Original Article

Patient-Reported Outcomes Enhance the Survival Prediction of Traditional Disease Risk Classifications: An International Study in Patients With Myelodysplastic Syndromes

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BACKGROUND: Current prognostic systems for myelodysplastic syndromes (MDS) are based on clinical, pathologic, and laboratory indicators. The objective of the current study was to develop a new patient-centered prognostic index for patients with advanced MDS by including self-reported fatigue severity into a well-established clinical risk classification: the International Prognostic Scoring System (IPSS). **METHODS:** A total of 469 patients with advanced (ie, IPSS intermediate-2 or high-risk) MDS were analyzed. Untreated patients (280 patients) were recruited into an international prospective cohort observational study to create the index. The index then was applied to an independent cohort including pretreated patients with MDS from the Dana-Farber Cancer Institute in Boston, Massachusetts (189 patients). At baseline, patients completed the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). **RESULTS:** A new prognostic index was developed: the FA-IPSS(h), in which FA stands for fatigue and h for higher-risk. This new risk classification enabled the authors to distinguish 3 subgroups of patients with distinct survival outcomes (ie, risk-1, risk-2, and risk-3). Patients classified as FA-IPSS(h) risk-1 had a median overall survival (OS) of 23 months (95% confidence interval [95% CI], 19-29 months), whereas those with risk-2 had a median OS of 16 months (95% CI, 12-17 months) and those with risk-3 had a median OS of 10 months (95% CI, 4-13 months). The predictive accuracy of this new index was higher than that of the IPSS alone in both the development cohort as well as in the independent cohort including pretreated patients. **CONCLUSIONS:** The FA-IPSS(h) is a novel patient-centered prognostic index that includes patients' self-reported fatigue severity. The authors believe its use might enhance physicians' ability to predict survival more accurately in patients with advanced MDS. ***Cancer* 2018;124:1251-9.** *© 2017 American Cancer Society.*

KEYWORDS: fatigue, myelodysplastic syndromes, patient-reported outcomes, quality of life, survival.

INTRODUCTION

Myelodysplastic syndromes (MDS) are a heterogeneous group of myeloid disorders that are characterized by ineffective hematopoiesis, resulting in different types of peripheral blood cytopenias.[1] Because of the large variability of the disease course, outcome prediction at the time of clinical presentation is critical and decision making is challenging.[2] Therefore,

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Additional supporting information may be found in the online version of this article.

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the scientific community has historically made major efforts to develop risk scoring systems that would help clinicians to adopt personalized treatment strategies.[3]

In routine practice, one of the most widely used prognostic indices at the time of diagnosis is the International Prognostic Scoring System (IPSS),[3-5] which was developed for untreated patients, and its use is recommended by major international guidelines.[1] This index is based on the following laboratory data: percentage of bone marrow blasts, number of peripheral cytopenias, and cytogenetic abnormalities. Based on the scores from these 3 broad disease variables, patients are assigned to 4 risk groups with distinct overall survival (OS): low-risk, intermediate-1, intermediate-2, and high-risk MDS.[5] Patients classified in these latter 2 groups (ie, those with advanced disease) at the time of diagnosis have poor life expectancy,[4] making accurate prediction of OS a critical issue for optimal clinical management.

However, the IPSS is not dynamic and is meant to be applied only at the time of diagnosis. Moreover, it is less able to distinguish the 2 highest groups from one another, especially for patients who have received prior treatment. Given that affected patients often are of advanced age, the difference might suggest aggressive treatment versus supportive care among those with advanced disease. Therefore, there is a critical need to further increase prognostic accuracy among patients with IPSS intermediate-2 and high-risk MDS.

In a previous study, we demonstrated that patients' self-reported fatigue provides independent prognostic information for OS in newly diagnosed patients with advanced MDS.[6] These data have laid the groundwork for further investigation regarding how the inclusion of self-reported fatigue could be implemented into already existing prognostic models to possibly improve survival prediction.[7] Within the last decade, there has been mounting evidence that patient-reported outcomes (PROs), including self-reported symptoms, provide prognostic information for survival above and beyond traditional disease factors.[8-13] However, to the best of our knowledge, studies in this area have been confined to descriptive data analysis and the clinical implication of this evidence has been challenged.[14]

The main objective of the current study was to develop a patient-centered prognostic index for patients with advanced MDS to be used in the clinic. We aimed to do this by incorporating self-reported fatigue into the well-established IPSS classification for patients with advanced disease. With the goal of clinical usefulness, and understanding that many patients with advanced disease as seen in the clinic having received prior treatments, the secondary objective of the current study was to investigate whether this new index could enhance the predictive accuracy of IPSS in an independent cohort that included pretreated patients.

MATERIALS AND METHODS

International Development Cohort

The development cohort resulted from an international prospective observational study of patients with newly diagnosed MDS from 37 centers in 9 countries. The primary outcome was the investigation of the value of patients' self-reported fatigue severity as a predictor of OS, and the results were published elsewhere.[6] Herein, we report the results of a prespecified additional aim of the research protocol, namely the development of a patient-centered prognostic index.

Adult patients diagnosed with MDS with an IPSS risk score of intermediate-2 or high-risk (ie, advanced disease) within 6 months before the date of registration were eligible. At baseline (ie, before treatment for advanced disease other than supportive therapy with transfusions [ie, untreated patients]), all patients were asked to complete a health-related quality-of-life (HRQOL) assessment and could be enrolled regardless of the type of therapy that they might receive after baseline evaluation. Additional details have been previously reported.[6,15]

All patients provided written informed consent and the study was approved by the ethics committees of each participating center. The study was conducted in accordance with the Declaration of Helsinki and registered at ClinicalTrials.gov (ClinicalTrials.gov identifier NCT00809575).

Independent Validation Cohort

Patients for the independent cohort were taken from a database maintained at the Dana-Farber Cancer Institute (DFCI) in Boston, Massachusetts. This overall cohort has been described elsewhere.[16,17] None of these patients was part of the development cohort. Briefly, beginning in 2006, adult patients with biopsy-confirmed MDS presenting for initial evaluation at DFCI (hereafter denoted as "baseline" for the DFCI cohort) were eligible for enrollment into the Dana-Farber/Harvard Cancer Center MDS Clinical Research Information System database; 85% of eligible patients consented to enrollment. Starting in 2011, an ongoing effort was made to enrich the database for patients with higher risk disease.[18] Patients enrolled through October 2016 were included in this analysis. The Clinical Research Information System database includes clinical, pathologic, and laboratory data from the initial

evaluation at DFCI, which was used to determine the original IPSS score for each patient. For this analysis, only those patients classified with IPSS intermediate-2 risk and high-risk disease were included. At baseline, enrolled patients also completed a series of HRQOL questionnaires. It is important to note that although their HRQOL assessment was performed concurrently with their assessment of having intermediate-2 or high-risk disease, patients could have been treated with agents other than supportive care before their presentation to DFCI, unlike the international cohort above.

Baseline HRQOL Assessment and Primary Scale for Prognostic Analysis

At baseline, all patients in both cohorts completed the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30),[19] an internationally validated HRQOL questionnaire suitable for use with a generic cancer population. The EORTC QLQ-C30 is a 30-item questionnaire comprising 5 function scales (physical, role, emotional, cognitive, and social), 3 symptom scales (fatigue, nausea/vomiting, and pain), 6 single-item scales (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a global health status scale. The EORTC QLQ-C30 scores were calculated using the recommended EORTC procedures.[20]

Based on previous evidence demonstrating that fatigue is a major concern for patients with MDS,[21] we defined in the development protocol a priori that the fatigue scale would be regarded as the primary HRQOL outcome for OS prognostic factor analysis. In addition, in our development cohort, fatigue was found to demonstrate the highest prognostic value for OS compared with all other EORTC QLQ-C30 outcomes (data not shown). Instructions regarding how we scored the fatigue scale are available in Supporting Information Table 1.

Statistical Analysis

Definitions and methods

OS was measured from the date of diagnosis (development cohort) or date of initial evaluation at DFCI (independent validation cohort) up to death from any cause. Patients were censored at the date of their last follow-up if they were not dead at the time of analysis. Univariate and multivariable Cox proportional hazards regression analyses were performed to estimate hazard ratios (HRs) with 95% confidence intervals (95% CIs). The log-rank test was used to assess differences in Kaplan-Meier survival curves by risk groups. The predictive performance of the new prognostic index was assessed with both discrimination, using the Harrell C-index,[22] and calibration. Model fit of the prognostic index was assessed by Akaike information criterion (AIC). Statistical significance for all tests was set as 2-sided $\alpha = .05$.

Identification of the prognostic index and sensitivity analyses

A fatigue threshold defining 4 risk groups was chosen that provided both the highest predictive performance for OS and the smallest possible heterogeneity between risk groups. Based on this threshold, a final prognostic index was identified defining 3 risk categories. Kruskal-Wallis and Fisher exact tests were performed to investigate possible differences in baseline sociodemographic and clinical characteristics by the 3 risk groups. In addition, a bootstrap resampling procedure[23] was run to assess the robustness of the novel index, based on stepwise selection of a Cox proportional hazards multivariable model controlling for key confounding variables (5000 resamples).

Internal and external validation

Discrimination and calibration were evaluated for both the development (internal validation) and independent application (external validation) data sets. Calibration was evaluated by estimating the standardized incidence ratio (SIR) and performing a goodness-of-fit chi-square test for the effect of risk group, using a Poisson regression model-based approach.[24] SIR is the percentage of observed out of expected events from the prognostic index, with a value equal to 1 indicating the best performance. For external validation, calibration was evaluated by comparing the risk-stratified Kaplan-Meier survival estimates between data sets. All analyses were performed using SAS statistical software (version 9.4; SAS Institute Inc, Cary, North Carolina).

RESULTS

The development cohort enrolled 280 patients with MDS with a median age of 71 years (range, 32-89 years). At a median follow-up of 15 months (interquartile range, 8-27 months), 113 deaths were observed. The median OS of the overall cohort was 17 months (95% CI, 15-19 months). Additional characteristics of these patients are reported in Table 1.

Identification of New Risk Categories by Adding Self-Reported Fatigue to the IPSS Classification

The final cutoff value of 45 points was selected for the EORTC QLQ-C30 fatigue scale. This cutoff value

TABLE 1. Main Characteristics of the Development Cohort (N=280)

Baseline Variables	
Age, y	
Mean (SD)	70.02 (10.51)
Median	71.25
Interquartile range	64.25-77.50
Sex, no.(%)	
Male	176 (62.86)
Female	104 (37.14)
Living arrangements, no. (%)	
Living alone	38 (13.62)
Living with someone	241 (86.38)
Transfusion dependency, no.(%)[a]	
No	224 (80)
Yes	56 (20)
Evolution from lower IPSS scores, no.(%)	
No	212 (75.71)
Yes	68 (24.29)
ECOG performance status, no. (%)	
0	73 (26.07)
1	148 (52.86)
2	46 (16.43)
3	13 (4.64)
HCT comorbidity index	
Mean (SD)	1.46 (2.63)
Median	0.00
Interquartile range	0.00-2.00
Time from diagnosis, wk[b]	
Mean (SD)	2.55 (4.39)
Median	0.00
Interquartile range	0.00-4.35
IPSS risk group, no. (%)	
Intermediate-2	206 (73.6)
High	74 (26.4)
Time-dependent variables	
Treatment, no. (%)	
No therapy	13 (4.64)
Supportive only	43 (15.36)
Low intensity	16 (5.71)
Hypomethylating agents	165 (58.93)
Intensive chemotherapy	43 (15.36)
AML progression, no. (%)	
No	162 (57.86)
Yes	118 (42.14)
Stem cell transplantation, no. (%)	
No	254 (90.71)
Yes	26 (9.29)

Abbreviations: AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; HCT, hematopoietic cell transplantation; IPSS, International Prognostic Scoring System; SD, standard deviation.
[a] Defined a priori in the protocol as having received at least 1 red blood cell transfusion every 8 weeks over a period of 4 months.
[b] Diagnosis of intermediate-2 or high-risk myelodysplastic syndromes according to the IPSS risk index categories.

provided the best result in terms of predictive performance for OS and heterogeneity between the 4 groups identified: 1) IPSS intermediate-2 with low fatigue (<45 points) (123 patients); 2) IPSS intermediate-2 with high fatigue (≥45 points) (83 patients); 3) IPSS high-risk with low fatigue (<45 points) (44 patients); and 4) IPSS high-risk with high fatigue (≥45 points) (30 patients). OS curves of these 4 initial risk group categories were estimated. Patients with IPSS intermediate-2 and high fatigue and patients with IPSS high-risk and low fatigue were found to have a similar median OS and HRs (as defined vs the lowest risk category according to the new classification [ie, the first group described above]): 16 months (95% CI, 13-19 months; HR, 1.676 [95% CI, 1.075-2.612]) and 15 months (95% CI, 10-17 months; HR, 1.703 [95% CI, 1.213-2.389]), respectively. Therefore, these 2 groups were combined and the resulting new risk score classification was named FA-IPSS(h), in which FA stands for fatigue and h for higher-risk (patients).

According to the new FA-IPSS(h) index, patients were categorized into 3 groups: risk-1 (123 patients), risk-2 (127 patients), and risk-3 (30 patients). Details regarding how we defined these categories are reported in Supporting Information Table 2.

OS According to the New FA-IPSS(h) Index

After reclassification of patients from the development cohort into the FA-IPSS(h) index, survival analyses were performed. Patients with the most favorable prognosis (risk-1) were found to have a median OS of 23 months (95% CI, 19-29 months), whereas those with risk-2 had a median OS of 16 months (95% CI, 12-17 months) and those with the least favorable prognosis (risk-3) had a median OS of 10 months (95% CI, 4-13 months). In contrast, the median OS times were 20 months (95% CI, 17-24 months) and 13 months (95% CI, 9-16 months), respectively for patients with IPSS intermediate-2 and high-risk scores.[6] Survival curves of the 3 risk group categories of the new FA-IPSS(h) index and those of the traditional IPSS are depicted in Figures 1A and 1B, respectively. In univariate analysis, the risk-2 and risk-3 categories of the FA-IPSS(h) index were found to be significantly associated with a shorter OS compared with risk-1 (ie, the lowest risk category). Risk-2 had an HR of 1.694 (95% CI, 1.243-2.307 [$P < .001$]) and risk-3 had an HR of 3.123 (95% CI, 1.787-5.456 [$P < .001$]). The original IPSS high-risk category showed an HR of 3.178 (95% CI, 1.742-5.798) compared with the intermediate-2 group.[6] In addition, the FA-IPSS(h) index provided a lower AIC (1767.4) with respect to the IPSS index (1775.2), demonstrating a better model fit.

According to the new classification, 83 patients belonging to the IPSS intermediate-2 risk group and 44 patients with IPSS high-risk were reclassified as FA-IPSS(h) risk-2, thereby identifying an additional risk category with respect to the original IPSS index. OS rates at 6

months, 1 year, and 2 years were markedly different among the 3 groups (Table 2).

Internal Validation and Calibration

The Harrell C-index for FA-IPSS(h) was 0.610 in comparison with 0.565 for the IPSS, indicating an important improvement in discriminatory ability. The SIR was equal to 1 overall and for each FA-IPSS(h) index group category, which demonstrated optimal calibration performance. In addition, the group-based goodness-of-fit tests indicated that observed and predicted events were not statistically different among FA-IPSS(h) risk groups.

Sensitivity Analyses

Sociodemographic and clinical characteristics by novel risk group categories are reported in Table 3. In multivariable analysis, the FA-IPSS(h) risk categories remained the only baseline variable independently associated with OS (Table 4). The FA-IPSS(h) risk-2 and risk-3 categories were simultaneously selected in 85.9% of the bootstrap-generated multivariable models (4294 of 5000 models), thus confirming their independent prognostic value.

External Application of the FA-IPSS (h) in an Independent Cohort Including Pretreated Patients

The median age of patients in the independent cohort was 68 years, and 67% were male. It is important to note that 24% of these patients received a hypomethylating agent during the month before treatment (see Supporting Information Table 3). At a median follow-up of 13 months, we observed 124 deaths. Applying the FA-IPSS(h) definition to these data, 52%, 41%, and 7% of patients, respectively, were classified as risk-1, risk-2, and risk-3. The median OS in the independent cohort data by FA-IPSS(h) risk was similar to that of the development cohort for each of the 3 risk groups, indicating good external calibration. Patterns of OS throughout 2 years also were found to be distinct between risk groups as in the development cohort of untreated patients (Table 2), with one exception: the 2-year OS was similar for the FA-IPSS(h) risk-3 and risk-2 categories. In this regard, we performed additional analyses to assess possible systematic differences in baseline characteristics and risk classification between pretreated (46 patients) and untreated (143 patients) patients (see Supporting Information Table 3). We also investigated OS patterns through 2 years by these 2 groups (see Supporting Information Table 4). Overall, these results suggested that an association between FA-IPSS(h) and survival was not confounded by prior treatment in the independent cohort.

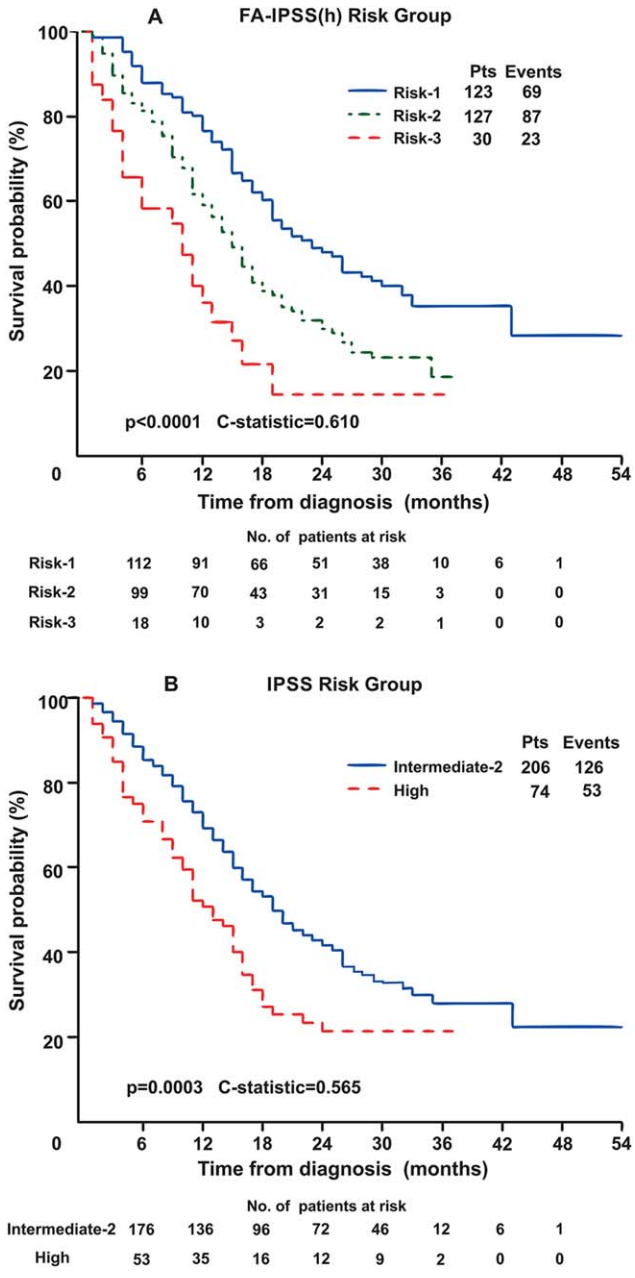

Figure 1. Overall survival in the development cohort, using (A) the new Fatigue International Prognostic Scoring System(h) (FA-IPSS(h), in which FA stands for fatigue and h for higher-risk) and (B) the standard IPSS risk group classification. Fatigue is the patient (pt)'s self-reported fatigue scale from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30).

Although the FA-IPSS(h) was significantly associated with OS ($P = .026$), the IPSS index was not ($P = .472$) within the data from the independent cohort (see Supporting Information Fig. 1). Correspondingly,

TABLE 2. OS by FA-IPSS(h) Index Risk Group Categories in the Development Cohort (All Untreated) and Independent Cohort (Including Some Treated Patients)

FA-IPSS(h) Risk Group	Median OS, Months (95% CI)	6 Months[a] OS (95% CI)	1 Year[a] OS (95% CI)	2 Years[a] OS (95% CI)
Development cohort (N=280)				
Risk-1 (N=123)	23 (19-29)	92.2 (87.4-97.2)	80.3 (73.4-87.8)	48.9 (40.3-59.1)
Risk-2 (N=127)	16 (12-17)	81.4 (74.7-88.9)	60.5 (52.3-70.0)	29.4 (23.8-41.1)
Risk-3 (N=30)	10 (4-13)	61.5 (46.4-81.4)	37.6 (23.9-59.1)	13.4 (4.9-35.8)
Independent cohort (N=189)				
Risk-1 (N=99)	20 (14-31)	91.3 (83.3-95.6)	69.7 (58.9-78.1)	46.7 (35.7-56.9)
Risk-2 (N=77)	13 (9-18)	73.7 (61.9-82.3)	50.6 (38.4-61.5)	30.3 (19.7-41.5)
Risk-3 (N=13)	9 (3-41)	58.3 (27.0-80.1)	41.7 (15.3-66.5)	33.3 (10.3-58.8)

Abbreviations: 95% CI, 95% confidence interval; FA-IPSS(h), Fatigue International Prognostic Scoring System (in which FA stands for fatigue and h for higher-risk); OS, overall survival.
[a] This column reports the percentage of patients alive at 6 months, 1 year, and 2 years.

the FA-IPSS(h) index provided a lower AIC versus the IPSS index (1118.0 vs 1122.6) and enhanced discriminative accuracy (Harrell C-index of 0.581 vs 0.535), thus demonstrating an improvement in model fit and predictive performance with FA-IPSS(h) versus IPSS in this independent cohort.

DISCUSSION

We developed the FA-IPSS(h) index, a novel patient-centered prognostic index for individuals with advanced MDS, by including patient's self-reported fatigue into a well-established and widely used disease prognostic index (ie, the IPSS). It is important to note that this new index enhanced survival prediction in both the development and independent cohorts by making a more refined distinction among subgroups of patients. This finding has major clinical implications considering the importance of OS prediction in patients with advanced MDS.

The better stratification of patients that results from using the FA-IPSS(h) index may improve the clinical management of patients in routine practice. For example, it might be helpful in the management of the most vulnerable patients by improving timely palliative care referrals. Indeed, previous studies of patients with other advanced cancers, who have median survival rates similar to those of the study population, have demonstrated that the early integration of palliative care with standard oncologic care resulted in better HRQOL outcomes as well as improved survival.[25] Conversely, the FA-IPSS(h) also might guide clinicians in the early identification of patients with favorable prognosis who can benefit the most from more aggressive therapies.

Implementation of this index in standard practice also might have important implications for eliciting more active patient participation during initial consultations. Unlike other prognostic tools currently used for patients with MDS, use of the FA-IPSS(h) index requires clinicians to engage patients by asking them to briefly self-assess their fatigue severity. Considering the importance of engaging patients in shared decision making[26] and that patient-physician communication in patients with advanced hematologic cancers often is challenging,[27] it will be important to evaluate in future studies whether the use of this novel index also might facilitate patient-centeredness in treatment decisions.

Historically, prognostic tools in oncology have not considered PROs, such as self-reported symptoms, but rather laboratory and pathologic markers related to disease progression. However, there currently is ample evidence indicating that patient-reported symptoms provide clinically meaningful information that suitably complements such traditional clinical data.[28] Using the same questionnaire used in the current study with a large cohort of patients with mixed cancers, Quinten et al[29] investigated the extent to which patients' and clinicians' symptom ratings contributed toward the estimation of OS. They found that both clinicians' and patients' scorings contributed independently and positively to the predictive accuracy of survival.[29] In addition, major clinical benefits, including better HRQOL and fewer hospitalizations and emergency room visits, as well as superior quality-adjusted survival, were demonstrated in a randomized controlled trial investigating the value of systematic Web data collection of patient-reported symptoms versus usual care.[30] Finally, the prominent role of patient self-report of symptoms in clinical research has been documented by the recent development of the National Cancer Institute's PRO-Common Terminology Criteria for Adverse Events,

TABLE 3. Characteristics of Patients by the 3 Risk Group Categories of the FA-IPSS(h) Development Cohort (N=280)

Baseline Variables	Risk-1 Group	Risk-2 Group	Risk-3 Group	*P*
Age, y				
Mean (SD)	69.59 (9.02)	69.87 (11.09)	72.39 (13.42)	.104
Median	70.17	72.67	75.75	
Interquartile range	64.25-75.67	64.25-77.50	62.00-83.50	
Sex, no. (%)				
Male	85 (69.11)	76 (59.84)	15 (50)	.094
Female	38 (30.89)	51 (40.16)	15 (50)	
Living arrangements, no. (%)				
Living alone	17 (13.82)	16 (12.70)	5 (16.67)	.771
Living with someone	106 (86.18)	110 (87.30)	25 (83.33)	
Transfusion dependency, no. (%)[a]				
No	102 (82.93)	102 (80.31)	20 (66.67)	.148
Yes	21 (17.07)	25 (19.69)	10 (33.33)	
Evolution from lower IPSS scores, no. (%)				
No	93 (75.61)	95 (74.8)	24 (80)	.901
Yes	30 (24.39)	32 (25.2)	6 (20)	
ECOG performance status, no. (%)				
0	42 (34.15)	28 (22.05)	3 (10)	.005
1	64 (52.02)	68 (53.54)	16 (53.34)	
2	15 (12.2)	21 (16.54)	10 (33.33)	
3	2 (1.63)	10 (7.87)	1 (3.33)	
HCT comorbidity index				
Mean (SD)	1.19 (1.98)	1.81 (3.27)	1.13 (1.68)	.236
Median	0	1	1	
Interquartile range	0.00-2.00	0.00-3.00	0.00-2.00	
Serum LDH, U/L				
Mean (SD)	401.70 (315.71)	415.45 (247.35)	477.82 (377.32)	.355
Median	325	355.5	321	
Interquartile range	193.00-519.00	260.00-501.00	227.00-596.50	
White blood cell count, $\times 10^9$/L				
Mean (SD)	4.35 (4.55)	4.24 (6.07)	6.55 (8.91)	.075
Median	2.84	2.27	3.25	
Interquartile range	1.90-4.62	1.60-4.42	2.03-6.10	
IPSS risk group, no. (%)				
Intermediate-2	123 (100)	83 (65.35)	0 (0)	<.001
High	0 (0)	44 (34.65)	30 (100)	
Time-dependent variables				
Treatment, no. (%)				
No therapy	4 (3.25)	7 (5.51)	2 (6.67)	.117
Supportive care only	16 (13.01)	19 (14.96)	8 (26.67)	
Low intensity	4 (3.25)	8 (6.30)	4 (13.33)	
Hypomethylating agents	81 (65.85)	73 (57.48)	11 (36.67)	
Intensive chemotherapy	18 (14.63)	20 (15.75)	5 (16.67)	
AML progression, no. (%)				
No	75 (60.98)	73 (57.48)	14 (46.67)	.364
Yes	48 (39.02)	54 (42.52)	16 (53.33)	
Stem cell transplantation, no. (%)				
No	107 (86.99)	119 (93.7)	28 (93.33)	.195
Yes	16 (13.01)	8 (6.3)	2 (6.67)	

Abbreviations: AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; FA-IPSS(h), Fatigue International Prognostic Scoring System (in which FA stands for fatigue and h for higher-risk); HCT, hematopoietic cell transplantation; IPSS, International Prognostic Scoring System; LDH, lactate dehydrogenase; SD, standard deviation.

[a] Defined a priori in the protocol as having received at least 1 red blood cell transfusion every 8 weeks over a period of 4 months.

which points out the central role of the patient's voice in health care management.[31]

The current study has limitations. We could not perform an external validation of this new index in a sample of newly diagnosed patients with untreated MDS given the lack of QOL research in patients with MDS,[32] which has limited the availability of similar data sets in this area. However, we noted that our additional analysis of patients included in the independent cohort demonstrated that the novel FA-IPSS(h) index performed similarly well in both subgroups of pretreated and untreated patients. Indeed, it distinguished 3 risk group categories with distinct median OS rates in both subgroups. Next, it should be noted there is a revised version of the IPSS (ie, IPSS-

TABLE 4. Multivariable Cox Regression Analyses for OS in the Development Cohort (N=280)

	Multivariable Analysis	
Variable	HR (95% CI)	*P*
Baseline covariates		
Age, y	1.012 (0.994-1.030)	.2077
Transfusion dependency[a]	1.234 (0.813-1.871)	.3231
ECOG performance status ≥ 2	1.425 (0.987-2.058)	.0591
White blood cell count, $\times 10^9$/L	1.013 (0.994-1.033)	.1699
FA-IPSS(h) risk score		
Risk-2 vs risk-1	1.551 (1.137-2.116)	.0057
Risk-3 vs risk-1	2.372 (1.418-3.968)	.0010
Time-dependent covariates		
Treatment		
Hypomethylating agents vs lower intensity	0.753 (0.512-1.110)	.1517
Chemotherapy vs lower intensity	0.744 (0.441-1.190)	.2027
AML progression	1.900 (1.354-2.665)	.0002
Stem cell transplantation	0.864 (0.448-1.667)	.6639

Abbreviations: 95% CI, 95% confidence interval; AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; FA-IPSS(h), Fatigue International Prognostic Scoring System; HR, hazard ratio; OS, overall survival.
[a] Defined a priori in the protocol as having received at least 1 red blood cell transfusion every 8 weeks over a period of 4 months.

R)[33] and further research is needed in this area. In our previous work, we found that self-reported fatigue is indeed independently associated with OS beyond the IPSS-R and that it also is weakly correlated with hemoglobin levels.[6] However, more in-depth analyses are needed to ascertain whether the inclusion of self-reported fatigue also may be integrated successfully into the IPSS-R index to further increase its prognostic accuracy. The current study also has notable strengths. We developed a prognostic tool that can be implemented easily and inexpensively in clinical practice and that also possibly could enhance a more patient-centered approach during the initial diagnostic workup. In addition, unlike many other studies in this area that used secondary data analyses, the current study was specifically designed and adequately powered to test the prognostic value of fatigue severity for survival. Patients also were recruited in a multicenter and international observational setting, lending further credit to the generalizability of the current study findings to patients typically seen in clinical practice. Finally, the FA-IPSS(h) index outperformed the original IPSS index both in the development and independent cohorts, and validation data were independently collected and analyzed.

The results of the current study demonstrate how self-reported fatigue can be implemented successfully into a well-established laboratory risk classification, thereby enabling a more accurate survival prediction in patients with advanced MDS, either untreated or pretreated. The FA-IPSS(h) index is an additional prognostic tool that might enhance clinicians' ability to provide more personalized treatment strategies. The current analysis offers a model for the integration of PROs into prognostic systems for patients with other cancers and advanced illnesses.

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CONFLICT OF INTEREST DISCLOSURES

Fabio Efficace has received personal fees from Seattle Genetics, Bristol-Myers Squibb, and Incyte; grants and personal fees from Teva and Amgen; and grants from Lundbeck for work performed outside of the current study. Gianluca Gaidano has acted as a paid member of the advisory boards of Roche, Janssen, Gilead, AbbVie, and MorphoSys for work performed outside of the current study. Franck Bonnetain has received personal fees from Nestle and Invectys; grants and personal fees from Roche, Novartis, and Celgene; and nonfinancial support from Merck Serono, Bristol-Myers Squibb, Eisai, and Integragen for work performed outside of the current study. Amelie Anota has received nonfinancial support from Pfizer/Hospira and Novartis for work performed outside of the current study. Massimo Breccia has received personal fees from Novartis, Pfizer, Incyte, and Bristol-Myers Squibb for work performed outside of the current study. Giuseppe A. Palumbo has acted as a paid member of the advisory boards of Novartis, Celgene, Janssen, and Hospira for work performed outside of the current study.

AUTHOR CONTRIBUTIONS

Fabio Efficace and **Franco Mandelli** had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: **Fabio Efficace** and **Franco Mandelli**. Acquisition, analysis, or interpretation of the data: **Fabio Efficace, Francesco Cottone, Gregory Abel, Pasquale Niscola, Gianluca Gaidano, Franck Bonnetain, Amelie Anota, Giovanni Caocci, Angel Cronin, Luana Fianchi, Massimo Breccia, Reinhard Stauder, Uwe Platzbecker, Giuseppe A. Palumbo, Mario Luppi, Rosangela Invernizzi, Micaela Bergamaschi, Lorenza Borin, Anna Angela Di Tucci, Huiyong Zhang, Mirjam Sprangers, Marco Vignetti**, and

Franco Mandelli. Drafting of the article: **Fabio Efficace, Francesco Cottone, Gregory Abel**, and **Angel Cronin**. Critical revision of the article for important intellectual content: **Fabio Efficace, Francesco Cottone, Gregory Abel, Pasquale Niscola, Gianluca Gaidano, Franck Bonnetain, Amelie Anota, Giovanni Caocci, Angel Cronin, Luana Fianchi, Massimo Breccia, Reinhard Stauder, Uwe Platzbecker, Giuseppe A. Palumbo, Mario Luppi, Rosangela Invernizzi, Micaela Bergamaschi, Lorenza Borin, Anna Angela Di Tucci, Huiyong Zhang, Mirjam Sprangers, Marco Vignetti**, and **Franco Mandelli**. Statistical analysis: **Francesco Cottone, Angel Cronin**, and **Fabio Efficace**. Obtained funding: **Fabio Efficace** and **Franco Mandelli**. Administrative, technical, or material support: **Fabio Efficace, Marco Vignetti**, and **Franco Mandelli**. Study supervision: **Fabio Efficace** and **Franco Mandelli**.

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