HemaSphere

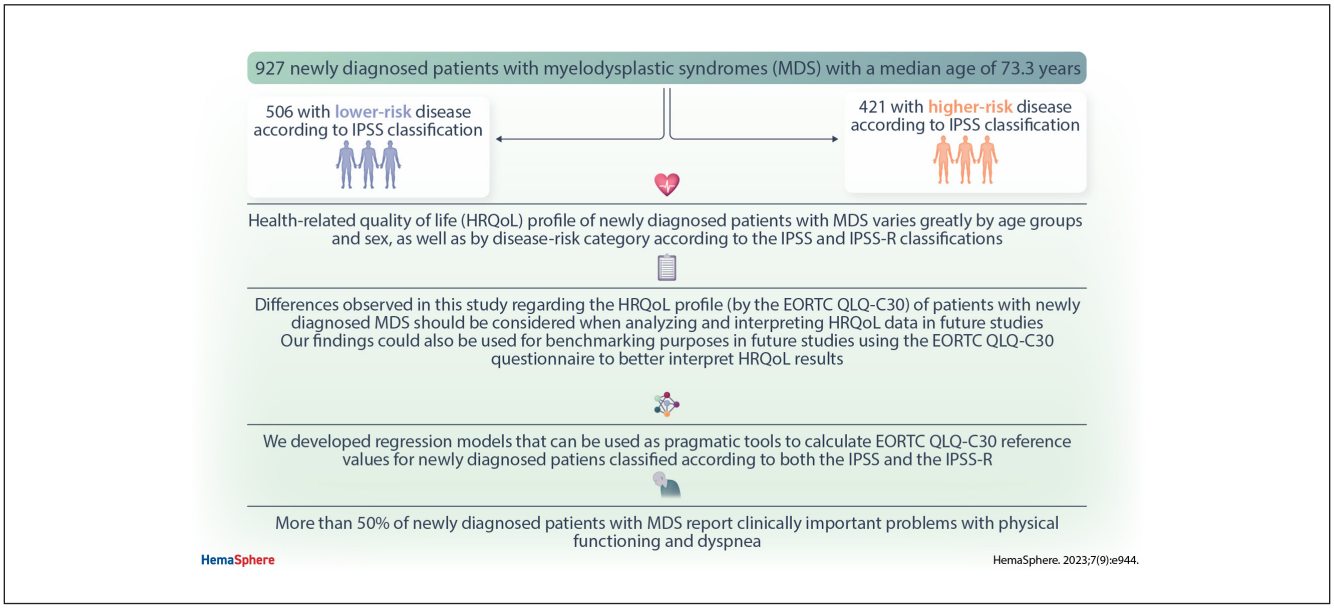
EHA EUROPEAN HEMATOLOGY ASSOCIATION

Article
Open Access

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 Efficace[1], Wael Al Essa[2], Uwe Platzbecker[3], Pasquale Niscola[4], Giuseppe A. Palumbo[5], Giovanni Caocci[6], Francesco Cottone[1], Massimo Breccia[7], Mario Luppi[8], Reinhard Stauder[9], Alessandra Ricco[10], Duska Petranovic[11], Frederic Baron[12], Maria Teresa Voso[13], Luana Fianchi[14], Chiara Frairia[15], Isabella Capodanno[16], Chiara Sarlo[17], Marilena Fedele[18], Roberto Massimo Lemoli[19,20], Rosangela Invernizzi[21], Daniele Vallisa[22], Nicola Di Renzo[23], Claudio Fozza[24], Maribel Doro[25], Johannes M. Giesinger[26], Marco Vignetti[1]

GRAPHICAL ABSTRACT



HemaSphere

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Article
Open Access

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 Efficace[1], Wael Al Essa[2], Uwe Platzbecker[3], Pasquale Niscola[4], Giuseppe A. Palumbo[5], Giovanni Caocci[6], Francesco Cottone[1], Massimo Breccia[7], Mario Luppi[8], Reinhard Stauder[9], Alessandra Ricco[10], Duska Petranovic[11], Frederic Baron[12], Maria Teresa Voso[13], Luana Fianchi[14], Chiara Frairia[15], Isabella Capodanno[16], Chiara Sarlo[17], Marilena Fedele[18], Roberto Massimo Lemoli[19,20], Rosangela Invernizzi[21], Daniele Vallisa[22], Nicola Di Renzo[23], Claudio Fozza[24], Maribel Doro[25], Johannes M. Giesinger[26], Marco Vignetti[1]

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 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 (interquartile 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.

[1]*Data Center and Health Outcomes Research Unit, Italian Group for Adult Haematologic Diseases (GIMEMA), Rome, Italy*
[2]*Division of Hematology, Department of Translational Medicine, University of Eastern Piedmont, Novara, Italy*
[3]*Clinic and Policlinic of Hematology and Cellular Therapy, Oncology and Hemostaseology, University Hospital Leipzig, Germany*
[4]*Hematology Unit, Sant'Eugenio Hospital, Rome, Italy*
[5]*Dipartimento di Scienze Mediche, Chirurgiche e Tecnologie Avanzate "G.F. Ingrassia," University of Catania, Italy*
[6]*Department of Medical Sciences and Public Health, University of Cagliari, Italy*
[7]*Hematology, Department of Translational and Precision Medicine, Azienda Ospedaliera Policlinico Umberto I, Sapienza University of Rome, Italy*
[8]*University of Modena and Reggio Emilia, AOU Modena, Italy*
[9]*Department of Internal Medicine V (Hematology and Oncology), Innsbruck Medical University, Innsbruck, Austria*
[10]*Hematology and Transplants Unit, University of Bari, Italy*
[11]*Department of Hematology, Clinical Hospital Center Rijeka, Croatia*
[12]*Department of Hematology, CHU de Liège, University of Liege, Belgium*
[13]*Department of Biomedicine and Prevention, University of Rome Tor Vergata, Italy*
[14]*Dipartimento Scienze Radiologiche Radioterapiche ed Ematologiche, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Roma, Italy*
[15]*Department of Oncology, Division of Hematology, AOU Città della Salute e della Scienza, Turin, Italy*
[16]*Hematology Unit, Azienda Unità Sanitaria Locale-IRCCS, Reggio Emilia, Italy*
[17]*Hematology and Stem Cell Transplantation Unit, University Campus Bio-Medico, Rome, Italy*
[18]*Hematology, Ospedale San Gerardo, Monza, Italy*
[19]*Cattedra di ematologia, Dipartimento di Medicina Interna (DiMI), Università di Genova, Italy*
[20]*Clinica Ematologica, IRCCS Policlinico San Martino, Genova, Italy*
[21]*Department of Internal Medicine, San Matteo IRCCS Policlinic Foundation, University of Pavia, Italy*
[22]*Ematologia, Ospedale di Piacenza, Italy*
[23]*Hematology and Stem Cell Transplant Unit, "Vito Fazzi" Hospital, Lecce, Italy*
[24]*Department of Medicine, Surgery, and Pharmacy, University of Sassari, Italy*
[25]*Unidade de Hematologia, Hemoterapia e Oncologia (UHHO), Serviço de Transplante de Medula Óssea (STMO), Complexo Hospital de Clínicas da Universidade Federal do Paraná, Curitiba, Brazil*
[26]*University Hospital of Psychiatry II, Medical University of Innsbruck, Austria*
Supplemental digital content is available for this article.

HemaSphere (2023) 7:9(e944).
http://dx.doi.org/10.1097/HS9.0000000000000944.
Received: February 17, 2023 / Accepted: July 20, 2023

INTRODUCTION

Myelodysplastic syndromes (MDS) are a heterogenous 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 pretreatment 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 guidelines[21] 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 professionals[23] 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, SF, 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, SF, 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 (.)

[a]Red 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).

[b]Comorbidity has been measured using the Hematopoietic Cell Transplantation-Comorbidity index (HCT-CI). (Sorror ML, et al[20]).

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

	IPSS-risk Group		IPSS-R-risk Group[a]	
	Lower	Higher	Lower	Higher
	N = 506	N = 421	N = 381	N = 521
Scale	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)

[a]For 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 age[25–31]; 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

	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	Very High; N = 164
Scale	M (SD)	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)	68.0 (24.2)
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)	64.4 (31.8)
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)	70.0 (26.4)
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)	80.8 (24.9)
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)	69.7 (31.2)
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)	51.7 (25.0)
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)	43.9 (28.8)
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)	8.0 (17.6)
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)	20.0 (27.0)
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)	33.5 (31.4)
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)	25.6 (30.4)
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)	22.6 (32.0)
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)	21.7 (31.9)
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)	7.7 (20.1)
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)	17.5 (29.2)

[a]For 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

	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	N = 37	N = 58	N = 136	N = 70	N = 205	N = 27	N = 49	N = 81	N = 48
Scale	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	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

	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	N = 44	N = 67	N = 113	N = 43	N = 154	N = 18	N = 51	N = 51	N = 34
Scale	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	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 MIDs are 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 RCT[34] used the EORTC QLQ-C30 to evaluate the impact of treatment with luspatercept on HRQoL in lower-risk patients who had ring sideroblasts and received regular red blood cell transfusions. In this study, the authors[34] 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 practice[35]; 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.

ACKNOWLEDGMENTS

We are very grateful to all patients who participated in this study. We also thank all local Investigators and research staff of all participating centers.

AUTHOR CONTRIBUTIONS

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

FE: Consultancy or advisory role for AbbVie, Incyte, Janssen, and Syros, outside the submitted work. CF: Research support da Amgen, Sanofi e BMS. ML: Advisory boards: Abbvie, Novartis, MSD, Gilead, Jazz Pharma, Grifols, Sanofi, outside the submitted work. GAP: Speaker fees from AbbVie, Bristol Myers Squibb (BMS), Incyte, and Novartis, has participated in advisory boards of Abbvie, AOP Orphan Pharmaceuticals, AstraZeneca, BMS, GSK, Morphosys, and Novartis, and received support for attending meetings from Abbvie, BeiGene, BMS, Jannsen, Novartis. UP: Honoraria and research support: Geron, BMS, Amgen, Abbvie, Curis, Jazz. AR: Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: Novartis, Sobi, Alexion. Participation on Advisory Board: Novartis, Sobi, Alexion, BMS. RS: Celgene/BMS (Advisory board); Celgene/BMS (Honoraria); Celgene/BMS (Research funding). MV: Honoraria from Amgen, Incyte, Novartis, Dephaforum Srl, Abbvie, and Astrazeneca. Advisory board for Amgen, outside the submitted work. All the other authors have no conflicts of interest to disclose.

SOURCES OF FUNDING

The authors declare no sources of funding.

REFERENCES

1. Malcovati L, Hellstrom-Lindberg E, Bowen D, et al. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. *Blood*. 2013;122:2943–2964.
2. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood*. 1997;89:2079–2088.
3. Greenberg PL, Tuechler H, Schanz J, et al. Revised International Prognostic Scoring System for myelodysplastic syndromes. *Blood*. 2012;120:2454–2465.
4. Stauder R, Yu G, Koinig KA, et al. Health-related quality of life in lower-risk MDS patients compared with age- and sex-matched reference populations: a European LeukemiaNet study. *Leukemia*. 2018;32:1380–1392.
5. Efficace F, Cottone F, Oswald LB, et al. The IPSS-R more accurately captures fatigue severity of newly diagnosed patients with myelodysplastic syndromes compared with the IPSS index. *Leukemia*. 2020;34:2451–2459.
6. Stauder R, Lambert J, Desruol-Allardin S, et al. Patient-reported outcome measures in studies of myelodysplastic syndromes and acute myeloid leukemia: Literature review and landscape analysis. *Eur J Haematol*. 2020;104:476–487.
7. Kornblith AB, Herndon JE 2nd, Silverman LR, et al. Impact of azacytidine on the quality of life of patients with myelodysplastic syndrome treated in a randomized phase III trial: a Cancer and Leukemia Group B study. *J Clin Oncol*. 2002;20:2441–2452.
8. Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. *N Engl J Med*. 2020;382:140–151.
9. Santini V, Almeida A, Giagounidis A, et al. Randomized phase III study of lenalidomide versus placebo in RBC transfusion-dependent patients with lower-risk non-del(5q) myelodysplastic syndromes and ineligible for or refractory to erythropoiesis-stimulating agents. *J Clin Oncol*. 2016;34:2988–2996.
10. Yu ZP, Ding JH, Sun AN, et al. A randomized study comparing stem cell transplantation versus conventional therapy for low- and intermediate-risk myelodysplastic syndromes patients. *Stem Cells Dev*. 2017;26:1132–1139.
11. Kantarjian H, Issa JP, Rosenfeld CS, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. *Cancer*. 2006;106:1794–1803.
12. Rochau U, Stojkov I, Conrads-Frank A, et al. Development of a core outcome set for myelodysplastic syndromes – a Delphi study from the EUMDS Registry Group. *Brit J Haematol*. 2020;191:405–417.
13. Efficace F, Gaidano G, Breccia M, et al. Prognostic value of self-reported fatigue on overall survival in patients with myelodysplastic syndromes: a multicentre, prospective, observational, cohort study. *Lancet Oncol*. 2015;16:1506–1514.
14. Aaronson NK, Ahmedzai S, Bergman B, et al. The European organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85:365–376.

15. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A; on behalf of the EORTC Quality of Life Group. *The EORTC QLQ-C30 Scoring Manual*. 3rd ed. Brussels: Published by: European Organisation for Research and Treatment of Cancer; 2001.
16. Voso MT, Fenu S, Latagliata R, et al. Revised International Prognostic Scoring System (IPSS) predicts survival and leukemic evolution of myelodysplastic syndromes significantly better than IPSS and WHO Prognostic Scoring System: validation by the Gruppo Romano Mielodisplasie Italian Regional Database. *J Clin Oncol*. 2013;31:2671–2677.
17. Fenaux P, Platzbecker U, Ades L. How we manage adults with myelodysplastic syndrome. *Br J Haematol*. 2019;189:1016–1027.
18. Platzbecker U. Treatment of MDS. *Blood*. 2019;133:1096–1107.
19. Pfeilstocker M, Tuechler H, Sanz G, et al. Time-dependent changes in mortality and transformation risk in MDS. *Blood*. 2016;128:902–910.
20. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood*. 2005;106:2912–2919.
21. Cocks K, King MT, Velikova G, et al. Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *J Clin Oncol*. 2011;29:89–96.
22. Giesinger JM, Loth FLC, Aaronson NK, et al. Thresholds for clinical importance were established to improve interpretation of the EORTC QLQ-C30 in clinical practice and research. *J Clin Epidemiol*. 2020;118:1–8.
23. Giesinger JM, Aaronson NK, Arraras JI, et al. A cross-cultural convergent parallel mixed methods study of what makes a cancer-related symptom or functional health problem clinically important. *Psychooncology*. 2018;27:548–555.
24. Mierzynska J, Taye M, Pe M, et al. Reference values for the EORTC QLQ-C30 in early and metastatic breast cancer. *Eur J Cancer*. 2020;125:69–82.
25. Derogar M, van der Schaaf M, Lagergren P. Reference values for the EORTC QLQ-C30 quality of life questionnaire in a random sample of the Swedish population. *Acta Oncol*. 2012;51:10–16.
26. Hinz A, Singer S, Brahler E. European reference values for the quality of life questionnaire EORTC QLQ-C30: Results of a German investigation and a summarizing analysis of six European general population normative studies. *Acta Oncol*. 2014;53:958–965.
27. Schwarz R, Hinz A. Reference data for the quality of life questionnaire EORTC QLQ-C30 in the general German population. *Eur J Cancer*. 2001;37:1345–1351.
28. Finck C, Barradas S, Singer S, et al. Health-related quality of life in Colombia: reference values of the EORTC QLQ-C30. *Eur J Cancer Care (Engl)*. 2012;21:829–836.
29. van de Poll-Franse LV, Mols F, Gundy CM, et al. Normative data for the EORTC QLQ-C30 and EORTC-sexuality items in the general Dutch population. *Eur J Cancer*. 2011;47:667–675.
30. Hjermstad MJ, Fayers PM, Bjordal K, et al. Health-related quality of life in the general Norwegian population assessed by the European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire: the QLQ=C30 (+ 3). *J Clin Oncol*. 1998;16:1188–1196.
31. Yun YH, Kim SH, Lee KM, et al. Age, sex, and comorbidities were considered in comparing reference data for health-related quality of life in the general and cancer populations. *J Clin Epidemiol*. 2007;60:1164–1175.
32. Maggioni G, Bersanelli M, Travaglino E, et al. A sex-informed approach to improve the personalised decision making process in myelodysplastic syndromes: a multicentre, observational cohort study. *Lancet Haematol*. 2023;10:e117–e128.
33. Stojkov I, Conrads-Frank A, Rochau U, et al. Determinants of low health-related quality of life in patients with myelodysplastic syndromes: EUMDS registry study [Online ahead of print]. *Blood Adv*. 2023;7:2772–2783.
34. Oliva EN, Platzbecker U, Garcia-Manero G, et al. Health-related quality of life outcomes in patients with myelodysplastic syndromes with ring sideroblasts treated with luspatercept in the MEDALIST phase 3 trial. *J Clin Med*. 2021;11:27.
35. Kennedy-Martin T, Curtis S, Faries D, et al. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. *Trials*. 2015;16:495.
36. Efficace F, Koinig K, Cottone F, et al. Raising the standards of patient-centered outcomes research in myelodysplastic syndromes: clinical utility and validation of the subscales of the QUALMS from the MDS-RIGHT project. *Cancer Med*. 2022;12:7529–7539.
37. Abel GA, Efficace F, Buckstein RJ, et al. Prospective international validation of the Quality of Life in Myelodysplasia Scale (QUALMS). *Haematologica*. 2016;101:781–788.
38. Oliva EN, Nobile F, Dimitrov BD. Development and validation of QOL-E© instrument for the assessment of health-related quality of life in myelodysplastic syndromes. *Cent Eur J Med*. 2013;8:835–844.