BRIEF REPORT

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Myeloproliferative Neoplasm Symptom Assessment Total Symptom Score (MPN-SAF TSS) in Chronic Myeloproliferative Neoplasms with Relation to Genetic Burden and Thrombosis

Kronik Miyeloproliferatif Neoplazilerde; Miyeloproliferatif Neoplazi Semptom Değerlendirme Toplam Semptom Skoru (MPN-SAF TSS) ve Genetik Yük ve Tromboz ile İlişkisi

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Abstract

The Myeloproliferative Neoplasm Symptom Assessment Total Symptom Score (MPN-SAF TSS) is a surrogate marker for symptom evaluation in chronic myeloproliferative neoplasms (MPNs). However, insufficient data are available regarding the relationship among the MPN-SAF TSS, *JAK*2 mutation allele burden, and thrombosis. In this retrospective analysis, we aimed to determine the genetic burdens, clinical features, and relationships with MPN-SAF TSS in MPN patients. One hundred thirty *JAK*2V617F-positive patients with MPNs were included in our study. We calculated the MPN-SAF TSS for all patients and compared it with their clinical characteristics. Patients with higher *JAK*2V617F mutation allele burden had higher MPN-SAF TSS values (p=0.008). Patients with thrombosis had higher MPN-SAF TSS than patients without thrombosis (p=0.003). The mean MPN-SAF TSS was higher in patients with primary myelofibrosis compared to those with polycythemia vera and essential thrombocythemia. 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, the 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 the MPN-SAF TSS in routine clinical practice to enhance patient care and management.

Keywords: Myeloproliferative neoplasms, MPN-SAF TSS, Symptom burden, Thrombosis, *JAK*2V617F

Öz

Miyeloproliferatif Neoplazi Semptom Değerlendirme Toplam Semptom Skoru (MPN-SAF TSS), kronik miyeloproliferatif neoplazilerde (MPN) semptom değerlendirmesi için kullanılan önemli bir araçtır. Bununla birlikte, MPN-SAF TSS ile *JAK*2 mutasyon alel yükü ve tromboz arasındaki ilişkiye dair yeterli veri mevcut değildir. Bu retrospektif analizde, MPN hastalarında genetik yükleri, klinik özellikleri ve MPN-SAF TSS ile ilişkilerini belirlemeyi amaçladık. Yüz otuz *JAK*2V617F-pozitif MPN hastası çalışmamıza dahil edildi. Hastaların MPN-SAF TSS skorlamaları hesaplandı ve klinik özellikleriyle karşılaştırıldı. *JAK*2V617F mutasyon alel yükü daha yüksek olan hastaların MPN-SAF TSS değerleri daha yüksekti (p=0,008). Trombozu olan hastalar, trombozu olmayan hastalara göre daha yüksek MPN-SAF TSS değerlerine sahipti (p=0,003). Primer miyelofibrozisli hastalarda ortalama MPN-SAF TSS değeri polisitemi vera ve esansiyel trombositozlu hastalara kıyasla daha yüksekti. Tromboz; yorgunluk, abdominal rahatsızlık, hareketsizlik, gece terlemesi, kaşıntı, kilo kaybı ve erken doyma gibi çeşitli alanlarda artan semptom şiddeti ile ilişkilendirilmiştir. Ayrıca, *JAK*2 alel yükündeki artış daha yüksek semptom skorlarıyla birlikte gözlenmiştir. MPN-SAF TSS'nin Türk MPN hastalarında semptom yükünü değerlendirmek için güvenilir bir araç olduğu kanıtlanmıştır. Bunun yanında, tromboz oluşumu ile semptom şiddeti arasındaki anlamlı ilişki, trombotik olayların semptom gelişimine katkıda bulunabileceğini düşündürmektedir. Özellikle, artan *JAK*2 alel yükü daha şiddetli semptomlarla korelasyon göstermiş ve hastalık yükünü öngörmedeki potansiyel rolünü vurgulamıştır. Bu çalışma MPN hastalarında semptom değerlendirmesinin önemini vurgulamakta ve hasta bakımı ve yönetimini geliştirmek için MPN-SAF TSS'nin rutin klinik uygulamaya dahil edilmesini desteklemektedir.

Anahtar Sözcükler: Miyeloproliferatif neoplaziler, MPN-SAF TSS, Semptom yükü, Tromboz, *JAK*2V617

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Introduction

BCR::ABL1-negative myeloproliferative neoplasms (MPNs) are a group of clonal stem cells associated with each other that originate from hematopoietic stem cells. By a categorization established in 2008 and updated in 2016, MPNs are generally classified as polycythemia vera (PV), essential thrombocythemia (ET), or primary myelofibrosis (PMF) [1,2]. The mutation of the Janus-type tyrosine kinase 2 (*JAK2*) gene was first shown in 2005 in these diseases, and it is found in approximately 97% of PV patients and approximately half of ET and PMF patients [3]. The other somatic driver mutations of MPN are the calreticulin (*CALR*) and myeloproliferative leukemia (*MPL*) genes. *CALR* and *MPL* mutations have been found in *JAK2* mutation-negative patients [4,5].

Symptoms of MPNs 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 symptoms may be disease-related or associated with splenomegaly. 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 MPNs [8,9,10]. While many cases are diagnosed incidentally, symptoms may arise due to the increased number of peripheral myeloid cells or complications [11,12]. However, as they are not diagnostic for the disease or disease subtype and lack objectivity, they have generally been neglected and whole blood counts are regarded as preferable tools for follow-up.

MPNs are regarded as a disease of the aged due the median age at diagnosis for these neoplasms being over 60 years. Therefore, the life expectancy of these patients does not change. Since certain comorbid conditions may arise due to aging, such as cardiovascular diseases, only specific complications of MPNs are investigated. Thrombosis is one of the major complications of MPNs and it has been found to be associated with disease manifestations, such as blood count abnormalities, as well as clone size [13,14,15,16].

There have been many obstacles to the evaluation of fatigue and quality of life in cases of MPN [17]. Although various scales and quality of life measures have been developed, the MPN Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) has most recently helped address the unmet needs in this area [12]. Symptom assessment was previously evaluated by various groups with the MPN-SAF TSS and the tool was validated in various languages (Table 1) [11,12,18,19,20]. The MPN-SAF adds another dimension to assessment efforts by revealing the importance of patient-reported outcomes in evaluating the response of patients to treatment [21]. In this study, we aimed to determine the severity of symptoms in patients with MPNs and probable contributing factors related to the disease, including laboratory abnormalities and clonal size, which have been connected to complications.

Materials and Methods

Patients

A total of 130 patients who were diagnosed with *BCR::ABL1*-negative MPN based on the 2016 World Health Organization Update on Myeloid Neoplasms [1] at a single center were enrolled in this study in a cross-sectional manner. Disease characteristics were recorded from patient files. Mutational status (*JAK2* clone size), demographic features, and treatments were all recorded from the patients' files. Splenomegaly was defined as spleen size greater than 13 cm and massive splenomegaly was defined

Table 1. Myeloproliferative Neoplasm Symptom Assessment Total Symptom Score (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:	0 (absent), 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)	0 (absent), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 (worst imaginable)
Abdominal discomfort	0 (absent), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 (worst imaginable)
Inactivity	0 (absent), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 (worst imaginable)
Problems with concentration - compared to before the diagnosis	0 (absent), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 (worst imaginable)
Night sweats	0 (absent), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 (worst imaginable)
Itching (pruritus)	0 (absent), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 (worst imaginable)
Bone pain (diffuse, not joint pain or arthritis)	0 (absent), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 (worst imaginable)
Fever	0 (absent), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 (worst imaginable)
Unintentional weight loss in last 6 months	0 (absent), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 (worst imaginable)

as spleen size greater than 20 cm. Disease outcomes included thrombosis as one of the major complications. Since this study was an observational, cross-sectional study, only thrombosis was included as an outcome and other long-term outcomes such as transformation were not considered.

The MPN-SAF TSS was calculated for all patients under the supervision of the same physician (Table 1). The MPN-SAF TSS consists of ten items including fatigue, early satiety, abdominal discomfort, inactivity, problems with concentration, night sweats, pruritus, bone pain, fever, and unintentional weight loss. It is a self-report questionnaire, and patients assign a score for each item ranging from 0 for minimum severity to 10 for maximum severity. We translated the original MPN-SAF TSS into Turkish and the translation process was conducted according to the relevant guidelines [22].

Informed written consent was obtained from all patients. The study was approved by the Trakya University Ethics Committee with the number TUTF BAEK (protocol code: 2018-126, decision no: 09/08, date: 21.05.2018) and was conducted in accordance with the 1964 Declaration of Helsinki and its subsequent amendments.

Statistical Anaysis

Using IBM SPSS Statistics 21 as a statistical analysis tool, continuous variables were assessed for normality with the Kolmogorov-Smirnov test. Categorical variables from the baseline data were presented as counts and percentages. To compare the differences between two groups for continuous or ordered categorical variables, either the paired or unpaired t-test was utilized, and the Mann-Whitney U test was also applied. For unordered categorical variables, the chi-square test was used. All statistical analyses used two-sided p values with significance set at 0.05. Multivariate analysis was performed for significant relationships.

Results

General Features

This study included 130 *BCR::ABL1*-negative *JAK2*V617F-positive MPN patients. Of these patients, 73 were female (56.2%) and 57 were male (43.8%). The mean age was 65.42±10.61 (range: 28-88) years. When the diagnostic subgroups of the patients were considered, 63 patients had ET (48.5%), 45 patients had PV (34.6%), and 22 patients had PMF (16.9%). When all patients were evaluated together, 7 patients had *JAK2* positivity of 75%-100%, 16 patients had positivity of 50%-75%, 45 patients had positivity of 25%-50%, and 62 patients had positivity of <25%. For the treatment of the patients, 12 patients were followed with low-dose aspirin (9.3%), 84 with hydroxyurea (64.6%), 18 with anagrelide (13.8%), 5 with interferon (5.4%), and 7 with ruxolitinib (6.9%).

Splenomegaly was observed in 44 patients (33.8%) and massive splenomegaly was observed in 11 patients (8.4%). Venous or arterial thromboembolism during follow-up was observed in 26 patients (20%). The general features and clinical findings of the patients are summarized in Table 2.

MPN-SAF Symptom Scores

Mean symptom scores were 2.98 (range: 0-8) for fatigue, 1.58 (0-10) for early satiety, 1.97 (0-10) for abdominal discomfort, 1.72 (0-9) for inactivity, 2.06 (0-10) for problems with concentration, 2.31 (0-10) for night sweats, 2.63 (0-10) for pruritus, 2.46 (0-10) for bone pain, 1.78 (0-10) for fever, and 1.21 (0-10) for weight loss.

MPN-SAF TSS and Clinical Characteristics

The total symptom score of the PMF patients was 37.64, while the mean score was 19.93 for PV patients and 23.81 for ET patients.

Regarding thrombosis, the mean MPN-SAF TSS of the patients without thrombosis was 20.18±11.404, while it was 45.27±20.626 for patients with thrombosis. As patients with a thrombosis episode in the course of their disease had higher total symptom scores, we aimed to identify which dimension of symptoms were most affected by thrombosis. 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 found to be significantly affected by a history of thrombosis.

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)
***JAK2*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 and venous)		26 (20)

ET: Essential thrombocythemia; PV: polycythemia vera; PMF: primary myelofibrosis.

While thrombosis has been associated with JAK2 allele burden, we could not observe such an association in our group of patients (p=0.409). However, certain symptoms were found to vary with allele variation. In the group with *JAK2* positivity of 0%-25%, the mean total symptom score was 18.47±15.199, while in the group with 25%-50% positivity, it was 28.96±22.84; in the group with 50%-75% positivity, it was 33.31±16.64; and in the group with 75%-100% positivity, it was 34.86±10.33. As the JAK2 allele load increased, there was an increase in the symptom scores of the patients (p=0.003). Relationships between MPN-SAF TSS scores and disease outcomes are summarized in Tables 3, 4, and 5.

Multivariate analysis was performed to assess the relationship between *JAK2* allele burden and both thrombosis and symptom burden, and no relationships were observed with a history of thrombosis episodes or higher symptom burden in cases of high allele burden.

Discussion

The severity of symptoms and the occurrence of complications are known to vary in cases of MPNs. Patients with PMF 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 to the occurrence of constitutional symptoms [2]. In this study, we similarly observed worse symptom burdens in patients with PMF, suggesting the value of symptom assessment.

The effect of allele size on disease complications including thrombosis remains unclear, but a majority of studies have suggested a possible relationship of increased allele burden with increased thrombosis prevalence [23,24]. In one previous study, a *JAK2* mutation allele burden of more than 20% was found to indicate a 7.4-fold increased risk of venous thrombosis regardless of MPN type [25]. In a prospective analysis, Vannucchi et al. [26] identified a high-risk group of PV patients with elevated thrombotic risk and a *JAK2* allele burden of >75%. In another recent analysis, a *JAK2* allele burden cutoff value of >90.4% was suggested for thrombosis in PV patients [27]. Similarly, in a retrospective analysis of 1537 MPN patients, a higher median *JAK2*V617F allele burden was reported in patients with thrombosis [24]. In our study, we observed an increase in MPN-SAF TSS values in patients with thrombosis and increased *JAK*2 allele burden in univariate analysis, but we could not obtain significant results in multivariate analysis, which was most likely due to our limited number of patients. As another limitation, other factors that might contribute to thrombosis besides age, allele burden, and disease subtype were not explored, which could contribute further insights, with the majority of thrombosis events in patients with MPNs being related to the splanchnic area.

The MPN-SAF TSS evaluation form is included in the National Comprehensive Cancer Network guidelines and the importance of monitoring and evaluating MPNs with this tool has been demonstrated [28,29,30,31]. In the present study, we investigated the validity of the MPN-SAF TSS in a group of Turkish patients and we observed a relationship between thrombosis and symptom severity. We believe that the relationship between *JAK2* allele burden and thrombosis may be significant in predicting patients' symptoms.

Table 3. Myeloproliferative Neoplasm Symptom Assessment Total Symptom Score (MPN-SAF TSS) values and evaluations by disease subtype.

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=0.001
	PV	19.93	
	MF	37.64	

ET: Essential thrombocythemia; PV: polycythemia vera; PMF: primary myelofibrosis.

Table 4. Myeloproliferative Neoplasm Symptom Assessment Total Symptom Score (MPN-SAF TSS) values and *JAK2* mutation allele burdens.

Symptom scores	*JAK2* burden (%)	Mean (standard deviation)	p
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 (number of patients)	<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. Myeloproliferative Neoplasm Symptom Assessment Total Symptom Score (MPN-SAF TSS) in patients with and without thrombosis.

Mean symptom scores	Patients with thrombosis (n=26)	Patient without thrombosis (n=104)	p
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**

Conclusion

Our study has limitations that include its small sample size and its cross-sectional and observational design. However, our aim was to call attention to the value of symptoms in MPNs. We believe that regular symptom assessment will increase the quality of care for MPN patients.

Ethic

Ethics Committee Approval: The study was approved by the Trakya University Ethics Committee with the number TUTF BAEK (protocol code: 2018-126, decision no: 09/08, date: 21.05.2018) and was conducted in accordance with the 1964 Declaration of Helsinki and its subsequent amendments.

Informed Consent: Informed written consent was obtained from all patients.

Authorship Contributions

Surgical and Medical Practices: E.G.Ü., M.B., H.O.K., A.M.D.; Concept: E.G.Ü., M.B.; Design: E.G.Ü., M.B.; Data Collection or Processing: E.G.Ü., M.B., H.O.K.; Analysis or Interpretation: E.G.Ü., M.B., H.O.K., A.M.D.; Literature Search: E.G.Ü., M.B., H.O.K.; Writing: E.G.Ü., M.B., A.M.D.

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