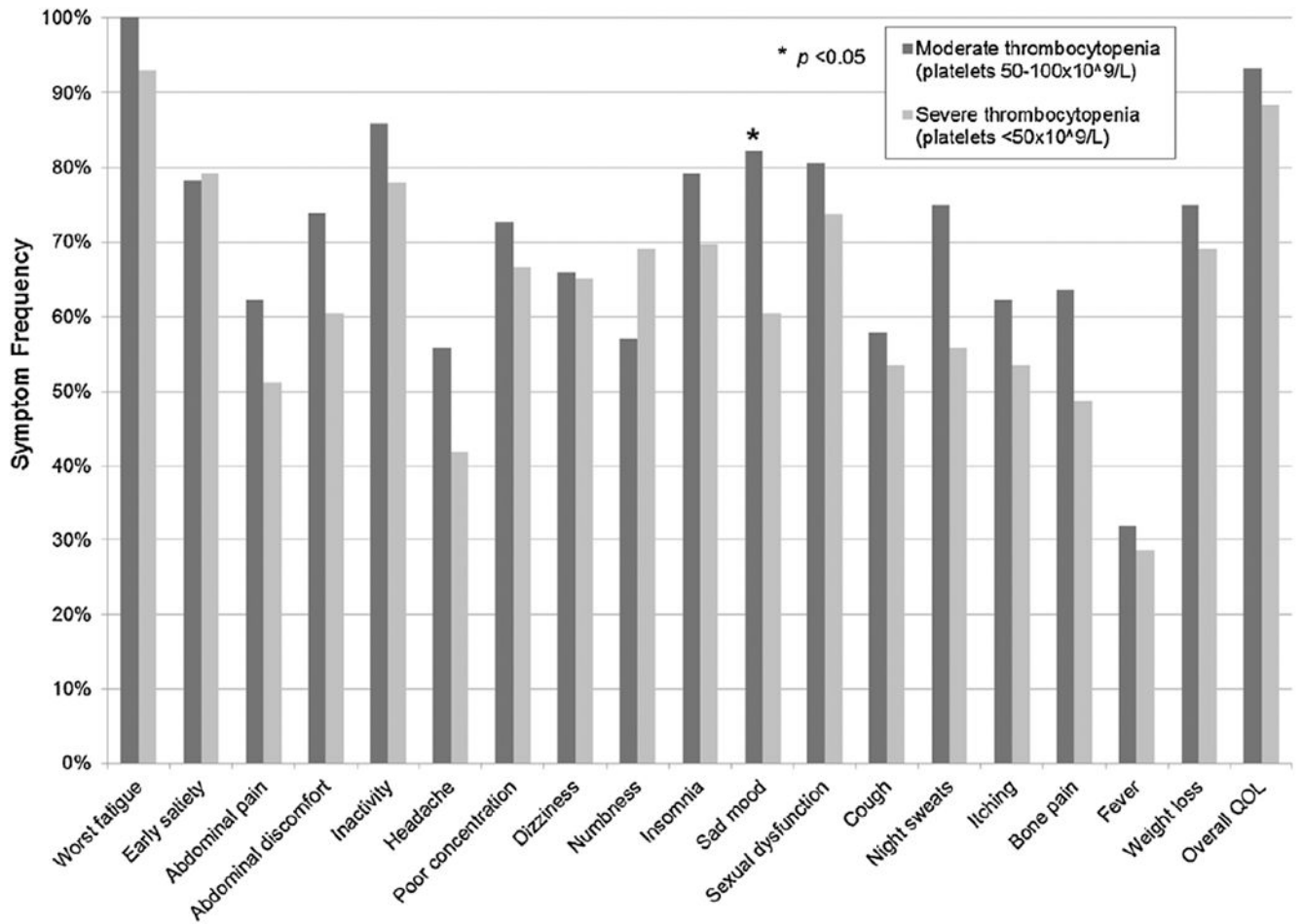


Fig. 4. Moderate versus severe thrombocytopenia by individual MPN-SAF symptom frequency.

Table 1
Demographics and clinical characteristics of MF patients with and without thrombocytopenia.

| | Normal (Plt > 100 × 10 ⁹ /L) | Thrombocytopenia (Plt < 100 × 10 ⁹ /L) | Total | p-value |
|---|---|---|--------------|---------|
| | n = 329 | n = 89 | n = 418 | |
| Age (mean, SD) | 61.0 (12.15) | 57.4 (12.67) | 60.2 (12.34) | 0.01 |
| Gender (male) | 156 (47.4%) | 42 (47.2%) | 198 (47.4%) | 0.97 |
| MF subtype | | | | 0.01 |
| Primary MF | 217 (66%) | 73 (82%) | 290 (69.4%) | |
| ET-MF | 64 (19.5%) | 7 (7.9%) | 71 (17%) | |
| PV-MF | 48 (14.6%) | 9 (10.1%) | 57 (13.6%) | |
| DIPSS risk | | | | 0.07 |
| Low | 38 (19.3%) | 5 (13.9%) | 43 (18.5%) | |
| Intermediate-1 | 113 (57.4%) | 15 (41.7%) | 128 (54.9%) | |
| Intermediate-2 | 41 (20.8%) | 14 (38.9%) | 55 (23.6%) | |
| High | 5 (2.5%) | 2 (5.6%) | 7 (3%) | |
| Anemia (Hgb < 11 g/dL) | 147 (44.8%) | 68 (76.4%) | 215 (51.6%) | < 0.001 |
| Leukopenia (WBC < 3.5 × 10 ⁹ /L) | 35 (10.6%) | 26 (29.2%) | 61 (14.6%) | < 0.001 |
| Lab abnormality | 172 (52.3%) | 89 (100%) | 261 (62.4%) | < 0.001 |
| Prior thrombosis | 42 (12.9%) | 5 (5.6%) | 47 (11.3%) | 0.06 |
| Prior hemorrhage | 14 (4.3%) | 7 (7.9%) | 21 (5.1%) | 0.17 |
| Required RBC transfusion | 62 (19.1%) | 31 (34.8%) | 93 (22.5%) | 0.002 |
| Mean MPN duration (years, SD) | 8.8 (8.33) | 11.9 (10.86) | 9.3 (8.81) | 0.049 |

DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; Hgb, hemoglobin; MF, myelofibrosis; Plt, platelets; PV, polycythemia vera; RBC, red blood cell; SD, standard deviation; WBC, white blood cell.

Table 2
Demographics and clinical characteristics of MF patients with moderate and severe thrombocytopenia.

| | Moderate Thrombocytopenia (Plt 51–100 × 10 ⁹ /L) | Severe Thrombocytopenia (Plt < 50 × 10 ⁹ /L) | Total | p-value |
|---|---|---|---------------|---------|
| | <i>n</i> = 46 | <i>n</i> = 43 | <i>n</i> = 89 | |
| Age (mean, SD) | 57.9 (11.29) | 56.9 (14.11) | 57.4 (12.67) | 0.72 |
| Gender (male) | 21 (45.7%) | 21 (48.8%) | 42 (47.2%) | 0.76 |
| MF subtype | | | | 0.87 |
| Primary MF | 38 (82.6%) | 35 (81.4%) | 73 (82%) | |
| ET-MF | 4 (8.7%) | 3 (7%) | 7 (7.9%) | |
| PV-MF | 4 (8.7%) | 5 (11.6%) | 9 (10.1%) | |
| DIPSS risk | | | | 0.09 |
| Low | 4 (21.1%) | 1 (5.9%) | 5 (13.9%) | |
| Intermediate-1 | 10 (52.6%) | 5 (29.4%) | 15 (41.7%) | |
| Intermediate-2 | 5 (26.3%) | 9 (52.9%) | 14 (38.9%) | |
| High | 0 (0%) | 2 (11.8%) | 2 (5.6%) | |
| Anemia (Hgb < 11 g/dL) | 31 (67.4%) | 37 (86.0%) | 68 (76.4%) | 0.04 |
| Leukopenia (WBC < 3.5 × 10 ⁹ /L) | 9 (19.6%) | 17 (39.5%) | 26 (29.2%) | 0.04 |
| Lab abnormality | 46 (100%) | 43 (100%) | 89 (100%) | |
| Prior thrombosis | 2 (4.3%) | 3 (7%) | 5 (5.6%) | 0.59 |
| Prior hemorrhage | 2 (4.3%) | 5 (11.6%) | 7 (7.9%) | 0.20 |
| Required RBC transfusion | 9 (19.6%) | 22 (51.2%) | 31 (34.8%) | 0.002 |
| Mean MPN duration (years, SD) | 12.3 (12.52) | 11.5 (8.58) | 11.9 (10.86) | 0.83 |

DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; Hgb, hemoglobin; MF, myelofibrosis; Plt, platelet; PV, polycythemia vera; RBC, red blood cell; SD, standard deviation; WBC, white blood cell.

Table 3

Association between clinical characteristics and MPN-SAF Total Symptom Score in MF patients

| | Total Symptom Score (TSS) (mean, SD) | <i>p</i> -value |
|---|--------------------------------------|-----------------|
| <i>n</i> = 418 | | |
| Anemia (Hgb < 11 g/dL) | | < 0.001 |
| Yes | 29.6 (18.4) | |
| No | 22.3 (15.6) | |
| Leukopenia (WBC < 3.5 × 10 ⁹ /L) | | 0.06 |
| Yes | 29.9 (19.3) | |
| No | 25.3 (17.1) | |
| Lab abnormality | | < 0.001 |
| Yes | 28.7 (18.1) | |
| No | 21.5 (15.6) | |
| Required RBC transfusion | | 0.003 |
| Yes | 30.8 (19.0) | |
| No | 24.6 (16.8) | |
| DIPSS risk | | < 0.001 |
| Low | 15.2 (11.1) | |
| Intermediate-1 | 23.3 (15.4) | |
| Intermediate-2/High | 31.5 (17.1) | |

DIPSS, Dynamic International Prognostic Scoring System; Hgb, hemoglobin; MF, myelofibrosis; RBC, red blood cell; SD, standard deviation; WBC, white blood cell.

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