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The IPSS-R more accurately captures fatigue severity of newly diagnosed patients with myelodysplastic syndromes compared with the IPSS index

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Abstract

We aimed to compare fatigue of newly diagnosed patients with myelodysplastic syndromes (MDS) with that of the general population (GP). We also investigated the ability of the IPSS and IPSS-R to capture severity of patient-reported fatigue at diagnostic workup. A sample of 927 newly diagnosed patients with MDS was consecutively enrolled in a large international observational study and all patients completed the FACIT-Fatigue questionnaire at baseline. Fatigue was compared with that of the GP ($N = 1075$) and a 3-point difference in mean scores was considered as clinically meaningful. Fatigue of MDS patients was on average 4.6 points below the mean of the GP (95% CI, −5.9 to −3.2, $p < 0.001$), reflecting clinically meaningful worse fatigue. Unlike the IPSS, the IPSS-R identified clearly distinct subgroups with regard to burden of fatigue. Mean scores differences compared with GP ranged from nonclinically relevant for very low risk ($\Delta = -1.8$, 95% CI, −4.0 to 0.5, $p = 0.119$) to large clinically meaningful differences for very high-risk IPSS-R patients ($\Delta = -8.2$, 95% CI, −10.3 to −6.2, $p < 0.001$). At diagnostic workup, fatigue of MDS is clinically meaningful worse than that reported by the GP. Compared with the IPSS classification, the IPSS-R provides a better stratification of patients with regard to fatigue severity.

Introduction

Myelodysplastic syndromes (MDS) are a group of clonal diseases characterized by ineffective hematopoiesis, molecular and cytogenic abnormalities, bone marrow failure, and risk for progression to acute myeloid leukemia (AML) [1, 2]. As anemia is a common peripheral blood abnormality at clinical presentation [3], some patients might also be transfusion-dependent already at the time of diagnosis, which is a known indicator of greater disease severity and poor prognosis [4].

As the disease course of MDS is highly variable in terms of progression to AML and survival outcomes, major efforts have been made over the years to develop prognostic indices to help inform clinical decision-making [5]. The two most frequently used disease-risk classifications in the MDS diagnostic workup are the International Prognostic Scoring System (IPSS) [6] and the IPSS-Revised (IPSS-R) [7]. While the IPSS-R was more recently developed, the IPSS is still a very often used index in clinical practice to guide individual treatment decisions [8].

Two decades ago, the international working group standard response criteria for evaluation of MDS therapies recommended that health-related quality of life (HRQOL) be included in clinical research [9]. However, only recently have there been major international efforts to develop disease specific HRQOL measures [10] or to conduct large-scale HRQOL studies of MDS [11, 12]. Critical to the global HRQOL of patients with MDS, more than degree of anemia, is fatigue [13]. Fatigue is a hallmark of MDS reported by the vast majority of patients [14], it is associated with substantial level of distress [15] and, at least in high-risk patients, it was shown to provide independent prognostic information for survival beyond well-established prognostic indices [16].

However, very little data are available on patient-reported fatigue in MDS. For example, it is not known if the level of fatigue experienced by newly diagnosed patients with MDS is different from that reported by the general population (GP) and whether standard disease-risk classifications used in the diagnostic workup capture this key symptom. This data could be critical to understanding the initial burden of fatigue in this population, before possible changes due to commonly used therapies for MDS, such as erythropoiesis-stimulating agents or hypomethylating agents [17, 18]. Such information could also lay the groundwork for developing more timely and personalized treatment approaches and enhancing patients' management in clinical practice.

Our primary objective was to compare self-reported fatigue between patients with newly diagnosed MDS and the GP. Secondary objectives were to examine burden of fatigue by transfusion dependency status and by risk-group categories defined by the routinely used IPSS and IPSS-R risk classifications.

Methods

Between November 2008 and December 2018, 927 newly diagnosed patients with MDS were consecutively enrolled in an international prospective cohort observational study involving 53 centers across eleven countries (Austria, Belgium, Brazil, China, Croatia, Czech Republic, France, Germany, Italy, UK, USA). The primary objective of this study was to investigate the prognostic value of baseline patients' reported fatigue for overall survival and follow-up of patients is ongoing. Patients were diagnosed and classified according to the World Health Organization criteria [19, 20]. The initial protocol only included patients with MDS with higher risk disease (i.e., IPSS *intermediate-2* or *high*-risk classifications) but was later amended in September 2014 to also include patients diagnosed with lower risk disease (i.e., IPSS *low* and *intermediate-1* risk classifications) within 3 months of the date of registration. Baseline assessment of patient-reported HRQOL was mandatory for inclusion in this study and the EORTC QLQ-C30 [21] and the FACIT-Fatigue [22] questionnaires were administered to patients at study entry. Exclusion criteria included having received any kind of therapy (other than transfusions) and having any kind of psychiatric disorder or major cognitive dysfunction.

The study was approved by all Ethic Committees of each participating center, and all patients provided informed consent according to local national regulations. The study was

conducted in accordance with the Declaration of Hel-sinki and registered at ClinicalTrials.gov (NCT00809575).

General population (GP)

For these analyses, data from patients with MDS were compared with data from a GP sample for whom self-reported fatigue was assessed using the same well-validated FACIT-Fatigue questionnaire [22]. Data for the GP reference group were collected by Knowledge Networks (KN; Menlo Park, CA), a marketing information and decision support system. KN drew a random sample of individuals at least 18 years old in the United States from an internet-based survey panel of more than 100,000 individuals who were a demographically representative sample of the GP and responded to one survey per month in exchange for free installation of WebTV internet service. The FACIT-Fatigue was one such survey that was presented electronically to the panel members to complete in their homes. Of 1075 individuals who completed the FACIT-Fatigue, 61 were excluded from these analyses because they reported a current or historic cancer diagnosis and an additional 203 were excluded because they were <30 years old (the minimum age in the sample of patients with MDS). In total, 811 participants (47.6% male, mean age 50.1 years) were retained from the GP; these participants are a largely overlapping subset of individuals that have previously been used as a GP reference group by which to compare the fatigue levels of patients with MDS [14] and anemic cancer patients [23].

Assessment of patient-reported fatigue in both samples

The 13-item FACIT-Fatigue scale assesses self-reported tiredness, weakness, and difficulty participating in usual activities due to fatigue over the past seven days [22, 24] (Fig. 1). Respondents indicate the veracity of statements related to fatigue (e.g., “I feel weak all over,” “I have trouble starting things because I am tired”) on a Likert scale from *not at all* (0) to *very much* [4]. Per the scoring guidelines, negatively worded items were reverse scored and summed such that higher total values (range 0–52) indicate better functioning; thus, lower values indicate more fatigue [22]. For comparison purposes, a difference of at least 3 points in the FACIT-Fatigue score is considered clinically meaningful [22, 25]. For the purpose of this study, only baseline fatigue scores of the MDS population were used in order to ensure that comparison of their fatigue scores with the GP were not confounded by factors such as receipt of active MDS treatments.

Statistical analyses

We summarized the main characteristics of patients with MDS and the GP by frequencies, proportions, means, standard deviations, medians, and interquartile ranges as appropriate. All patients were described based on widely used broader risk categories, that is: “lower” and “higher” risk patients [18]. For the IPSS risk classification, these included, respectively, those patients classified as *low* and *intermediate-1* risk vs. those classified as *intermediate-2* and *high* risk. For the IPSS-R risk classification, these included, respectively, those patients classified as *very low*, *low*, and *intermediate* (with an IPSS-R score ≤ 3.5), vs. those classified as *intermediate* (with an IPSS-R score >3.5), *high*, and *very high* [26].

We estimated the overall mean difference in FACIT-Fatigue scores between patients with MDS and the GP, adjusted by age, sex, and presence of at least one comorbidity [27] (yes vs. no) using a multivariable linear regression (MLR) model also including a binary status indicator (MDS vs. GP). We separately ran the same MLR model to estimate adjusted mean differences in fatigue between patients with MDS and the GP also by MDS-based subgroups. These were defined respectively by IPSS risk categories (*low*, *intermediate-1*, *intermediate-2*, and *high*), IPSS-R (*very low*, *low*, *intermediate*, *high*, and *very high*) and transfusion dependency (yes vs. no). This latter was defined a priori in the protocol as having received at least one red blood cell transfusion every 8 weeks over a period of 4 months [4]. We also performed supportive analysis, estimating the mean differences in fatigue scores between MDS and GP on an exact age–sex matched subsample. For descriptive purposes, we also computed the cumulative distribution of fatigue scores in patients with MDS and the GP. In addition, we reported the proportions of patients with MDS with a level of fatigue severity equal to or worse than the mean and the median fatigue levels in the GP, respectively, both by IPSS and IPSS-R risk categories. All statistical tests were two-sided and statistical significance was set as $\alpha = 0.05$. All analyses were performed by SAS software v.4 (SAS Institute Inc., Cary, NC, USA).

Results

The overall sample of patients with MDS was comprised of mostly males ($n = 568/927$, 61.3%) with a mean age of 71.6 years (SD = 10.7). Patients with MDS were further classified into lower and higher risk disease according to both the IPSS and IPSS-R risk classifications and described by the following characteristics: age, sex, time since diagnosis, ECOG performance status, peripheral cytopenias (i.e., hemoglobin levels, platelets, and absolute neutrophils count), presence of comorbidities, and transfusion dependency. The top three most prevalent MDS subtypes were RAEB-2 ($n = 317$, 34.2%), RCMD ($n = 208$, 22.4%) and RAEB-1 ($n = 175$, 18.9%), while the median percentage of blasts was 5.6% (interquartile range from 2% to 12%). Overall, there were 153 (16.5%) patients who were transfusion-dependent at baseline. Details of patient's characteristics are reported in Table 1.

Fatigue in patients with MDS compared with the GP

In the GP, the mean FACIT-Fatigue score was 40.6 (SD = 10, median 44) compared with patients with MDS who reported a mean score of 36.3 (SD = 11.4, median 39). FACIT-Fatigue scores among patients with MDS were on average 4.6 points below the mean of the GP (95% CI, −5.9 to −3.2, $p < 0.001$), reflecting clinically meaningful worse fatigue in patients with MDS (Table 2). The magnitude and direction of the estimated mean difference in fatigue scores between patients with MDS and GP were also confirmed in supportive analysis (data not shown).

Figure 2 shows the cumulative distribution of FACIT-Fatigue scores in patients with MDS and the GP. Overall, 59% ($n = 542/923$) and 71% ($n = 659/923$) of patients with MDS reported fatigue levels equal to or worse than the mean and the median fatigue level in the GP.

Fatigue in patients with MDS by transfusion dependency compared with the GP

The mean FACIT-Fatigue scores were statistically and clinically meaningfully worse than in the GP in both groups of transfusion-independent (Δ = −3.7, 95% CI, −5.1 to −2.3, $p < 0.001$) and transfusion-dependent (Δ = −8.5, 95% CI, −10.6 to −6.4, $p < 0.001$) patients with MDS (Table 2).

Figure 3 shows the cumulative distribution of FACIT-Fatigue scores in patients with MDS by transfusion dependency status and the GP. There were 56% (n = 425/764) and 73% (n = 112/153) of transfusion-independent and transfusion-dependent patients, respectively, who reported fatigue levels equal to or worse than the mean fatigue level in the GP. In addition, 69% (n = 526) and 83% (n = 127) of transfusion-independent and transfusion-dependent patients, respectively, reported fatigue levels equal to or worse than the median fatigue level in the GP.

Fatigue in patients with MDS compared with the GP by IPSS risk categories

Adjusted mean score differences of patients with MDS compared with the GP reached the clinically meaningful threshold of 3 points in both lower risk groups; patients with MDS with low risk reported FACIT-Fatigue scores an average of 3 points lower than the GP (95% CI, −4.8 to −1.1, $p = 0.002$) and patients with MDS with intermediate-1 risk reported FACIT-Fatigue scores an average of 3.3 points lower than the GP (95% CI, −5.0 to −1.5, $p < 0.001$). With regard to higher risk patients with MDS, mean score differences with the GP exceeded twice the 3-point meaningful difference in both the intermediate-2 (Δ = −6, 95% CI, −7.7 to −4.3, $p < 0.001$) and the high (Δ = −8.1, 95% CI, −10.3 to −5.8, $p < 0.001$) risk groups (Table 2).

Fatigue in patients with MDS compared with the GP by IPSS-R risk categories

The adjusted mean difference in FACIT-Fatigue scores between patients with very low risk and the GP was neither statistically nor clinically significant. In contrast, patients in the all other risk categories showed both statistically significant and clinically meaningful adjusted mean differences in FACIT-Fatigue scores, indicating progressively worse fatigue levels as IPSS-R risk category increased. These were patients with low (Δ = −3.3, 95% CI, −5.2 to −1.5, $p < 0.001$), intermediate (Δ = −4.1, 95% CI, −6.0 to −2.1, $p < 0.001$), high (Δ = −5.2, 95% CI, −7.1 to −3.3, $p < 0.001$), and very high-risk classifications (Δ = −8.2, 95% CI, −10.3 to −6.2, $p < 0.001$) (Table 2). The difference in fatigue reported by patients with very high risk vs. the GP exceeded twice the clinically meaningful threshold.

For descriptive purposes, the trend found between increased fatigue severity by IPSS-R risk-group categories is graphically depicted in Fig. 4.

Discussion

We have shown that the burden of fatigue experienced by newly diagnosed patients with MDS at the time of diagnostic workup is worse, both statistically and clinically, than that reported by the GP. Notably, we observed that this holds true not only for patients who were transfusion-dependent at clinical presentation, but also for those who were not, thereby

showing the major negative impact of the disease itself on patients' lives. To the best of our knowledge, this is the first study to also document fatigue severity in MDS across the whole spectrum of baseline risk-group categories, covering both lower and higher risk patients, as defined by the most widely used disease-risk classifications (i.e., IPSS and IPSS-R).

Steensma and colleagues [14] performed an internet-based survey on 359 pretreated patients with MDS (mean time since diagnosis was slightly more than 2 years), of whom 66% had received treatments beyond transfusion support therapies. They found that fatigue was associated with significant impairment in broader HRQOL domains and, similar to our findings, they noted that fatigue reported by patients with MDS was greater than that reported by the GP. However, it is difficult to make a direct comparison with our results, as patients in the prior study had already begun treatment whereas ours were treatment naïve. Moreover, being an internet-based survey, data on disease-risk classification were not available for more refined analyses in the prior study. Another internet-based survey conducted with 145 patients with MDS also observed that fatigue was a key concern in this population, even after many years post diagnosis (mean time from diagnosis was 6.6 years). This study found that patient perceived energy preservation, physical activity, and naps were the most helpful strategies for managing fatigue [28].

Another finding from our study was the difference in the ability of the IPSS and the IPSS-R indices to capture baseline fatigue burden. This data have major clinical implications for further improving risk-adapted strategies for managing MDS. When investigating the magnitude of difference in fatigue severity between patients MDS and the GP by stratifying patients according to the IPSS, there was a lack of sensitivity in capturing the burden of fatigue across its four risk-group categories. For example, patients classified in the two lower risk disease groups (i.e., *low* and *intermediate-1*) both reported clinically meaningful worse fatigue than the GP.

Conversely, when using the IPSS-R, we found a rather proportional rise of fatigue severity as IPSS-R risk-group categories increased in severity. Indeed, patients with the lowest risk (i.e., *very low*) did not report a level of fatigue different from the GP, while those classified in the highest risk-group category (i.e., *very high*) reported differences that exceeded twice the magnitude of a clinically meaningful difference in fatigue severity. A possible explanation of the markedly different ability of these two prognostic indices in reflecting fatigue severity is the more refined classification of the variables that are used to compute the IPSS-R compared with the IPSS. For example, the IPSS-R distinguishes between five cytogenetic subgroups (compared with the three of the IPSS), and has more detailed threshold of blast percentages, for example, separating marrow blasts <5% into 0–2% and >2–<5%. In addition, the IPSS-R includes more clinically relevant cutoff points of cytopenias, and it also considers the depth of cytopenias, rather than just the number of them as it is for the IPSS index [7].

While both scoring systems are widely used in routine practice, it should be noted that all drugs approved for this disease have been developed using the traditional IPSS classification [17] and this is still a commonly used index in clinical practice to decide the choice of therapy for individual patients [8].

Our findings of the better performance of the IPSS-R (compared to the IPSS) in capturing patient-reported fatigue suggest its use in clinical practice may enhance patient management. For example, one of the key challenges of treatment decision-making is to determine when patients with lower risk disease at presentation should start therapy [29] and to identify lower risk patients who may benefit the most from earlier treatments [30]. Notably, we found variations within the mostly broad lower risk group of patients by the IPSS-R (i.e., *very low*, *low*, and *intermediate* risk). Specifically, we observed that while the *very low*-risk group did not report clinically meaningful worse fatigue than that of the GP, this was not the case for those with *low* or *intermediate* risk. This suggests that for these latter two groups, interventions aimed at improving fatigue can be of particular value.

This study has limitations. Although we considered the two most commonly used disease-risk classification in MDS to examine their ability to capture fatigue severity, it should be noted that other prognostic indices are also available [5]. In addition, further analyses will be necessary to elucidate the possible relationships between burden of fatigue and other symptoms or broader HRQOL aspects.

Our study also has notable strengths. We used a well-validated patient-reported measure of fatigue which allowed us to determine not only the statistical significance of our findings but, most importantly, the magnitude of the clinical impact of fatigue impairment. Also, to the best of our knowledge, this is the largest study ever conducted to examine fatigue in this population. Finally, given the observational nature of the study across several centers, we included patients with MDS who are most likely to be seen in daily practice, hence providing further confidence in generalizability of our findings.

In conclusion, our results indicate that fatigue reported by newly diagnosed patients with MDS is clinically meaningful worse than that reported by the GP. Also, compared with the IPSS classification, the IPSS-R provides a better stratification of patients with regard to their fatigue severity and, therefore, its use may further enhance more personalized treatments.

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Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Fig. 1. The Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Questionnaire.
This is the questionnaire that was used to assess patient-reported fatigue in the current study.

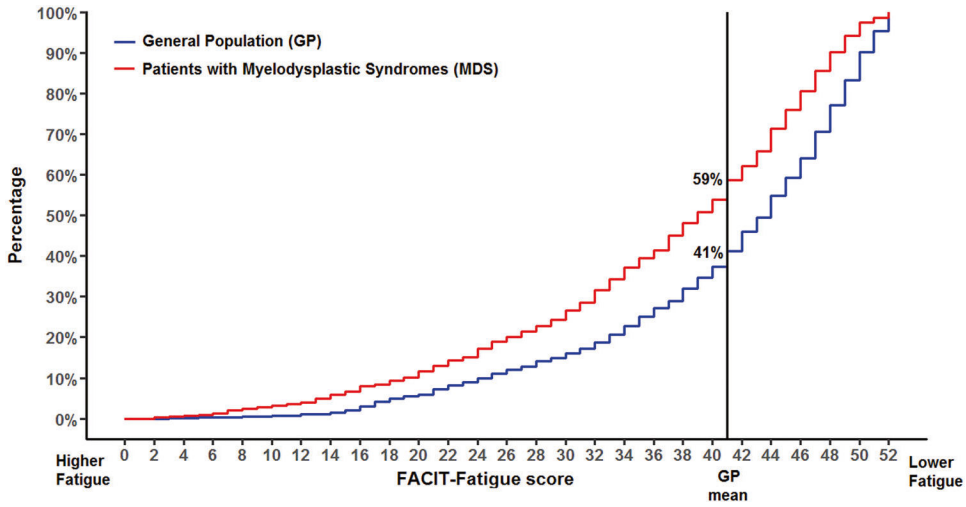

Fig. 2. Cumulative distribution of FACIT-Fatigue scores in patients with MDS and the general adult population.

Starting from the left side of the figure, the height of each curve represents the overall proportion of individuals reporting an equal or higher fatigue burden than that represented by the corresponding FACIT-fatigue score. The vertical line represents the mean FACIT-Fatigue score in the general population.

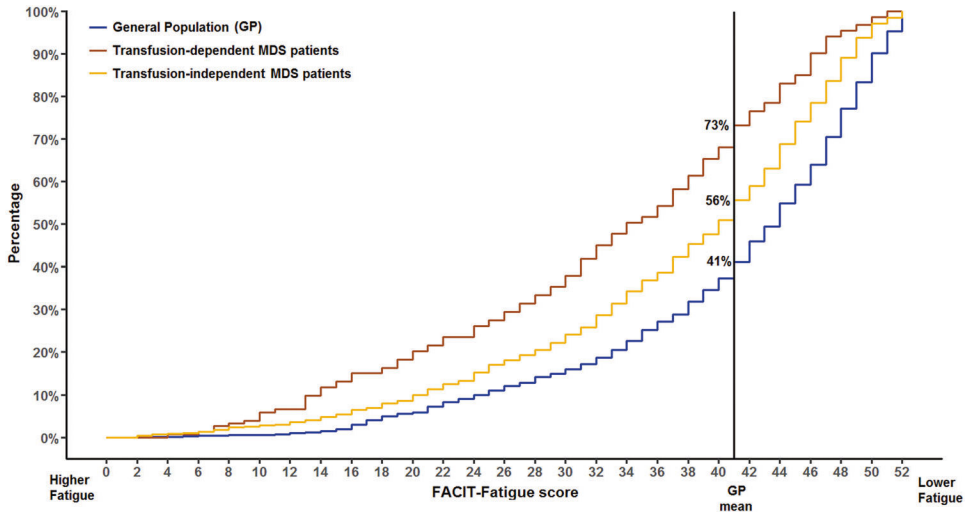

Fig. 3. Cumulative distribution of FACIT-Fatigue scores in patients with MDS by transfusion dependency and the general adult population.

Transfusion dependency was defined as having received at least one red blood cell transfusion every 8 weeks over a period of 4 months. Starting from the left side of the figure, the height of each curve represents the overall proportion of individuals reporting an equal or higher fatigue burden than that represented by the corresponding FACIT-fatigue score. The vertical line represents the mean FACIT-Fatigue score in the general population.

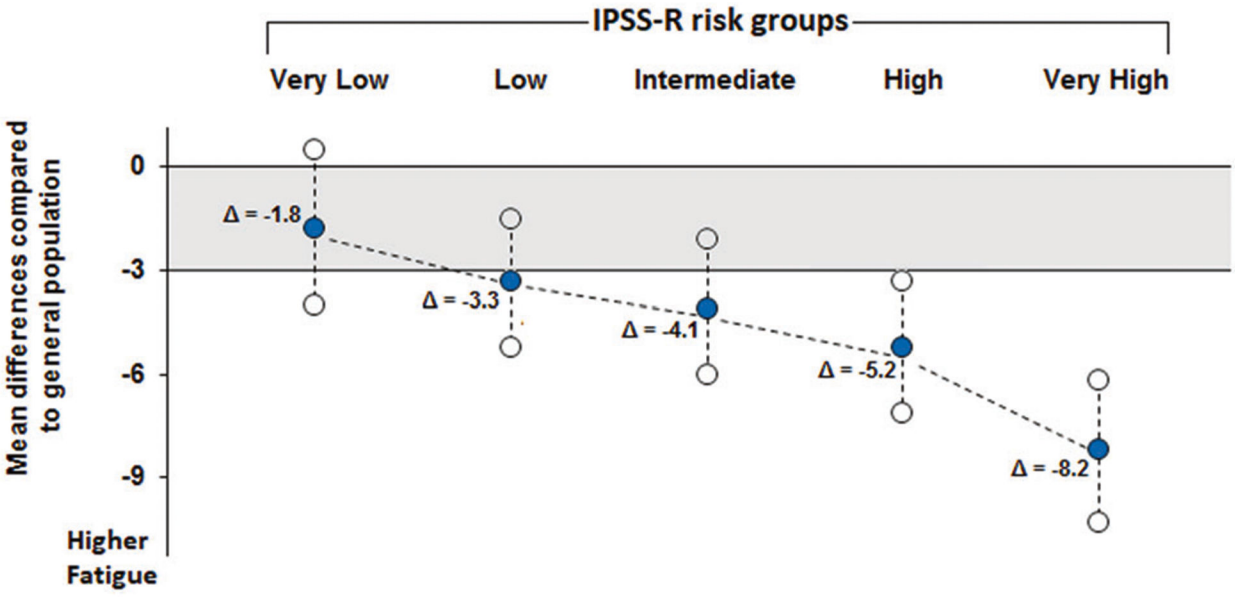

Fig. 4. Mean differences in FACIT-Fatigue scores between MDS patients and the GP by IPSS-R risk classification.

Mean differences were adjusted for age, sex, and presence of comorbidity. Connecting lines among adjusted mean differences of different MDS risk groups were plotted only for descriptive purposes. The gray shaded area indicates that the difference lies below the threshold for a clinically meaningful difference (3 points).

Table 1

Characteristics of patients with MDS by lower and higher risk disease according to IPSS and IPSS-R risk classifications.

	IPSS risk classification (*N* = 927)		IPSS-R risk classification (*N* = 902)[a]	
	Lower[b]	Higher[c]	Lower[d]	Higher[e]
Sex; *n* (%)				
Male	301 (59.5)	267 (63.4)	224 (58.8)	328 (63.0)
Female	205 (40.5)	154 (36.6)	157 (41.2)	193 (37.0)
Age, years				
Median	74.5	72.0	74.0	72.9
Range (IQR)	68.0–80.0	64.0–78.0	66.6–79.3	66.0–78.8
Time since diagnosis (weeks)				
Median	0.0	0.0	4.3	0.0
Range (IQR)	0.0–4.4	0.0–4.4	0.0–4.3	0.0–4.3
ECOG performance status; *n* (%)				
0	229 (46.0)	136 (32.5)	193 (51.3)	167 (32.4)
1	220 (44.2)	199 (47.5)	157 (41.8)	247 (47.8)
≥2	49 (9.8)	84 (20.0)	26 (6.9)	102 (19.8)
Missing	8 (.)	2 (.)	5 (.)	5 (.)
Hemoglobin levels; g/dL				
Median	9.9	9.1	10.3	9.0
Range (IQR)	8.8–11.6	8.2–10.4	9.1–12.0	.8.1–10.2
Platelets count; 10^9/L				
Median	127.5	71.0	139.0	73.0
Range (IQR)	70.0–239.0	37.0–120.0	84.0–249.0	39.0–132.0
Absolute neutrophil count; 10^9/L				
Median	2.1	1.0	2.3	1.1
Range (IQR)	1.2–3.6	0.5–1.9	1.4–3.8	0.6–2.1
Presence of comorbidities[f]; *n* (%)				
No	223 (44.3)	198 (47.1)	180 (47.4)	231 (44.5)
Yes (at least one)	281 (55.7)	222 (52.9)	200 (52.6)	288 (55.5)
Missing	2 (.)	1 (.)	1 (.)	2 (.)
Transfusion dependency[g]; *n* (%)				
No	437 (87.1)	330 (78.9)	338 (89.0)	415 (80.6)
Yes	65 (12.9)	88 (21.1)	42 (11.0)	100 (19.4)
Not available	4 (.)	3 (.)	1 (.)	6 (.)

IPSS International Prognostic Scoring System, *IPSS-R* International Prognostic Scoring System-Revised, *IQR* interquartile range.

[a] *N* = 902, 25 patients with MDS were missing IPSS-R classification.

[b] Including patients with IPSS low and intermediate-1 risk.

[c] Including patients with IPSS intermediate-2 and high-risk.

[d] The “lower” category includes patients classified according to the IPSS-R index as “very low”, “low,” and those “intermediate” with an IPSS-R score ≤3.5.

[e] The “higher” category includes patients classified according to the IPSS-R index as “high”, “very high,” and those “intermediate” with an IPSS-R score >3.5.

[f] Comorbidity has been measured using the hematopoietic cell transplantation-comorbidity index (HCT-CI).

[g] Transfusion dependency was defined as having received at least one red blood cell transfusion every 8 weeks over a period of 4 months.

Table 2

Adjusted mean differences in FACIT-Fatigue scores between the GP and patients with MDS, overall, by transfusion dependency and by IPSS and IPSS-R risk classifications.

	Mean	SD	Mean difference from GP (95% CI)[a]	*P*	Magnitude of clinical significance[b]
General population (GP)	40.6	10.0			
MDS total sample[c]	36.3	11.4	−4.6 (−5.9, −3.2)	<0.001	*
Transfusion dependency[d]					
No	37.1	11.1	−3.7 (−5.1, −2.3)	<0.001	*
Yes	32.4	12.0	−8.5 (−10.6, −6.4)	<0.001	**
MDS by IPSS risk					
Low	38.3	11.2	−3.0 (−4.8, −1.1)	0.002	*
Intermediate-1	37.1	10.7	−3.3 (−5.0, −1.5)	<0.001	*
Intermediate-2	35.2	11.7	−6.0 (−7.7, −4.3)	<0.001	**
High	33.3	11.6	−8.1 (−10.3, −5.8)	<0.001	**
MDS by IPSS-R risk					
Very low	39.9	9.1	−1.8 (−4.0, 0.5)	0.119	NR
Low	37.7	11.7	−3.3 (−5.2, −1.5)	<0.001	*
Intermediate	36.3	11.2	−4.1 (−6.0, −2.1)	<0.001	*
High	35.3	10.7	−5.2 (−7.1, −3.3)	<0.001	*
Very high	33.6	12.5	−8.2 (−10.3, −6.2)	<0.001	**

CI confidence intervals, *GP* general population, *MDS* myelodysplastic syndromes, *IPSS* International Prognostic Scoring System, *IPSS-R* International Prognostic Scoring System-Revised, *NR* not reached, *SD* standard deviation.

[a] Mean difference score adjusted for age, sex, and presence of comorbidity.

[b] * = reaching at least a 3-points difference,

** = reaching at least a 6-points difference.

[c] Four patients with MDS were excluded due to not evaluable FACIT-Fatigue questionnaire; for the FACIT-Fatigue measure, lower scores indicate worse fatigue levels.

[d] Transfusion dependency was defined as having received at least one red blood cell transfusion every 8 weeks over a period of 4 months.