BRIEF REPORT
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Myeloproliferative Neoplasm Symptom Assessment Total Symptom Score (MPN-SAF TSS) in Chronic Myeloproliferative Neoplasms, Related with Genetic Burden, and Thrombosis

Ümit E. et al: MPN SAF TSS in MPN; Genetic Burden and Thrombosis

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Abstract
Myeloproliferative Neoplasm Symptom Assessment Total Symptom Score (MPN-SAF TSS) is a surrogate marker for symptom evaluation in Chronic Myeloproliferative Neoplasms. There is not enough data to show the relationship between MPN-SAF TSS, *JAK*2 mutation allele burden, and thrombosis. In this retrospective analysis, we aimed to determine the genetic burdens, clinical features, and relationship with MPN-SAF TSS in MPN patients. One hundred thirty *JAK*2V617F positive MPN were included in our study. We have calculated MPN-SAF TSS and compared it with clinical features. Patients with higher *JAK*2V617F mutation allele burden had higher MPN-SAF TSS (p-value 0,008). Patients with thrombosis had higher MPN-SAF TSS scores than patients without thrombosis (p-value 0.003). The mean MPN-SAF TSS was higher in primary myelofibrosis (PMF) patients compared to PV and ET patients. Thrombosis was associated with increased symptom severity in several domains, including fatigue, abdominal discomfort, inactivity, night sweats, pruritus, weight loss, and early satiety. Additionally, an increase in *JAK*2 allele burden was observed with higher symptom scores. The MPN-SAF TSS proved to be a reliable tool for assessing symptom burden in Turkish MPN patients. Furthermore, a significant association between thrombosis occurrence and symptom severity suggests that thrombotic events may contribute to symptom development. Notably, increasing *JAK*2 allele burden was correlated with more severe symptoms, highlighting its potential role in predicting disease burden. This study emphasizes the importance of symptom assessment in MPN patients and supports the incorporation of MPN-SAF TSS in routine clinical practice to enhance patient care and management.
Keywords: MPN, SAF-TSS; Symptom burden, Thrombosis; *JAK*2V617F

Introduction

BCR-ABL1 negative Myeloproliferative neoplasms (MPN) are a group of clonal stem cells associated with each other originating from the hematopoietic stem cell. Categorized in 2008 and updated in 2016, MPNs were generally classified as polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) (1, 2). The mutation of *JAK*2 (Janus-type Tyrosine Kinase 2) was first shown in 2005 in these diseases and is found in approximately 97% of PV patients, and in approximately half of ET and PMF patients (3). The other somatic driver mutations of MPN are Calreticulin (*CALR*) and Myeloproliferative Leukaemia Gene (*MPL*). *CALR* or *MPL* mutations were found in *JAK*2 mutation-negative patients (4, 5)

Symptoms may include fatigue, headache, dizziness, neurological deficits, low-grade fever, night sweats, pruritus, early satiety, and erythromelalgia while complications may include thrombosis, bleeding, and transformation to acute myeloid leukemia or extensive bone marrow fibrosis. Some of the symptoms may be disease-related or associated with splenomegaly. Even the burden of symptoms may be higher when disease complications arise (6). It has also been shown that an inflammatory milieu contributes to the burden of symptoms (7). Elevations in cytokines and many growth factors have been shown in patients with MPN (8-10). While many patients are diagnosed incidentally, symptoms may arise due to the increased number of peripheral myeloid cells or complications (11, 12). As they have been not diagnostic for the disease or disease subtype and lack objectivity, they have been rather neglected and whole blood counts were regarded as preferable tools for follow-up. Since MPNs are regarded as a disease of the aged due the median age at diagnosis for these neoplasms are over 60 years, life expectancy of patients has remained the same. Since certain co-morbid conditions may arise due to aging such as cardiovascular diseases, only specific complications of MPNs could have been investigated. Thrombosis have been one of the major complications of MPN and have been associated with disease manifestations such as blood count abnormalities as well as the clone size (13-16) .

Evaluating fatigue and quality of life in MPN patients has been a great obstacle (17). Although various scales and quality of lie measures have been developed, most recently the MPN Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) has helped to eliminate the unmet need in this topic (12). Symptom assessment was previously evaluated by certain groups with MPN-SAF TSS and validated in various languages (Table 1) (11, 12, 18-20). MPN-SAF adds another dimension by revealing the importance of patient-reported outcomes in evaluating the response of patients to treatment. (21) In our study, we aimed to determine the severity of the symptoms and their probable contributing factors which are related with the disease including laboratory abnormalities, clonal size as it had been connected with complications.

Methods

Patients

130 patients who were diagnosed as *BCR::ABL1* negative MPN based on 2016 World Health Organization Update on Myeloid Neoplasms at a single center (1) were enrolled in the study in a cross sectional manner. Disease characteristics were recorded from patient files. Mutational status (clone size of *JAK*2), demographic features, treatments were all recorded from the patients' files. Splenomegaly defined as spleen size greater than 13 cm and massive splenomegaly is defined as spleen size greater than 20 cm. Disease outcomes included thrombosis as one of the major complications. Since this study is an observational, cross-sectional study, only thrombosis is included as an outcome, long-term outcomes such as transformation were not applicable.

MPN-SAF TSS was performed by all patients in the supervision of the same physician (Table1) MPN-SAF TSS consisted of ten items including fatigue, early satiety, abdominal

discomfort, inactivity, problems with concentration, night sweats, pruritus, bone pain, fever, and unintentional weight loss. As a self-completion questionnaire, patient can give points to each item; 0 for minimum, 10 for maximum severity. We have translated the original MPN-SAF TSS into the Turkish language and the translation process were conducted according to the proposed guidelines (22).

Informed written consent was obtained from all patients and ethical approval was obtained from local ethical committee.

With using IBM-SPSS V21 as a statistical analysis tool, continuous variables were assessed for normality using the Kolmogorov-Smirnov test. Categorical variables in the baseline data were presented as counts and percentages. To compare the differences between the two groups (for continuous or ordered categorical variables), either the paired or unpaired t-test was utilized, or the Mann-Whitney U test was applied. For disordered categorical variables, the Chi-square test was used. All statistical analyses used two-sided P-values, with a significance level set at 0.05. Multivariate analysis was performed for significant relations.

Results

General Features

In our study, 130 *BCR::ABL1* negative *JAK*2V617F positive MPN patients were included. Of the patients, 73 were female (56.2%) and 57 were male (43.8%). The mean age of the patients was 65.42 ± 10.61 years (28-88 years). When the diagnostic subgroups of the patients were considered, 63 patients were ET (48.5%), 45 patients were PV (34.6%), and 22 patients were PMF (16.9%). When all patients were evaluated together, 7 patients had 75-100% *JAK*2 positivity, 50-75% positive in 16 patients, 25-50% positive in 45 patients, and less than 25% in 62 patients.; according to treatments of the patients, 12 patients were followed low dose aspirin (9.3%), 84 patients with hydroxyurea (64.6%), 18 patients with anagrelide (13.8%), 5 patients with interferon (5.4%) and 7 patients with ruxolitinib (6.9%).

Splenomegaly was observed in 44 patients (33.8%) and massive splenomegaly was observed in 11 patients. Venous or arterial thromboembolism within their follow up was observed in 26 patients (20%). General features and clinical findings of the patients were summarized in Table2.

MPN-SAF Total Symptom Scores

Mean score of fatigue was 2,98 (0-8), early satiety 1,58 (0-10), abdominal discomfort 1,97 (0-10), inactivity 1,72 (0-9), problems with concentration 2,06 (0-10), night sweats 2,31 (0-10), pruritus 2,63 (0-10), bone pain 2,46 (0-10), fever 1,78 (0-10), weight loss 1,21 (0-10).

MPN-SAF and Clinical Characteristics

Total symptom score of PMF patients was 37.64, while 19.93 in PV patients and 23.81 in ET patients.

Regarding thrombosis, mean MPN-SAF total score in patients without thrombosis was 20.18 (SD 11.404) and while 45.27 (SD 20.626) in patients with thrombosis. Since patients with a thrombosis episode in their course of disease showed higher total symptom scores, we aimed to identify which dimension of symptoms were most affected. Fatigue (p = 0,001), abdominal discomfort (p = 0,026), inactivity (p = 0,035), night sweats (p = 0,001), pruritus (p = 0.045), weight loss (p = 0.017) and early satiety (p = 0.023) were the majorly affected symptoms in patients with thrombosis history.

While thrombosis has been associated with *JAK*2 allele burden, we could not observe a relation in our group (p = 0.409). However, certain symptoms were observed to vary with the allele variation. In the group with *JAK*2 positivity between 0 and 25%, mean total of the symptom scale was 18.47 (SD 15.199), while in the 25-50% group 28.96 (SD 22.84), in the group with 50-75% 33.31 (SD 16, 64) and in the group of 75-100% was 34.86 (SD 10.33). As the *JAK* allele load increased, there was an increase in the symptom scale of the patients (p =

0.003). Relations with MPN -SAF scores and disease outcomes are summarized in Table 3, 4 and 5.
Multivariate analysis was performed to assess the relation between both *JAK*2 allele size-thrombosis and symptom burden and no relations were observed in high allele burden-history of a thrombosis episode with higher symptom burden.

Discussion

The severity of symptoms as well as complications are known to vary within MPNs. MF patients have been demonstrated to experience serious abdominal discomfort and early satiety due to more distinctly increased spleen size. Likewise, the severity of bone marrow fibrosis is also related with the constitutional symptoms (2). We have observed a similar poorer symptom burden in patients with MF, which suggested the value of symptom assessment.
The effect of allele size on disease complications including thrombosis have been conflicting though the majority of studies have suggested a possible relation with an increased allele burden with an increased thrombosis prevalence (23) (24). Indeed, *JAK*2 mutation allele burden more than 20 % was found to be a 7.4-fold increased risk of venous thrombosis regardless of MPN type (25). In a prospective analysis authors identified a high-risk group of PV patients; which has an elevated thrombotic risk with a *JAK*2 allele burden of > % 75 (26). In a recent analysis a cutoff value of % > 90,4 *JAK*2 allele burden for thrombosis is suggested in PV patients (27). Similar to this finding; in a retrospective analysis of 1537 MPN patients; authors reported that a higher median *JAK*2 V617F allele burden in patients with thrombosis (24). In our study we observed an increase in MPN-SAF TSS s in patients with thrombosis and increased *JAK*2 allele size. Though we observed these increases in univariate analysis, we could not observe in multivariate analysis probably due to our limited number of patients. As another limitation, other factors that may contribute to thrombosis besides age, allele burden and disease subtype could bring more insight despite the majority of thrombosis in patients with MPN are related with splanchnic area.
The MPN-SAF total symptom score evaluation form has also taken place in the National Comprehensive Cancer Network (NCCN) guidelines and has demonstrated the importance of monitoring and evaluating this disease (28-31). In our study, we conducted the validity of MPN-SAF TSS in a group of Turkish patients. We also observed a relationship between thrombosis and symptom severity. We believe that the relationship between *JAK*2 allele burden and thrombosis can be significant in predicting the patients' symptoms.
There are limitations of our study including our sample size and our study being a cross-sectional and observational one. But our aim has been to attract attention to the value of symptoms in MPNs and we believe that repetitive symptom assessment will increase the quality of care for MPN patients.

Declarations

Funding: None

Data availability The data supporting the findings of the present study are available from the corresponding author upon reasonable request**.**

Ethical approval The study was approved by the Ethical Boards of Trakya University, TUTF BAEK(2018-126), and performed in compliance with the guidelines of the 1964 Declaration of Helsinki and its later amendments.
Consent to participate/for publication Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare no competing interest.

Declaration Of Competing Interest Statement All authors report no conflict of interest.

Author Contributions: E.U.& M.B. conceptualized the work acquired the data, did the interpretation and wrote the manuscript; H.K.O. worked for the data acquisition; A. M. D. worked for the data acquisition and critically reviewed the paper.

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Table 1. MPN-SAF TSS Evaluation Form

Item	Scale
Please rate your fatigue by circling the one number that best describes; your worst level of fatigue during the past 24 hours.	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (worst imaginable)
Circle the one number that describes how much difficulty you have had with each of the following symptoms during the past week:	
Filling up quickly when you eat (early satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10(worst imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10(worst imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10(worst imaginable)
Problems with concentration - compared with before the diagnosis	(Absent) 0 1 2 3 4 5 6 7 8 9 10(worst imaginable)
Night sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10(worst imaginable)
Itching (pruritus)	Absent) 0 1 2 3 4 5 6 7 8 9 10(worst imaginable)
Bone pain (diffuse, not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10(worst imaginable)
Fever	(Absent) 0 1 2 3 4 5 6 7 8 9 10(worst imaginable)
Unintentional weight loss in 1ast 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10(worst imaginable)

Table 2. General Features and Clinical Characteristics of the Patients

		Number and percentage of patients
Female/Male		73/57 (56.2%/43.8%)
Mean Age (Years)		65,42±10,61
Disease Subgroups	ET	63 (48.5%)
	PV	45 (34.6%)
	PMF	22 (16.9%)
*JAK*2 V617F mutation allele burden	75-100%	7
	50-75%	16
	25-50%	45
	<25%	62
Treatment	Low dose aspirin	12 (9.3%)
	Hydroxyurea	84 (64.6%)
	Anagrelide	18 (13.8%)
	Interferon	5 (5.4%)
	Ruxolitinib	7 (6.9%)
Splenomegaly		44 (33.8%)
Massive splenomegaly		11 (8.4 %)
Thrombosis (arterial & venous)		26 (20%)

Table 3. MPN-SAF Total Symptom Scores and Evaluation with Disease Subtypes

Symptom Scores		Mean (Standard Deviation)	
Fatigue	ET	3.07 (2.455)	
	PV	2.83 (2.767)	
	MF	3.06 (2.578)	
Early Satiety	ET	0.98 (1.882)	
	PV	1.45 (2.587)	
	MF	3.83 (3.666)	
Abdominal Discomfort	ET	1.27 (1.921)	
	PV	2.36 (3.304)	
	MF	3.39 (3.760)	
Inactivity	ET	1.25 (1.800)	
	PV	1.93 (2.726)	
	MF	2.78 (3.457)	
Concentration Problems	ET	1.80 (2.049)	
	PV	2.26 (2.706)	
	MF	2.44 (3.148)	
Night Sweats	ET	2.40 (2.883)	
	PV	1.86 (2.799)	
	MF	3.06 (3.472)	
Pruritus	ET	2.15 (2.851)	
	PV	2.90 (3.498)	
	MF	3.61 (3.432)	
Bone pain	ET	2.35 (2.483)	
	PV	2.24 (2.739)	
	MF	3.33 (3.254)	
Weight loss	ET	0.78 (1.329)	
	PV	0.71 (1.195)	
	MF	3.78 (4.081)	
Total Score	ET	23.81	P value: 0.001
	PV	19.93	
	MF	37.64	

Table 4. MPN-SAF Total Symptom Scores and JAK2 Mutation Allele Burden

Symptom Scores	JAK Burden (Number of Patients)	Mean (Standard Deviation)	p value
Fatigue	<25%	2.61 (2.342)	0.008
	25-50%	3.00 (2.542)	
	50-75%	3.28 (3.211)	
	>75%	4.43 (2.992)	
Early Satiety	<25%	1.54 (2.794)	0.041
	25-50%	1.60 (2,629)	
	50-75%	1.07 (1.817)	
	>75%	2.71 (2.812)	
Abdominal Discomfort	<25%	1.95 (3.014)	0.865
	25-50%	2.00 (2.909)	
	50-75%	1.57 (1.989)	
	>75%	2.71 (3.251)	
Inactivity	<25%	1.80 (2.796)	0.564
	25-50%	1.53 (1.987)	
	50-75%	2.36 (2.872)	
	>75%	0.86 (1.069)	
Concentration Problems	<25%	1.75 (2.390)	0.530
	25-50%	2.50 (2.783)	
	50-75%	2.07 (1.730)	
	>75%	2.14 (2.545)	
Night Sweats	<25%	2.34 (3.133)	0.864
	25-50%	2.23 (2.922)	
	50-75%	2.00 (2.855)	
	>75%	3.14 (1.864)	
Pruritus	<25%	2.25 (3.299)	**0,004**
	25-50%	2.36 (2.023)	
	50-75%	3.13 (3.510)	
	>75%	3.57 (2.070)	
Bone pain	<25%	2.34 (3.196)	**0,005**
	25-50%	2.60 (2.373)	
	50-75%	2.64 (2.499)	
	>75%	2.89 (2.752)	
Weight loss	<25%	0.95 (1.960)	**0,003**
	25-50%	1.40 (2.697)	
	50-75%	2.00 (1.797)	
	>75%	3.29 (2.215)	
Total Score	<25% (59)	18.64 (15.513)	**0,003**
	25-50% (40)	29.53 (24.026)	
	50-75% (14)	30.93 (16.457)	
	>75% (7)	34.86 (10.335)	

Table 5. MPN-10 Total Symptom Score in patients with and without thrombosis

Mean Symptom scores	Patients with thrombosis (n.26)	Patient without thrombosis (n:104)	P value
Fatigue	6.98	2.08	**0,001**
Early Satiety	4.49	2.02	**0,023**
Abdominal Discomfort	4.78	1.63	**0,026**
Inactivity	2.99	1.54	**0,035**
Concentration Problems	3.66	3.37	0.564
Night Sweats	7.67	2.11	**0,001**
Pruritus	5.63	2.35	**0,045**
Bone pain	3.12	2.98	0.064
Weight loss	5.95	2.10	**0,017**
Total Score	45.27	20.18	**0.003**

Abbreviations: ET: Essential Thrombocythemia; PV: Polycythemia Vera; PMF: Primary Myelofibrosis