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Health-related Quality of Life Profile of Newly Diagnosed Patients With Myelodysplastic Syndromes by Age, Sex, and Risk Group: A Real-world Study by the GIMEMA

Fabio Efficace¹, Wael Al Essa², Uwe Platzbecker³, Pasquale Niscola⁴, Giuseppe A. Palumbo⁵, Giovanni Caocci⁶, Francesco Cottone¹, Massimo Breccia⁷, Mario Luppi⁸, Reinhard Stauder⁹, Alessandra Ricco¹⁰, Duska Petranovic¹¹, Frederic Baron¹², Maria Teresa Voso¹³, Luana Fianchi¹⁴, Chiara Frairia¹⁵, Isabella Capodanno¹⁶, Chiara Sarlo¹⁷, Marilena Fedele¹⁸, Roberto Massimo Lemoli^{19,20}, Rosangela Invernizzi²¹, Daniele Vallisa²², Nicola Di Renzo²³, Claudio Fozza²⁴, Maribel Doro²⁵, Johannes M. Giesinger²⁶, Marco Vignetti¹

GRAPHICAL ABSTRACT

927 newly diagnosed patients with myelodysplastic syndromes (MDS) with a median age of 73.3 years

506 with **lower-risk** disease
according to IPSS classification



421 with **higher-risk** disease
according to IPSS classification



Health-related quality of life (HRQoL) profile of newly diagnosed patients with MDS varies greatly by age groups and sex, as well as by disease-risk category according to the IPSS and IPSS-R classifications



Differences observed in this study regarding the HRQoL profile (by the EORTC QLQ-C30) of patients with newly diagnosed MDS should be considered when analyzing and interpreting HRQoL data in future studies. Our findings could also be used for benchmarking purposes in future studies using the EORTC QLQ-C30 questionnaire to better interpret HRQoL results



We developed regression models that can be used as pragmatic tools to calculate EORTC QLQ-C30 reference values for newly diagnosed patients classified according to both the IPSS and the IPSS-R



More than 50% of newly diagnosed patients with MDS report clinically important problems with physical functioning and dyspnea

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Correspondence: Fabio Efficace (f.efficace@gimema.it).

ABSTRACT

Health-related quality of life (HRQoL) is an important goal of therapy for patients with myelodysplastic syndromes (MDS); however, little is known about HRQoL of these patients at clinical presentation. We report HRQoL profile of newly diagnosed patients with MDS across both the International Prognostic Scoring System (IPSS) and IPSS-Revised (IPSS-R) classifications, stratified by sex and age group categories, aiming to also establish European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core30 (EORTC QLQ-C30) reference values for these patients. Analysis was based on 927 patients with a median age of 73.3 years (inter-quartile range, 66.0–79.2), of whom 506 and 421 with lower- and higher-risk disease respectively, according to the IPSS classification. HRQoL was assessed with the EORTC QLQ-C30 and substantial differences by age groups and sex, between and within lower- and higher-risk disease categories were observed. For example, within higher-risk disease patients, the youngest group (ie, 30–59 years) tended to report clinically meaningful worse outcomes across various functional and symptom domains compared with older age groups. We also developed 2 regression models allowing for the prediction of EORTC QLQ-C30 reference scores for patients classified according to either the IPSS or the IPSS-R. Investigation of prevalence rates for clinically important problems and symptoms at diagnosis revealed a substantial burden of the disease with >50% of patients reporting clinically important problems with physical functioning and dyspnea in both lower- and higher-risk disease. Our findings may help to enhance the interpretation of HRQoL outcomes in future MDS studies and to better contextualize HRQoL data from routine practice settings.

¹Data Center and Health Outcomes Research Unit, Italian Group for Adult Haematologic Diseases (GIMEMA), Rome, Italy

²Division of Hematology, Department of Translational Medicine, University of Eastern Piedmont, Novara, Italy

³Clinic and Policlinic of Hematology and Cellular Therapy, Oncology and Hemostaseology, University Hospital Leipzig, Germany

⁴Hematology Unit, Sant'Eugenio Hospital, Rome, Italy

⁵Dipartimento di Scienze Mediche, Chirurgiche e Tecnologie Avanzate "G.F. Ingrassia," University of Catania, Italy

⁶Department of Medical Sciences and Public Health, University of Cagliari, Italy

⁷Hematology, Department of Translational and Precision Medicine, Azienda Ospedaliera Policlinico Umberto I, Sapienza University of Rome, Italy

⁸University of Modena and Reggio Emilia, AOU Modena, Italy

⁹Department of Internal Medicine V (Hematology and Oncology), Innsbruck Medical University, Innsbruck, Austria

¹⁰Hematology and Transplants Unit, University of Bari, Italy

¹¹Department of Hematology, Clinical Hospital Center Rijeka, Croatia

¹²Department of Hematology, CHU de Liège, University of Liège, Belgium

¹³Department of Biomedicine and Prevention, University of Rome Tor Vergata, Italy

¹⁴Dipartimento Scienze Radiologiche Radioterapiche ed Ematologiche, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Roma, Italy

¹⁵Department of Oncology, Division of Hematology, AOU Città della Salute e della Scienza, Turin, Italy

¹⁶Hematology Unit, Azienda Unità Sanitaria Locale-IRCCS, Reggio Emilia, Italy

¹⁷Hematology and Stem Cell Transplantation Unit, University Campus Bio-Medico, Rome, Italy

¹⁸Hematology, Ospedale San Gerardo, Monza, Italy

¹⁹Cattedra di ematologia, Dipartimento di Medicina Interna (DIMI), Università di Genova, Italy

²⁰Clinica Ematologica, IRCCS Policlinico San Martino, Genova, Italy

²¹Department of Internal Medicine, San Matteo IRCCS Policlinic Foundation, University of Pavia, Italy

²²Ematologia, Ospedale di Piacenza, Italy

²³Hematology and Stem Cell Transplant Unit, "Vito Fazzi" Hospital, Lecce, Italy

²⁴Department of Medicine, Surgery, and Pharmacy, University of Sassari, Italy

²⁵Unidade de Hematologia, Hemoterapia e Oncologia (UHHO), Serviço de Transplante de Medula Óssea (STMO), Complexo Hospital de Clínicas da Universidade Federal do Paraná, Curitiba, Brazil

²⁶University Hospital of Psychiatry II, Medical University of Innsbruck, Austria

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INTRODUCTION

Myelodysplastic syndromes (MDS) are a heterogeneous group of hematopoietic stem-cell disorders characterized by cytopenia, hypercellular bone marrow, and variable risk of progression into acute myeloid leukemia. Given the large variability of disease course, and the fact that a substantial proportion of patients is not eligible for possible curative treatments, clinical decisions are challenging.¹ Therefore, major efforts have been directed by the scientific community to develop disease-risk classifications that may guide treatment decision-making in newly diagnosed patients. In current clinical practice, the International Prognostic Scoring System (IPSS)² and the IPSS-Revised (IPSS-R)³ are the most frequently used tools at diagnostic workup.

Already at the time of diagnosis, health-related quality of life (HRQoL) of MDS patients is impaired in many respects,⁴ and we recently observed that they also report clinically higher fatigue compared with their peers from the general population.⁵ Although various measures have been used to assess HRQoL in MDS research, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core30 (EORTC QLQ-C30) has been the most frequently used questionnaire.⁶ Already some 2 decades ago, results from this questionnaire helped to better understand the impact of hypomethylating agents on patients' wellbeing and functioning.⁷ Since then, it has been widely used in several other studies, including randomized controlled trials (RCTs).^{8–11}

The importance of rigorous assessment of HRQoL in patients with MDS has been emphasized in international guidelines,¹ and it has also been included in the list of core outcomes that should be reported in future studies to better understand overall treatment effectiveness.¹² However, interpretation of results from HRQoL questionnaires may be challenging if benchmarks data are lacking. To the best of our knowledge, there is no such comprehensive data (ie, reference values for HRQoL scores in newly diagnosed patients with MDS) that may help clinicians and investigators to better contextualize individual patient scores in routine care and to enhance interpretation of HRQoL scores for patient groups in clinical research. The availability of such reference values could also be important for better understanding the net clinical benefit of a given MDS therapy, by quantifying to what extent patients' HRQoL scores have returned to pre-treatment levels.

The main objective of this study was to assess HRQoL of newly diagnosed patients with MDS stratified by sex and age groups across IPSS and IPSS-R disease-risk categories, thereby also establishing EORTC QLQ-C30 reference values for these patients. A secondary objective was to describe the prevalence of clinically important problems and symptoms by disease risk at diagnosis.

PATIENTS AND METHODS

Patients

This analysis is based on the 927 newly diagnosed adult patients with MDS enrolled in the prospective international Patient-Reported Outcomes in Myelodysplastic Syndromes (PROMYS) observational study. The first patient was enrolled in November 2008 and the study was initially open for inclusion to only newly diagnosed higher-risk (ie, IPSS int-2 and high risk) patients, and main results on the first cohort of 280 patients were previously published.¹³ In 2014, the study was enlarged to also enroll IPSS lower-risk patients and the latest inclusion criteria included the following: adult patients (ie, at least 18 years old), diagnosis within 3 months before registration and written informed consent. At study entry, a baseline patient-reported outcome assessment, also including the EORTC QLQ-C30,¹⁴ was requested to be included. Patients who have received prior systemic therapy for MDS (eg, immunomodulators,

hypomethylating agents, immunosuppressive therapy, or chemotherapy) or hematopoietic cell growth factors were not eligible. Details are reported at ClinicalTrials.gov (NCT00809575). Ethical approval was obtained by the ethical committee of each participating center. Informed consent was received from all participants and the study was performed in accordance with the Helsinki declaration.

HRQoL assessment by the EORTC QLQ-C30

For the purpose of the study, we report the HRQoL data (ie, assessed at the time of study inclusion) of the EORTC QLQ-C30.¹⁴ This is an internationally widely used self-reported questionnaire, which consists of 5 functional scales: physical (PF), role (RF), social (SF), emotional (EF), and cognitive (CF) functioning and 1 global health status/quality of life (QoL) scale (ie, global QoL). It also assesses a core set of cancer-specific symptoms: fatigue (FA), pain (PA), nausea/vomiting (NV), dyspnea (DY), appetite loss (AP), insomnia (SL), diarrhea (DI), constipation (CO), and financial problems (FI). Questionnaire scoring has been performed in line with the official scoring algorithms.¹⁵ All scale standardized scores range from 0 to 100. For functioning scales and global QoL, higher scores indicate better outcomes, whereas for symptom scales high scores indicate more severe symptoms.

HRQoL reference data by IPSS and IPSS-R classifications stratified by age and sex

Prognosis for MDS patients was assessed with the IPSS. Risk classification according to the IPSS is based on the clinical and cytogenetic variables, that is, bone marrow blasts, karyotype, and cytopenias. The IPSS score was calculated according to the published scoring algorithms and this risk classification distinguishes between 4 risk groups: low-, intermediate-1-, intermediate-2-, and high-risk patients.² To refine the IPSS, the IPSS-R risk classification has been developed, which includes additional clinical and cytogenetic variables compared with the IPSS (ie, hemoglobin, platelets, and absolute neutrophil count). The IPSS-R distinguishes among 5 risk groups: very low-, low-, intermediate-, high-, and very high-risk patients.^{3,16}

For the IPSS-risk index, "lower-risk" patients comprised those with low or intermediate-1 IPSS-risk score, while "higher-risk" patients included those with intermediate-2 or high-risk IPSS-risk score. With respect to the IPSS-R risk index, patients were also classified in 2 major groups, that is lower-risk and higher-risk patients.^{17,18} Specifically, patients with IPSS-R intermediate risk score ≤ 3.5 were assigned to the lower-risk group, and those with an IPSS-R score > 3.5 were assigned to the higher-risk group.¹⁹

Statistical analysis

Main patients' characteristics were summarized by frequencies, proportions, means, SDs, medians, and interquartile ranges, depending on the type of variables. Mean scores with SDs were calculated for each scale of the EORTC QLQ-C30. Functional and symptom scores were reported by IPSS and IPSS-R risk groups (lower risk versus higher risk as defined above), overall and stratified by sex and age classes (ie, 30–59, 60–69, 70–79, and ≥ 80 years). We also performed a linear regression analysis for each EORTC QLQ-C30 scale separately for the IPSS and the IPSS-R to allow the estimation of HRQoL scores of any MDS patients according to their sex, age, presence of comorbidity,²⁰ and risk group category. For each scale of the EORTC QLQ-C30, we considered the following variables in the linear regression model: age, sex, comorbidity (yes versus no), an interaction term between age and sex, a quadratic term for age (to account for possible nonlinear dependencies on age), and either the IPSS or the IPSS-R risk group.

For descriptive purposes, we also assessed and reported the clinically meaningful differences in the mean scores of

each EORTC QLQ-C30 scale, between the youngest group of patients (ie, 30–59 years) versus older age classes. Criteria to evaluate clinically meaningful differences were scale-specific and based on the previously published guidelines²¹ that categorized mean differences between clinical groups as small, medium, or large based on the expert judgement of differences between clinically distinct groups, separately for each domain of the EORTC QLQ-C30.

We also assessed the prevalence of clinically important problems experienced by these patients, using recently developed thresholds for the EORTC QLQ-C30 questionnaire.²² The underlying definition of clinical importance was developed based on the interviews with patients and healthcare professionals²³ and comprises limitations of everyday life, worrying, and need for help and care related to a specific symptom or functional impairment. We reported the prevalence of clinically important problems separately for men and women, and separately for lower and higher IPSS-risk patients. For the purpose of this analysis, the FI scale was not considered. All analyses were performed using SAS software 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Overall, 927 patients with a mean age of 71.6 years (SD = 10.7) were enrolled between November 2008 and December 2018, across 53 centers. Median time since diagnosis was 0 weeks (interquartile range, 0.0–4.4 weeks) and 54.4% of the patients had at least 1 comorbidity. Most patients (70.3%) lived with spouse/partner, and had low (43.5%) or intermediate (42.8%) education level (Table 1). The majority of patients (n = 713; 76.9%) were enrolled in Italian centers, and there were 421 (45.6%) patients with no comorbidity. Additional clinical characteristics of study population by risk classifications have been previously reported.⁵

There were 506 (54.6%) and 381 (42.2%) patients classified as lower risk by the IPSS and IPSS-R, respectively, and 421 (45.4%) and 521 (57.8%) patients classified as higher risk by the IPSS and IPSS-R, respectively. HRQoL scores according to the disease-risk categories (lower versus higher) by the IPSS (N = 927) and IPSS-R (N = 902) classifications are reported in Table 2.

Further information on HRQoL scores by sex and by the original-risk categories of the IPSS and IPSS-R are provided in Table 3.

HRQoL by age and sex in lower-risk patients by the IPSS and IPSS-R

Clinically meaningful differences in mean scores across age groups were observed in men for 12 scales. Overall, at least 1 older age group, compared with the youngest age group, showed clinically meaningful worse outcomes in 11 scales (PF, RF, CF, SE, QL, FA, PA, AP, DY, SL, and CO) and better outcomes for one scale (FI). Further details on men are given in Table 4.

Among women, one or multiple older age groups, compared with the youngest age group, showed clinically meaningful worse outcomes in 6 scales out of 10 with clinically meaningful differences (PF, RF, QL, FA, AP, and CO). In 4 scales (CF, NV, SL, and FI), the youngest patients showed worse outcomes, and for 2 scales (FA, CO) there was a mixed pattern. The largest difference was observed for PF, indicating a medium clinically meaningful worse score for the oldest women age group compared with the youngest women age group. Further results on HRQoL profile of women are reported in Table 4.

Detailed HRQoL scores for lower-risk patients according to the IPSS-R index are reported in Suppl. Table S1.

HRQoL by age and sex in higher-risk patients by the IPSS and IPSS-R

Contrary to what was observed in lower-risk patients, we found that, in higher-risk patients (both sexes), the youngest

group tended to report a lower HRQoL profile compared with older age groups. However, there was a similar sex effect among higher-risk patients, that is, that men reported overall better HRQoL scores than women across all domains. For the IPSS classification, clinically meaningful differences across age groups were observed in men for 12 scales and in women for 8 scales. Regarding men, one or several older age groups, relative to the youngest age group, showed clinically meaningful better scores for 9 of the 12 (PF, RF, CF, SE, FA, DY, SL, AP, FI) scales. Further details on HRQoL profile of men are reported in Table 5.

Among women, one or more older age groups showed clinically meaningful better outcomes for 6 of 8 scales as compared with the youngest age group, (ie, PF, FA, PA, DY, AP, and FI), when classified by the IPSS. The major difference was observed

Table 1
Patient Characteristics (N = 927)

	Total N = 927
Sex, N (%)	
Men	568 (61.3)
Women	359 (38.7)
Age	
M (SD)	71.6 (10.7)
Median (IQR)	73.3 (66.0–79.2)
Time since diagnosis (wks)	
M (SD)	3.3 (5.7)
Median (IQR)	0.0 (0.0–4.4)
Transfusion dependency, N (%) ^a	
No	767 (83.4)
Yes	153 (16.6)
Missing	7 (.)
Comorbidity, N (%) ^b	
None	421 (45.6)
1	163 (17.6)
≥2	340 (36.8)
Missing	3 (.)
Living arrangements, N (%)	
Living alone	131 (14.5)
Living with spouse/partner only	635 (70.3)
Living with a child, child-in-law, or grandchild	96 (10.6)
Living with another relative	29 (3.2)
Living with unrelated people only	13 (1.4)
Missing	23 (.)
Education level, N (%)	
Low (eg, compulsory school or less)	388 (43.5)
Intermediate (eg, high school)	382 (42.8)
High (eg, university level or higher)	122 (13.7)
Missing	35 (.)
IPSS-risk group, N (%)	
Low	226 (24.4)
Intermediate-1	280 (30.2)
Intermediate-2	312 (33.6)
High	109 (11.8)
IPSS-R-risk group, N (%)	
Very low	117 (13.0)
Low	217 (24.1)
Intermediate	197 (21.8)
High	207 (22.9)
Very high	164 (18.2)
Missing	25 (.)

^aRed blood cell transfusion dependency was defined as having received at least 1 red blood cell transfusion every 8 weeks over a period of 4 months. (Malcovati L, et al. *J Clin Oncol*. 2007;25:3503–3510).

^bComorbidity has been measured using the Hematopoietic Cell Transplantation-Comorbidity index (HCT-CI). (Sorrer ML, et al²⁰).

IPSS = International Prognostic Scoring System; IPSS-R = International Prognostic Scoring System-Revised; IQR = interquartile range; M = mean.

Table 2**Health-related Quality of Life Profile by the EORTC QLQ-C30 According to Risk Categories of the IPSS and IPSS-R in Newly Diagnosed Patients With MDS**

Scale	IPSS-risk Group		IPSS-R-risk Group ^a	
	Lower	Higher	Lower	Higher
	N = 506	N = 421	N = 381	N = 521
	M (SD)	M (SD)	M (SD)	M (SD)
A. Functional scales and global health status/QoL				
Physical functioning	75.1 (21.8)	70.2 (23.4)	77.2 (21.3)	69.9 (23.2)
Role functioning	76.8 (28.7)	67.9 (30.4)	78.4 (28.8)	69.3 (29.9)
Emotional functioning	75.3 (20.9)	71.1 (24.1)	75.4 (20.8)	71.6 (23.8)
Cognitive functioning	82.2 (20.7)	81.6 (22.9)	82.6 (20.9)	81.3 (22.5)
Social functioning	85.0 (23.0)	74.0 (29.4)	87.1 (21.7)	75.1 (28.8)
Global health status/QoL	61.9 (22.5)	54.6 (23.1)	63.2 (22.9)	55.3 (22.6)
B. Symptom scales/items				
Fatigue	34.1 (25.8)	41.7 (27.0)	32.3 (25.7)	41.4 (26.8)
Nausea/vomiting	4.2 (9.8)	7.2 (15.6)	4.0 (10.1)	6.6 (14.5)
Pain	16.7 (23.1)	20.1 (25.3)	15.8 (22.0)	19.8 (25.4)
Dyspnea	26.0 (29.1)	29.7 (29.7)	23.8 (28.2)	29.8 (29.7)
Insomnia	25.0 (28.3)	25.9 (29.6)	25.4 (28.1)	25.7 (29.7)
Appetite loss	12.7 (23.8)	20.7 (29.2)	11.5 (23.1)	19.6 (28.7)
Constipation	15.2 (24.3)	18.5 (28.9)	14.5 (23.7)	18.8 (28.6)
Diarrhea	6.9 (16.9)	6.7 (17.5)	7.0 (17.5)	6.7 (17.0)
Financial problems	9.8 (22.9)	14.4 (26.2)	9.0 (22.8)	13.7 (25.4)

^aFor 25 patients, the IPSS-R classification was not available in the dataset.

EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core30; IPSS = International Prognostic Scoring System; IPSS-R = International Prognostic Scoring System-Revised; QoL = quality of life; M = mean.

for FA, indicating a large clinically meaningful better score for women aged between 60 and 69 years compared with the youngest age group. Additional information is reported in Table 5.

Detailed HRQoL scores for higher-risk patients according to the IPSS-R are reported in Suppl. Table S2.

Regression models for the prediction of EORTC QLQ-C30 scores

To allow for the estimation of EORTC QLQ-C30 reference scores for patient populations with specific distributions of age, sex, and also the presence of comorbidity, we have developed regression models from our data. The 2 separate types of models generated allow the prediction of scores for patients for whom either the IPSS or the IPSS-R risk scores are available. Details on how to use these models to generate HRQoL expected scores for a given patient with specific characteristics (ie, by age, sex, comorbidity, and risk group) are provided in Suppl. Tables S3 and S4 for the IPSS and IPSS-R respectively.

Description of the prevalence of clinically important problems and symptoms

More than 50% of patients reported clinically important problems with physical functioning and dyspnea in both lower- and higher-risk disease patients already at diagnosis.

Suppl. Figure S1 depicts the prevalence of problems by sex in IPSS lower-risk patients. Women with IPSS lower risk tended to report a higher percentage of clinically important problems across all functional aspects and symptoms compared with men. The 3 most frequently reported clinically important problems among men were as follows: PF (54%), DY (53%), and FA (29%). With respect to women, the most prevalent problems were PF (65%), DY (55%), and EF (42%).

Suppl. Figure S2 depicts the prevalence of problems by sex in IPSS higher-risk patients. Women tended to report a higher percentage of clinically important problems compared with men across all scales of the EORTC QLQ-C30 except for CO and DI. The 3 most prevalent clinically important problems were the same for both sexes, that is, PF (men = 61%; women = 77%), DY (men = 60%; women = 62%), and FA (men = 41%; women = 52%).

DISCUSSION

Substantial HRQoL differences by age groups and sex, between and within lower- and higher-risk disease categories were observed already at the time of MDS diagnosis. This finding emphasizes the importance of considering such variations to further optimize patients' management, for example, by paying special attention to patient groups most in need of supportive care.

To illustrate, we observed a remarkable age-related difference by disease risk. Surprisingly, regardless of the risk classification used at diagnostic workup (IPSS or IPSS-R), patients with higher-risk disease aged between 30 and 59 years tended to report a worse functional status and a higher symptomatology compared with 1 or multiple older age groups across various domains. These data were particularly relevant for key symptoms including fatigue and dyspnea.

However, this trend of a generally worse HRQoL profile across various functional and symptom domains in the youngest group was not observed in patients with lower-risk disease. This finding is partly corroborated by previous research in solid tumors patients indicating that younger age groups with metastatic disease tended to report higher symptom severity than older age groups, but this was not the case for patients with earlier stage disease.²⁴ Evidence from previous studies using the EORTC QLQ-C30 in the general population have shown that HRQoL profile typically worsen with age²⁵⁻³¹; hence, our observation of HRQoL impairments in younger patients with high-risk disease cannot be explained by a more general trend of HRQoL reporting. Also, it is unlikely that age differences observed by disease status may reflect treatment-related influences, as in our study, HRQoL was assessed at the time of diagnostic workup. Future studies are needed to examine determinants of this age-related difference in lower- and higher-risk MDS.

To the best of our knowledge, this is the first study to present prevalence rates for key symptoms and functional impairments in patients with MDS across all disease-risk groups, using recently established patient-centered criteria.²² By relying on validated thresholds for the EORTC QLQ-C30,²² we observed clinically important problems regarding physical functioning and dyspnea in more than half of the patients reflecting the high burden of the disease already at the time of diagnosis. We found that women tended to report a higher prevalence of clinically important problems compared with men across several functional and symptom aspects, and this trend held true for those with lower- and higher-risk disease. This data emphasizes the importance of considering HRQoL sex variations at diagnosis as a relevant aspect to make more informed decisions in MDS. Our results indicating sex differences are in keeping with findings from a large recent study pointing to the unique relevance of sex in contributing to genomics and clinical heterogeneity in MDS.³² Also, female sex was recently found to be an independent determinant of low HRQoL early after diagnosis in a large sample of >2000 patients with MDS from the EUMDS Registry,³³ thereby further emphasizing the need to pay special attention to women diagnosed with MDS.

Our comprehensive presentation of EORTC QLQ-C30 scores at diagnosis by the IPSS and IPSS-R classifications may also

Table 3
Health-related Quality of Life Profile by the EORTC QLQ-C30 According to Patients' Sex and the Original-Risk Categories of the IPSS and IPSS-R in Newly Diagnosed Patients With MDS

Scale	Sex			IPSS-risk Group				IPSS-R-risk Group ^a			
	Men; N = 568	Women; N = 359		Low; N = 226	Int 1; N = 280	Int-2; N = 312	High; N = 109	Very Low; N = 117	Low; N = 217	Int; N = 197	High; N = 207
	M (SD)	M (SD)		M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
Functional scales and global health status/QoL											
Physical functioning	75.4 (21.8)	68.8 (23.4)		76.0 (22.0)	74.3 (21.6)	70.4 (23.6)	69.7 (23.0)	79.9 (19.0)	75.5 (22.6)	72.3 (22.5)	70.8 (22.4)
Role functioning	75.7 (28.3)	68.1 (31.5)		77.8 (28.9)	76.0 (28.6)	68.9 (30.3)	65.1 (30.5)	82.1 (23.4)	75.9 (31.7)	75.3 (28.2)	70.0 (28.8)
Emotional functioning	76.3 (20.5)	68.7 (24.7)		76.7 (20.4)	74.2 (21.3)	72.0 (23.3)	68.3 (26.1)	76.0 (18.7)	76.2 (21.2)	73.3 (21.1)	71.2 (24.1)
Cognitive functioning	83.3 (20.0)	79.9 (24.2)		82.4 (20.0)	82.0 (21.3)	82.4 (23.0)	79.5 (22.8)	82.2 (19.0)	82.7 (20.8)	82.2 (21.6)	81.1 (22.2)
Social functioning	81.6 (25.5)	77.6 (28.3)		86.6 (22.4)	83.8 (23.5)	75.7 (29.5)	69.3 (28.5)	90.0 (17.8)	85.3 (23.4)	82.2 (23.8)	75.6 (29.4)
Global health status/QoL	59.6 (22.8)	56.9 (23.4)		63.5 (23.8)	60.6 (21.3)	55.4 (22.9)	52.3 (23.6)	65.2 (20.6)	62.4 (24.5)	59.1 (21.1)	56.1 (21.2)
Symptoms scales/items											
Fatigue	35.6 (25.1)	40.7 (28.6)		32.4 (26.5)	35.5 (25.2)	41.0 (27.0)	43.9 (26.9)	29.6 (23.7)	33.4 (26.9)	37.3 (25.8)	41.4 (25.6)
Nausea/vomiting	4.3 (11.5)	7.6 (14.6)		3.5 (9.8)	4.8 (9.8)	7.3 (15.8)	7.2 (15.1)	2.0 (7.3)	5.1 (11.3)	4.7 (10.8)	6.8 (13.7)
Pain	17.0 (23.4)	20.2 (25.3)		15.5 (22.8)	17.6 (23.3)	19.8 (24.5)	20.9 (27.6)	16.2 (23.3)	15.4 (21.4)	17.8 (21.1)	20.7 (25.4)
Dyspnea	26.6 (28.8)	29.4 (30.4)		23.3 (28.9)	28.2 (29.1)	27.7 (28.3)	35.5 (32.8)	20.5 (25.1)	26.2 (30.0)	26.7 (29.1)	27.5 (28.2)
Insomnia	23.3 (27.3)	28.8 (31.0)		23.9 (27.9)	25.8 (28.7)	26.3 (29.7)	25.0 (29.6)	23.9 (26.9)	25.0 (28.4)	26.1 (29.3)	26.5 (29.5)
Appetite loss	14.8 (25.5)	18.7 (28.3)		10.8 (21.9)	14.2 (25.1)	19.8 (28.6)	23.2 (30.9)	6.8 (16.7)	13.5 (24.5)	15.2 (26.6)	20.0 (27.5)
Constipation	16.2 (26.1)	17.5 (27.3)		14.4 (24.1)	15.8 (24.4)	18.3 (28.9)	19.3 (29.1)	14.1 (22.9)	15.3 (24.2)	16.3 (26.3)	17.2 (26.9)
Diarrhea	6.2 (15.7)	7.8 (19.2)		5.9 (16.5)	7.6 (17.1)	7.3 (18.2)	5.2 (15.2)	3.4 (11.1)	8.2 (19.3)	6.5 (15.6)	6.9 (16.8)
Financial problems	11.4 (24.5)	12.6 (24.7)		9.8 (23.8)	9.8 (22.2)	13.5 (25.9)	16.8 (27.1)	8.5 (21.1)	9.4 (24.2)	9.1 (20.6)	13.8 (24.9)

^aFor 25 patients, the IPSS-R classification was not available in the dataset.

EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core30; Int = intermediate; IPSS = International Prognostic Scoring System; IPSS-R = International Prognostic Scoring System-Revised; M = mean; QoL = quality of life.

Table 4
Health-related Quality of Life Profile by the EORTC QLQ-C30 for Newly Diagnosed Patients With Lower-Risk IPSS

Scale	Men					Women				
	All	30–59 y	60–69 y	70–79 y	≥80 y	All	30–59 y	60–69 y	70–79 y	≥80 y
	N = 301 M (SD)	N = 37 M (SD)	N = 58 M (SD)	N = 136 M (SD)	N = 70 M (SD)	N = 205 M (SD)	N = 27 M (SD)	N = 49 M (SD)	N = 81 M (SD)	N = 48 M (SD)
A. Functional scales and global QoL										
Physical functioning	77.5 (20.3)	86.1 (18.8)	80.3 (20.5) ↓	78.6 (19.3) ↓	68.3 (19.8) ↓↓	71.5 (23.4)	81.0 (18.0)	79.2 (19.7)	70.9 (23.4) ↓	59.3 (24.3) ↓↓
Role functioning	80.3 (26.0)	87.8 (20.3)	79.6 (28.8) ↓	81.0 (25.7) ↓	75.5 (26.4) ↓	71.6 (31.7)	75.3 (30.8)	80.6 (28.1)	71.8 (31.0)	60.1 (34.0) ↓
Emotional functioning	79.2 (17.9)	77.0 (19.2)	75.4 (20.6)	80.6 (16.2)	80.8 (17.5)	69.5 (23.7)	58.6 (27.3)	69.2 (24.3)	72.2 (21.3)	71.5 (23.7)
Cognitive functioning	83.3 (18.6)	86.5 (18.4)	87.6 (17.3)	83.5 (16.9) ↓	77.8 (21.7) ↓	80.6 (23.5)	75.9 (29.0)	86.4 (19.7) ↑↑	82.3 (21.3) ↑	74.3 (25.7)
Social functioning	85.9 (22.6)	89.2 (18.9)	81.3 (29.3) ↓	88.1 (19.3)	83.8 (23.7) ↓	83.7 (23.6)	80.3 (24.5)	84.7 (25.7)	84.8 (22.9)	82.6 (22.5)
Global QoL	63.0 (21.8)	63.5 (26.7)	65.4 (22.8)	64.3 (20.6)	58.1 (20.1) ↓	60.3 (23.4)	65.1 (24.0)	63.5 (27.8)	60.6 (21.7) ↓	54.0 (20.4) ↓↓
B. Symptom scales										
Fatigue	32.1 (23.5)	28.5 (29.1)	31.0 (25.1)	30.4 (20.6)	38.1 (23.5) ↓	37.1 (28.7)	39.9 (30.1)	28.3 (27.7) ↑	34.8 (28.4) ↑	48.3 (26.5) ↓
Nausea/vomiting	3.0 (8.9)	3.2 (11.7)	2.6 (6.8)	2.9 (8.1)	3.3 (10.5)	6.0 (10.8)	8.6 (11.7)	5.4 (11.5) ↑	4.5 (9.1) ↑	7.6 (11.9)
Pain	14.7 (21.8)	9.0 (18.3)	14.9 (24.5)	14.2 (19.7)	18.6 (24.7) ↓	19.5 (24.6)	20.4 (25.0)	15.3 (19.2)	19.8 (26.8)	22.9 (25.6)
Dyspnea	24.1 (27.5)	13.5 (24.2)	22.4 (27.5) ↓	25.9 (28.1) ↓↓	27.6 (27.2) ↓↓	28.8 (31.2)	27.2 (29.3)	27.9 (31.4)	30.9 (33.7)	27.1 (28.1)
Insomnia	21.8 (26.1)	16.2 (23.1)	22.4 (27.5) ↓	20.3 (24.4) ↓	27.1 (29.1) ↓	29.6 (30.8)	32.1 (35.2)	22.5 (27.5) ↑	33.7 (31.0)	28.5 (30.7)
Appetite loss	11.1 (22.3)	9.9 (23.4)	13.2 (24.9)	8.1 (19.2)	15.7 (24.6) ↓	15.0 (25.6)	14.8 (23.3)	10.2 (22.8)	11.9 (22.6)	25.0 (31.9) ↓
Constipation	14.1 (23.4)	3.6 (10.5)	8.6 (18.3) ↓	14.2 (22.1) ↓	24.0 (30.4) ↓↓↓	16.8 (25.5)	18.5 (26.7)	10.4 (18.4) ↑	14.4 (24.7)	26.4 (29.9) ↓
Diarrhea	6.0 (15.2)	8.1 (14.5)	6.9 (17.4)	5.4 (15.8)	5.4 (12.4)	8.1 (18.9)	9.9 (20.3)	8.8 (19.0)	7.4 (17.5)	7.6 (20.9)
Financial problems	8.4 (21.4)	11.7 (25.1)	10.3 (26.6)	7.4 (19.3) ↑	7.3 (18.0) ↑	11.7 (25.0)	19.8 (32.4)	9.5 (19.3) ↑↑	10.3 (26.2) ↑	11.8 (23.3) ↑

Data for the youngest group (ie, 30–59 years) are reported in bold. If there is at least a small clinically meaningful difference based on the previously defined criteria for the EORTC QLQ-C30 (Cocks et al. *J Clin Oncol*. 2011;29:89–96) with one other age group (please note that in this publication no clinically meaningful differences were established for the Emotional Functioning scale and, therefore, the magnitude of differences for this scale is not interpreted here).
↑, ↑↑, ↑↑↑, indicates respectively a small, medium, or large clinically meaningful better outcome (ie, higher score in the functional scales or global QoL scale and lower score in symptom scales) compared with the youngest age group category (ie, 30–59 years).
↓, ↓↓, ↓↓↓, indicates respectively a small, medium, or large clinically meaningful worse outcome (ie, lower score in the functional scales or global QoL scale and higher score in symptom scales) compared with the youngest age group category (ie, 30–59 years).
EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core30; IPSS = International Prognostic Scoring System; M = mean; QoL = quality of life; y = years.

Table 5
Health-related Quality of Life Profile by the EORTC QLQ-C30 for Newly Diagnosed Patients With Higher-risk IPSS

Scale	Men					Women				
	All	30–59 y	60–69 y	70–79 y	≥80 y	All	30–59 y	60–69 y	70–79 y	≥80 y
	N = 267 M (SD)	N = 44 M (SD)	N = 67 M (SD)	N = 113 M (SD)	N = 43 M (SD)	N = 154 M (SD)	N = 18 M (SD)	N = 51 M (SD)	N = 51 M (SD)	N = 34 M (SD)
A. Functional scales and global QoL										
Physical functioning	73.1 (23.1)	72.7 (27.5)	79.9 (19.4) ↑	73.0 (19.3)	63.0 (29.0) ↓	65.2 (23.1)	67.4 (16.8)	73.1 (21.1) ↑	60.0 (24.6) ↓	59.8 (23.9) ↓
Role functioning	70.5 (29.9)	63.6 (31.2)	77.1 (27.4) ↑	73.8 (27.2) ↑	58.9 (35.0)	63.4 (30.9)	63.0 (28.9)	68.6 (28.4)	58.2 (34.5)	63.7 (29.4)
Emotional functioning	73.0 (22.8)	64.2 (26.1)	78.6 (19.7)	72.9 (21.0)	73.6 (25.8)	67.7 (25.9)	66.2 (18.4)	66.5 (24.0)	64.5 (29.4)	74.9 (26.3)
Cognitive functioning	83.2 (21.4)	81.8 (24.9)	91.5 (13.4) ↑↑	82.3 (19.6)	74.0 (27.8) ↓	78.9 (25.1)	82.4 (23.2)	84.3 (18.1)	78.4 (25.9) ↓	69.6 (31.6) ↓↓
Social functioning	76.7 (27.5)	71.6 (27.7)	79.4 (23.0) ↑	77.9 (27.6) ↑	74.4 (33.0)	69.5 (32.0)	71.3 (26.1)	69.9 (30.2)	69.0 (36.4)	68.6 (31.7)
Global QoL	55.9 (23.3)	57.8 (25.3)	59.8 (23.3)	55.0 (22.9)	50.2 (21.6) ↓	52.3 (22.6)	52.8 (20.0)	55.6 (21.3)	50.0 (24.9)	50.7 (22.7)
B. Symptom scales										
Fatigue	39.5 (26.3)	46.2 (31.5)	32.8 (21.1) ↑↑	38.1 (24.5) ↑	47.0 (29.7)	45.5 (27.8)	54.9 (27.1)	35.5 (23.6) ↑↑↑	50.3 (28.0)	48.4 (30.6) ↑
Nausea/vomiting	5.9 (13.7)	4.2 (10.3)	3.5 (9.0)	6.8 (14.4)	8.9 (19.7) ↓	9.6 (18.3)	8.3 (15.4)	9.5 (13.0)	10.8 (23.8)	8.8 (17.5)
Pain	19.5 (24.8)	21.6 (27.0)	17.7 (25.1)	20.2 (24.7)	18.6 (23.1)	21.1 (26.3)	21.3 (28.5)	14.1 (21.2) ↑	23.5 (27.5)	27.9 (28.6) ↓
Dyspnea	29.3 (29.9)	40.2 (34.2)	24.4 (25.7) ↑↑↑	27.4 (29.3) ↑↑	31.0 (31.2) ↑↑	30.3 (29.4)	35.2 (29.1)	17.7 (22.5) ↑↑↑	39.9 (31.3) ↓	32.4 (30.1)
Insomnia	25.0 (28.6)	30.3 (32.8)	21.9 (27.6) ↑	24.2 (27.2) ↑	26.4 (29.6)	27.6 (31.4)	27.8 (23.6)	28.0 (31.1)	26.0 (33.2)	29.4 (33.6)
Appetite loss	19.0 (28.1)	22.0 (30.5)	8.5 (16.8) ↑	21.8 (29.5)	24.8 (32.6)	23.6 (30.9)	20.4 (30.6)	13.7 (21.3) ↑	31.4 (36.8) ↓	28.4 (30.9) ↓
Constipation	18.6 (28.6)	9.1 (22.0)	14.4 (24.1) ↓	20.9 (30.3) ↓	28.7 (33.0) ↓↓	18.4 (29.5)	14.8 (26.1)	19.0 (30.0)	20.3 (30.6) ↓	16.7 (29.9)
Diarrhea	6.4 (16.3)	6.1 (14.9)	3.5 (11.8)	7.4 (18.8)	8.5 (16.4)	7.4 (19.5)	7.4 (14.3)	4.6 (16.4)	9.2 (23.2)	8.8 (20.6)
Financial Problems	14.8 (27.3)	34.1 (39.0)	11.4 (22.9) ↑↑	9.7 (20.7) ↑↑	13.5 (26.6) ↑↑	13.7 (24.3)	14.8 (20.5)	15.0 (26.1)	11.3 (24.8) ↑	14.7 (23.5)

Data for the youngest group (ie, 30–59 years) are reported in bold, if there is at least a small clinically meaningful difference based on previously defined criteria for the EORTC QLQ-C30 (Cocks et al. *J Clin Oncol*. 2011;29:89–96) with one other age group (please note that in this publication no clinically meaningful differences were established for the Emotional Functioning scale and, therefore, the magnitude of differences for this scale is not interpreted here).

↑, ↑↑, ↑↑↑, indicates respectively a small, medium, or large clinically meaningful better outcome (ie, higher score in the functional scales or global QoL scale and lower score in symptom scales) compared to the youngest age group category (ie, 30–59 years).

↓, ↓↓, ↓↓↓, indicates respectively a small, medium, or large clinically meaningful worse outcome (ie, lower score in the functional scales or global QoL scale and higher score in symptom scales) compared to the youngest age group category (ie, 30–59 years).

EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core30; IPSS = International Prognostic Scoring System; M = mean; QoL = quality of life; y = years.

enhance interpretation of results in future MDS studies. In the context of comparative trials, EORTC QLQ-C30 scores are typically interpreted in a relative manner, analyzing mean differences between study arms and/or mean change between study time points. For this purpose, thresholds have been established that define the magnitude of a minimal important difference (MID).²¹ While such MID is helpful for the interpretation of HRQoL results within a given trial context, they provide little guidance for the interpretation of absolute scores from patient groups. Therefore, our reference data can be used to evaluate absolute scores as they provide information on how good or poor the HRQoL of a specific MDS population is in comparison to other MDS patients. For example, the recent MEDALIST RCT³⁴ used the EORTC QLQ-C30 to evaluate the impact of treatment with lusparcept on HRQoL in lower-risk patients who had ring sideroblasts and received regular red blood cell transfusions. In this study, the authors³⁴ also provided comparative HRQoL data from European general population and from patients with recurrent/metastatic cancer, but could not rely on MDS-specific benchmarks. Comparisons against HRQoL reference data of patients with the same diagnosis, as the one generated by our study, would have provided further insights. Additionally, it should be noted that patients included in RCTs may not be representative of those typically encountered in routine practice³⁵; therefore, our real-world HRQoL reference values for newly diagnosed patients can also be used to better contextualize health status profile of patients included in future MDS RCTs.

In routine practice, for example, our findings could be used to better contextualize EORTC QLQ-C30 scores of a patient receiving MDS therapy with respect to a patient who had not received prior systemic therapy for MDS. Such information may be used, for illustrative purposes, to elicit more focused discussion during the clinical encounter.

Our study has limitations. The majority of patients were enrolled in Italian centers thereby hampering a thorough analysis on potential differences by geographical regions. Also, our HRQoL profile description is confined to aspects measured by the EORTC QLQ-C30 and other MDS-specific HRQoL questionnaires^{36–38} could have revealed additional valuable information.

Our study also has key strengths. Our patients were recruited in a real-world study involving several centers, thereby increasing generalizability of findings to patients most typically seen in routine practice. Also, we have provided an in-depth description of the HRQoL profile across the whole spectrum of risk groups of the 2 most frequently used disease-risk classifications (ie, the IPSS and IPSS-R). Finally, our multivariable regression models could be used as pragmatic tools to calculate EORTC QLQ-C30 reference values for newly diagnosed patients classified according to both the IPSS and the IPSS-R.

In conclusion, the observed differences in the HRQoL profile of patients with newly diagnosed MDS should be considered when analyzing and interpreting HRQoL data. Our findings can also be used for benchmarking purposes in future MDS studies using the EORTC QLQ-C30 questionnaire.

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FE, JG, and MV did conception and design of the work. All authors did provision of study material or patients. All authors did collection and assembly of data. All authors did data analysis and interpretation. FC, JG, and FE did statistical analysis. FE did article writing. All authors did final approval of the article.

DISCLOSURES

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