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Original article

Myeloproliferative Neoplasm Symptom Assessment Form - Total Symptom Score (MPN-SAF TSS) questionnaire: translation, cultural adaptation and validation to Brazilian Portuguese

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ABSTRACT

Introduction: Constitutional symptoms and thrombohemorrhagic events are common in patients with myeloproliferative neoplasms (MPNs). Hence, the treatment's primary goal is to control symptoms and improve the quality of life (QoL). In order to assess response to therapy, symptom burden, and QoL among patients with MPN, the "Myeloproliferative Neoplasm Symptom Assessment Form - Total Symptom Score (MPN-SAF TSS)" questionnaire was developed in the USA in 2012. Herein, we translated and validated the MPN-SAF TSS questionnaire to Brazilian Portuguese.

Methods: The ten-item questionnaire was translated from the English language and its psychometric properties (reliability, convergent and construct validities) were evaluated in 101 MPN patients.

Results: There were 41 patients with essential thrombocythemia, 39 with myelofibrosis and 21 with polycythemia vera. The median age of all patients at diagnosis was 68 years and 59% were female. The Cronbach's alpha coefficient for the overall questionnaire was 0.78, ranging from 0.73 to 0.79, if each item was deleted. Validity analyses showed that the strongest item-item correlation were between early satiety and abdominal discomfort. Strong correlations were also found between physician and patient perceptions of itching ($r = 0.81$) and fatigue ($r = 0.70$). The Pearson coefficient correlation between the MPN-SAF TSS global score and the EORTC QLQ-C30 functional scales ranged from 0.51 to 0.64. The exploratory factor analysis showed that seven of the ten symptoms loaded into one single factor.

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Conclusion: The Brazilian Portuguese version of the MPN-SAF-TSS showed good psychometric properties and can be an available tool to assess symptom burden in this group of patients.

Introduction

According to The World Health Organization (WHO) classification of Tumors of Hematopoietic and Lymphoid Tissues, myeloproliferative neoplasms (MPNs), comprising essential thrombocythemia (ET), polycythemia vera (PV) and myelofibrosis (MF)[3] are a group of clonal diseases characterized by abnormal proliferation of one or more of the components of the myeloid lineage, absence ofthe Philadelphia chromosome and association with muta-tions involving the JAK/STAT signaling pathway (Janus kinase2 [JAK2], calreticulin [CALR], or thrombopoietin receptor [MPL]).[1,2] The main objective of the treatment of MPNs is to alleviate symptoms and prevent the occurrence of serious complications, such as hemorrhagic and thrombotic events, as they may have a high impact on the patient morbidity, quality of life (QoL) and mortality. The only curative treatment is the allogeneic hematopoietic stem cell transplantation (HSCT).[4–6]

Patients with MPN may present with a variety of symptoms that negatively affect their quality of life and productivity.[7] These include concentration problems, inactivity, night sweats, abdominal discomfort, weight loss, fever and fatigue.[8] Moreover, frequency and intensity of symptoms are different among the subtypes and patients with myelofibrosis usually have more symptoms than those with ET or PV.[9] Hence, the measurement of the disease burden is a mainstay in the management of these patients and the best way to evaluate this is through the patient's perception of how these symptoms affect his or her quality of life.[10,11]

In 2007, an internet-based symptom survey showed that fatigue was present in most of the patients with MPNs, even in the early stages of the disease, and identified the most common symptoms in this group of patients.[8] The study also showed how symptoms could compromise social and physical functioning and underscored the importance of QoL evaluation and the need for a tool to assess therapy response in clinical trials. Hence, the "Myelofibrosis Symptom Assessment Form (MFSAF)" was created in 2009 as the first patient-reported outcome (PRO) instrument developed for this purpose.[10] However, the questionnaire focused only on MF and did not capture symptoms commonly reported in ET and PV. Therefore, in 2011, the "Myeloproliferative Neoplasm Self-Assessment Form (MPN SAF)" was elaborated with seventeen items[11] and, in 2012, so was the MPN SAF Total Symptom Score (TSS); a questionnaire with the ten most clinically relevant symptoms reported by patients with MPNs.[9] Since then, the score has been successfully translated and culturally adapted to different languages, including Portuguese from Portugal.[12]

Instruments to evaluate fatigue and overall QoL in different populations with cancer are available in Brazil,[13–15] but none are specific for patients with MPNs. This study aimed to translate the MPN-SAF TSS questionnaire to Brazilian Portuguese and to validate it in a cohort of Brazilian patients with MPNs.

Methods

Study population

Patients 18 years or older diagnosed with ET, PV, or MF (WHO criteria) between November 1995 and December 2018, were included, and those with psychiatric or cognitive disorders were excluded. They were treated at the Rio de Janeiro State University and Federal Fluminense University Hospitals, two public institutions in Rio de Janeiro, Brazil. The ethics committees of the participating institutions approved the study and all patients signed an informed consent.

The sample size was calculated according to the guidelines of the PRO method for translation and cultural adaptation, which suggests 8–10 patients for each item of the questionnaire, thus requiring 80–100 patients to validate the MPN SAF-TSS.

Data were collected between February 2017 and March 2019 from the patient medical records using a standardized case report form. The following baseline demographic and clinical characteristics were collected: gender, age, underlying disease, date of diagnosis, mutational status and laboratory values (hemoglobin level and white blood cell and platelet counts) at diagnosis and history of thrombohemorrhagic complications.

Instrument

The MPN-SAF TSS is a one-dimensional questionnaire with nine items containing the most common symptoms reported by patients (concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss and fever), plus one item ("worst fatigue") from the "Brief Fatigue Inventory (BFI)".[16] Each item has a score that ranges from 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be), which means that the higher the score, the worse the symptom. In the present study, patients with a score >0 were considered symptomatic and each item of the questionnaire was designated as "moderate", if symptoms were rated between 4 and 6, and as "severe", if symptoms were rated ≥ 7. For patients who completed at least six of these ten items, the score was computed as the average of the observed items multiplied by 10 to achieve a 0-to-100 scale.[9] In addition, we considered the patient as "clinically deficient" if the question about QoL was rated 4–10. Patients were invited to answer the questionnaire during their visits to the treatment center, choosing between a self-administration form or an interview by one of the authors (M.G.).

Table 1 – Brazilian Portuguese version: "Questionário para avaliação dos sintomas em neoplasia mieloproliferativa - Escore total de sintomas (QAS - NMP- ETS)".

Sintoma	Classificação de 1 a 10 (0 se ausente, 1 mais favorável e 10 menos favorável)
Por favor, avalie seu cansaço (fadiga, exaustão), circulando o número que descreva seu PIOR nível de cansaço durante as **últimas 24 horas**	(Sem cansaço) 0 1 2 3 4 5 6 7 8 9 10 (Pior Possível)
Circule o número que descreva quanta dificuldade você teve com cada um dos seguintes sintomas, nas últimas 24 horas	
Se sente cheio quando se alimenta (saciedade precoce)	(Ausente) 0 1 2 3 4 5 6 7 8 9 10 (Pior possível)
Incomodo na barriga (Desconforto abdominal)	(Ausente) 0 1 2 3 4 5 6 7 8 9 10 (Pior possível)
Faz poucas atividades (Inatividade)	(Ausente) 0 1 2 3 4 5 6 7 8 9 10 (Pior possível)
Problemas de concentração - comparado ao período antes da doença	(Ausente) 0 1 2 3 4 5 6 7 8 9 10 (Pior possível)
Suor durante a noite (Sudorese noturna)	(Ausente) 0 1 2 3 4 5 6 7 8 9 10 (Pior possível)
Coceira (prurido)	(Ausente) 0 1 2 3 4 5 6 7 8 9 10 (Pior possível)
Dor difusa nos ossos (não é dor nas articulações nem artrite)	(Ausente) 0 1 2 3 4 5 6 7 8 9 10 (Pior possível)
Febre (>37,7 °C)	(Ausente) 0 1 2 3 4 5 6 7 8 9 10 (Diária)
Perda de peso não intencional nos últimos 6 meses	(Ausente) 0 1 2 3 4 5 6 7 8 9 10 (Pior possível)
Qual é a sua qualidade de vida geral?	(A melhor possível) 0 1 2 3 4 5 6 7 8 9 10 (A pior possível)

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30)[17] was also used to survey the patients. Physicians were queried on six patient symptoms, taken from the translated version of the MPN SAF-TSS (fatigue, itching, night sweats, bone pain, fever and weight loss) on a scale of 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be).

Translation procedure

Before the beginning of the study, an authorization to develop the Brazilian Portuguese translation and validation process was obtained from the MPN-SAF TSS authors. The translation and validation were conducted according to the proposed guidelines.[18] First, the questionnaire was translated into Brazilian Portuguese by two independent persons whose native language is Brazilian Portuguese and subsequently, it was back-translated into English by two other independent translators whose native language is English and who had no access to the original English version. A consensus English back-translated version was then compared with the original one. The new Portuguese version was submitted to a pilot testing in which the semantic equivalence was evaluated in ten patients and the final version was used in the study (Table 1).

Statistical analysis

Clinical and demographic characteristics were presented as descriptive statistics. Analysis of variance (ANOVA) F-tests were used to compare the means between groups. The MPN-SAF TSS results were compared among the MPN disease subtypes, clinically deficient patient-reported QOL and number of symptoms endorsed by the physician (if the physician rated ≥2 of 6 symptoms). The incidences (score >0) were compared using x^2 tests.

Internal consistency of the MPN-SAF TSS was measured by the Cronbach's alpha coefficient and was considered good if the value was >0.7.[19] The Pearson correlation coefficients were used to assess convergent validity and were calculated among the items of the MPN-SAF TSS and between the MPN-SAF TSS items and the EORTC QLQ-C30, the patient-reported overall QOL and physician symptom ratings. A correlation from 0.4 to 0.6 was considered moderate, and ≥0.7, strong.[20]

The construct validity was evaluated by the exploratory factor analysis to assess the correlation among items, following the procedure used in the original validation.[9] The factors retained were those with an eigenvalue >1. To examine the appropriateness of the data for the factor analysis, the Kaiser-Meyer-Olkin (KMO) and the Bartlett Sphericity Tests ($p < 0.05$) were used. The KMO statistic varies from 0 to 1 and values higher than 0.7 are recommended.[21] The p-values <0.05 were considered statistically significant.

Results

A total of 101 patients with MPNs were included in the study: 41% with ET, 39% with MF and 20% with PV. Among patients with MF, 30 had primary and 9, secondary MF. The median age was 68 years (20–90) and 59% were female. The median time from the diagnosis to the administration of the questionnaire was 4.7 years (0–22 years). The baseline patient characteristics are shown in Table 2.

All patients completed the ten items of the MPN-SAF TSS. A majority of the patients were symptomatic for fatigue (score >0) and 42% rated this symptom as moderate to severe. Fifty-five percent reported a clinically deficient quality of life (score-rated as at least 4 of 10). Regarding the symptom intensity, fatigue had a mean of 3.0 (standard deviation [SD] 3.3), followed by inactivity (mean 2.8, SD 3.5) and concentration problems (mean 2.4, SD 3.6). Overall, the MPN-SAF TSS mean was 18.5, 14.5 in ET, 19.3 in PV and 22.3 in MF ($p = 0.13$, Table 3). Patients with a clinically deficient QoL had a higher MPN-SAF TSS score (mean 24.8 vs. 10.6, $p < 0.001$), as well as patients whose physicians rated two or more of six common symptoms related to MPN (mean 25.64 vs. 7.59, $p < 0.001$).

Convergent validity analyses showed moderate item-item correlations of abdominal discomfort with early satiety ($r = 0.59$, $p < 0.001$), fatigue ($r = 0.53$, $p < 0.001$) and inactivity ($r = 0.49$, $p < 0.001$). Moreover, moderate correlations were found between fatigue and the following items: early satiety

Table 2 – Baseline characteristics of 101 patients with myeloproliferative neoplasms.

Characteristics	Total (n = 101)	ET (n = 41)	PV (n = 21)	MF (n = 39)
Age (median, range)	68 (20–90)	65 (20–87)	69 (45–88)	68 (49–90)
Median time from diagnosis, range (years)	5 (0–22)	6 (1–20)	3 (0–22)	4 (0–19)
Female gender (%)	60	73	43	54
Laboratory values at diagnosis (median, range)				
Median hemoglobin (range) – g/dl		13.0 (7.0–19.0)	17.9 (15.0–20.9)	11.8 (7.0–17.5)
Median WBC (range) – ($\times 10^9$/L)		7.7 (4.2–17.4)	12.6 (3.1–23.7)	12.2 (3.3–45.9)
Median platelet count (range) – $\times 10^9$/L		912 (252 – 2177)	373 (129 – 1013)	511 (121 – 2140)
JAK2V617F exon 14 positive (n)	71	23	19	29[a]
Previous thrombohemorrhagic event (%)				
Thrombosis	22	19	29	20
Hemorrhage	2	2	–	3

[a] Among 30 patients with primary MF, 77% presented JAK-2-positive.

Table 3 – Assessment of Symptom's Severity and Incidence (score > 0) and MPN Total Symptom Score.

Symptoms	TE (n = 41)			PV (n = 21)			MF (n = 39)			Total (n = 101)		
	Mean	SD	Incidence	Mean	SD	Incidence	Mean	SD	Incidence	Mean	SD	Incidence
Worst fatigue[a]	2.8	3.4	49	2.4	3.0	52	3.5	3.3	62	3.0	3.3	55
Early satiety	2.0	3.2	37	1.5	2.4	43	2.7	3.6	44	2.1	3.3	41
Abdominal discomfort	2.0	3.4	34	1.5	2.5	33	2.6	3.6	41	2.1	3.3	37
Inactivity	2.2	3.3	39	2.9	3.3	52	3.3	3.7	51	2.8	3.5	47
Concentration problems	2.4	3.8	34	2.1	3.3	38	2.6	3.7	39	2.4	3.6	37
Night sweats	0.7	2.2	17	1.6	3.0	33	1.8	3.1	33	1.3	2.7	27
Itching[b]	0.3	1.5	7	3.2	4.1	48	1.6	3.3	26	1.4	3.1	23
Bone pain	1.4	3.2	22	2.5	3.4	43	1.6	3.1	26	1.7	3.2	28
Weight loss[b]	0.5	1.6	12	1.6	2.2	43	2.2	3.3	39	1.4	2.6	29
Fever(>37.7)	0.0	0.0	0	0.0	0.0	0	0.4	1.8	5	0.7	1.1	2
MPN SAF-TSS[c]	**14.5**	**15.0**	–	**19.3**	**18.0**	–	**22.3**	**19.3**	–	**18.5**	**17.6**	–

[a] Item from the Brief fatigue inventory.
[b] Comparisons of incidence were evaluated by using x^2 tests. Comparisons of severity were evaluated by using analysis of variance *F* tests. Only itching and weight loss with $p < 0.05$ across groups.
[c] Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) has a possible range of 0–100, with 100 representing the highest level of symptom severity; ET, essential thrombocythemia; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PV, polycythemia vera. Comparisons of MPN SAF TSS were evaluated using analysis of variance *F* tests, all with $p = 0.13$, across groups.

($r = 0.51$, $p < 0.001$), inactivity ($r = 0.51$, $p < 0.001$), concentration problems ($r = 0.40$, $p < 0.001$) and quality of life ($r = 0.45$, $p < 0.001$). Fever and weight loss had a correlation coefficient of 0.42 ($p < 0.001$). Moderate to strong correlations (ranging from 0.52 to 0.81, $p < 0.001$) were found between all six physician symptom ratings, when compared to the same symptoms reported by the patients.

The MPN-SAF TSS global score had a moderate correlation with all the EORTC QLQ-C30 functional scales (0.50–0.64, all $p < 0.001$) and with the patient-reported overall QoL ($r = 0.45$, $p < 0.001$). Six items (fatigue, inactivity, concentration problems, bone pain, abdominal discomfort and early satiety) from the MPN-SAF TSS had a moderate correlation with the symptom scales from the EORTC QLQ C30 (Table 4).

The overall Cronbach's alpha coefficient was 0.78, ranging from 0.73 to 0.79 for each symptom, if the item was deleted. The construct validity was evaluated by the exploratory factor analysis and showed that all items were distributed in three components. The KMO test was 0.75 and the Bartlett's Test was <0.001. Of all ten symptoms, seven loaded into one single factor, fever and weight loss loaded into another and itching loaded separately into the third component.

Discussion

In the present study, the MPN-SAF TSS was translated and validated following international guidelines. The Brazilian Portuguese version was shown to be a reliable instrument for MPN patients. The PRO is a systematic approach used to assess QoL and intensity of symptoms through the patient's perception of the disease, treatment and health status.[22] Many PRO instruments have been developed for patients with cancer,[23,24] but a specific tool to assess MPN disease burden was lacking. The MPN-SAF TSS was created to measure symptoms and guide clinical management of MPN patients.

Fatigue is the most frequent and disabling symptom in patients with MPN, occurring in more than 80% of patients, even in the absence of anemia.[8] Fatigue has also been associated with other symptoms, such as inactivity, reduced QoL and decreased physical and social functioning.[25] During the

Table 4 – Pearson Correlation between selected MPN-SAF TSS Items and alternative instruments to measure quality of life.

Item	Measurement instrument	Associated measure	Pearson correlation[a]
Worst Fatigue (BFI)	QLQ-C30 Symptom Scale	Fatigue	0.70
	Overall QoL	Overall QoL	0.45
	Physician's perceptions	Fatigue	0.69
Inactivity	QLQ-C30 Functional scale	Physical	−0.41
	QLQ-C30 Functional scale	Role	−0.50
Concentration	QLQ-C30 Symptom Scale	Fatigue	0.46
	QLQ-C30 Functional scale	Social	−0.71
Bone pain	QLQ-C30 Symptom scale	Pain	0.43
	Physician perceptions	Bone pain	0.52
Abdominal discomfort	QLQ-C30 Functional scale	Physical	−0.41
Early satiety	QLQ-C30 Functional scale	Physical	−0.43
	QLQ-C30 Symptom scale	Nausea	0.42
MPN-SAF TSS	QLQ-C30 functional scale	Physical	−0.57
	QLQ-C30 functional scale	Role	−0.64
	QLQ-C30 functional scale	Emotional	−0.54
	QLQ-C30 functional scale	Cognitive	−0.51
	QLQ-C30 functional scale	Social	−0.50
	QLQ-C30 Symptom scale	Fatigue	0.68
	QLQ-C30 Symptom scale	Pain	0.42
	QLQ-C30	Global health/QoL	−0.55
	Overall QoL	Overall QoL	0.45

QoL: quality of life.
[a] All $p < 0.05$.

process of translation and validation, fatigue was reported by a majority of our patients, had the highest score among the nine most prevalent symptoms and was highly correlated with other symptoms, including inactivity and early satiety.

Splenomegaly is another frequent clinical manifestation of MPN and its occurrence is associated with abdominal discomfort and early satiety, especially in advanced stages of disease.[26] Thereby, new drugs have been developed aiming to reduce splenomegaly and thus, decrease the intensity of symptoms and improve the QoL.[27] Indeed, despite the lack of data about splenomegaly itself, we observed a moderate correlation between early satiety and abdominal discomfort and both correlated with fatigue.

Moreover, patients with MPN have a hypercatabolic state and elevated levels of proinflammatory cytokines, which is reflected in the presence of constitutional symptoms. This aspect may explain the correlation between fever and weight loss observed in our study.[28]

There is heterogeneity of symptoms among patients with MPN, even in those with the same disease. Furthermore, the intensity of symptoms is independent of the stage of disease and patients with low or intermediate risk may be more symptomatic than patients with high-risk features.[29] Our study confirmed that patients with MPN have a wide variety of symptoms and in different degrees. Additionally, patients with MF were more symptomatic and had a higher overall MPN-SAF TSS score than those with ET and PV.[9] The lack of statistical significance may be explained by the small number of patients.

Quality of life is a multidimensional construct and can be impaired by advanced age, comorbidities and by symptoms related to the disease itself and its treatment.[30] The MPN-SAF TSS is an instrument to measure symptoms. Therefore, to better evaluated QoL, an additional question was included and we found that more than half of the patients with MPN reported a clinically deficient quality of life. These patients also had higher MPN-SAF TSS scores, highlighting the negative impact of symptoms on the lives of these patients. It is noteworthy that the physician responses (≥2 of 6 symptoms) correlated with the clinically deficient patients, suggesting that physicians had a good perception of patient symptoms and quality of life.

Cultural adaptation and semantic validation are essential stages during the translation of a questionnaire. Both are important because specific expressions can be distinct between countries with the same language and even among regions in the same country.[18] Furthermore, economic aspects, as well as religion, climate and life habits should be considered, as all these factors may reflect how symptoms impact people lives and affect their quality of life. The MPN-SAF TSS was also translated to Portuguese from Portugal; however, we find differences between the two instruments.[12]

The convergent validity analysis showed a good correlation of the questionnaire with all the EORTC QLQ-C30 functional scales and the QoL question. These findings were in alignment with the original validation.[9] The reliability was also good with an overall Cronbach's alpha of 0.78, indicating a satisfactory internal consistency and suggesting that all items measure the same concept. The construct validity assessment showed that most of the items loaded into a single factor, reflecting the higher correlation among these seven symptoms, as compared to the remaining three items. This finding confirms the lack of correlation among some items in the Pearson analysis.

In conclusion, the Brazilian Portuguese version of the MPN-SAF TSS demonstrated good psychometric properties in this population. Therefore, it may be a useful tool in the symptom burden and quality of life evaluation of Brazilian MPN patients.

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Conflict of interest

One of the authors is a speaker for Novartis.

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