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Original Article

Quality of life and physicians' perception in myelodysplastic syndromes

Esther Natalie Oliva[1], Carlo Finelli[2], Valeria Santini[3], Antonella Poloni[4], Vincenzo Liso[5], Daniela Cilloni6, Stefana Impera[7], Adelmo Terenzi[8], Alessandro Levis[9], Agostino Cortelezzi[10], Riccardo Ghio[11], Pellegrino Musto[12], Gianpietro Semenzato[13], Cristina Clissa[2], Teresa Lunghi[3], Silvia Trappolini[4], Valentina Gaidano[6], Flavia Salvi[9], Gianluigi Reda[10], Oreste Villani[12], Gianni Binotto[13], Patrizia Cufari[1], Elena Cavalieri[14], Maria Antonietta Aloe Spiriti[15]

[1]Hematology, A.O. Bianchi-Melacrino-Morelli, Reggio Calabria, Italy; [2]Institute of Hematology "Seràgnoli", S.Orsola-Malpighi University Hospital, Bologna, Italy; [3]Hematology, AOU Careggi, University of Florence, Florence, Italy; [4]Hematology, Università Politecnica delle Marche, Ancona, Italy; [5]Hematology, Università degli Studi di Bari, Bari, Italy; [6]Department of Clinical and Biological Sciences, University of Turin, Orbassano, Italy; [7]Hematology, Presidio Ospedaliero Garibaldi-Nesima, Catania, Italy; [8]Oncology and Hematology Department, A.O. Silvestrini, Perugia, Italy; [9]Hematology, A.O. SS Antonio e Biagio, Alessandria, Italy; [10]Hematology, IRCCS Fondazione Ca' Granda and University, Milan, Italy; [11]Department of Hematology/Oncology, Azienda Ospedaliero Universitaria "San Martino", Genova, Italy; [12]IRCCS, Department of Onco-Hematology, Centro di Riferimento Oncologico della Basilicata, Rionero in Vulture (Pz), Italy; [13]Dep. Of Clinical and Experimental Medicine, Hematology Section, Padua University School of Medicine, Padua, Italy; [14]Hematology, A.O. Sant'Andrea, Rome, Italy; [15]Department of Clinical and Molecular Medicine, Università Sapienza medicina e Psicologia, Rome, Italy

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Abstract: To detect factors associated with quality of life (QOL) of patients with myelodysplastic syndrome (MDS) and to compare the MDS patients' self-assessed QOL with that perceived by their physicians. In an observational, non-interventional, prospective, multicentre study, QOL was evaluated in 148 patients with newly diagnosed low- and intermediate-risk IPSS MDS. QOL measures (QOL-E v.2, LASA and EQ-5D) and patient-related candidate determinants of QOL were assessed for up to 18 months. Patients' QOL scores were compared with those obtained by appointed hematologists' assessment and with ECOG performance status (PS). Fatigue was not prevalent at diagnosis, though physical QOL and energy levels were low. Transfusion-dependent patients had worse QOL scores. In multivariate analysis, Hb levels and comorbidities were a major determinant of QOL. Physicians' perception of patients' well-being correlated with patients' QOL. Physicians underestimated the impact of disturbances on patients' QOL, mainly in the MDS-specific components. ECOG PS did not discriminate patients according to QOL status. In conclusion, the association of anemia with QOL is confirmed, while co-morbidities emerge as an independent predictor of QOL in MDS. Fatigue is not a major concern. ECOG PS is not a valuable surrogate of patient's QOL, thus highlighting that physician's judgment of patient's well-being must not substitute patient-reported outcomes. Appropriate questionnaires should be used to assess MDS patients' QOL in order to improve communication and therapeutic choice.

Keywords: Myelodysplastic syndromes, quality of life, comorbidities, anemia, transfusion-dependence, patient-reported outcomes

Introduction

In oncology, it has been shown that physicians' perception of patient well-being is often inaccurate [1]. Patient reported outcomes (PROs) are not generally evaluated and may be ignored in the individual therapeutic design.

Myelodysplastic syndromes (MDS) are a group of clonal myeloid disorders characterized by symptomatic cytopenias, and a variable risk to evolve into acute myeloid leukemia (AML) [2]. The International Prognostic Scoring System (IPSS) Low and Intermediate-1 risk groups include the majority of patients, associated with relatively longer survival and lower incidence of progression to AML [3].

MDS primarily affect elderly patients. Chronic cytopenias, the risk of complications and progressive evolution, age and co-morbidities are associated with the changes in physical status.

Quality of Life (QOL) in MDS is compromised by functional and disease-specific components and has been found to be associated with hemoglobin (Hb) levels [4, 5] and with transfusion-dependence [6, 7].

Patients must still mainly depend on palliative care. Many are candidates for experimental therapy while a limited proportion may achieve long-term cure by stem cell transplantation. In patients with anemia, treatment includes erythropoietic stimulating agents (ESAs) and red blood cell transfusions [8-10]. Response to ESAs has been associated with improved QOL [5, 11, 12], although one study showed no such difference [13] and with a better overall survival [14-17].

Clinically meaningful hematological improvements must be assessed by PROs [18, 19] QOL in MDS patients has been measured mainly by Functional Assessment of Cancer Therapy-Anemia (FACT-An) and European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC-QLQ C30) questionnaires [20] validated in several malignant diseases. However, a specific instrument designed for MDS patients, QOL -E, is available [6, 20].

We performed a prospective, multicentre, observational study to detect factors associated with the QOL of MDS patients and to compare the MDS patients' self-assessed QOL with that perceived by their physicians.

Materials and methods

Patients and study design

Eligibility criteria consisted of adult age, newly diagnosed MDS, IPSS score ≤2, and at least one IPSS-defined cytopenia. Exclusion criteria included a history of neoplastic diseases, psychiatric disorders, or any form of mental impairment.

The study was conducted in 14 Italian sites. It was approved by the local Ethical Committees and the procedures followed were in accordance with the Helsinki Declaration of the World Medical Association. All patients gave written informed consent according to institutional regulations.

The investigators were not required to modify their standard clinical practice. Patients' demographics, history, concomitant diseases (Charlson's comorbidity index [21]) and diagnostic examinations, including ECOG PS score [22], were collected at the day the diagnosis was communicated to the patient (baseline visit). Clinical and laboratory evaluations were planned after 1, 2, 3, 6, 12 and 18 month timepoints.

Quality of life assessment

The QOL instruments used were QOL-E v.2 questionnaire, 6 Linear-Analogue Self-Assessment (LASA) scales, and EQ-5D questionnaire [23]. At all timepoints, the QOL-E and LASA instruments were completed by both patients and appointed hematologists (both blind to each other's responses), while the EQ-5D was administered to patients only.

QOL-E v.2 is a specific MDS QOL questionnaire consisting of 2 single items concerning general perception of well-being and 26 items addressing physical, functional, social, sexual, fatigue, and disease-specific domains. Each item is rescaled so that better health corresponds with higher numerical values. Raw scores are transformed to generate standardized scores which are then generated for each domain as the unweighted mean of the standardized scores of all items in that domain (scores range from 0 to 100).

The LASA is composed by three questions measuring respectively energy level, ability to carry out daily activities and overall QOL. Scores ranges from 0 to 100 (a higher score represents a better QOL).

The EQ-5D questionnaire consists of two parts: a health profile made of five domains: mobility, self care, anxiety or depression, usual activities and pain or discomforts, with three levels of severity. The second part consists of a visual analogue scale (VAS) measuring overall QOL ranging from 0 (worst) to 100 (best) [24].

Therapies

Given the observational nature of the study, the investigators were free to follow the therapeutic protocols in use at their institutions.

The number of units transfused 3 months prior

to diagnosis and during the study were recorded. Transfusion dependence was defined as a requirement of at least 1 unit per month for a time span of at least 3 months.

Statistical analysis

The sample size was defined to analyze with sufficient power the association between the QOL scores and the Hb level. Setting $\alpha = 0.05$ two-tailed and $\beta = 0.20$, it was calculated that 120 subjects were required, assuming a Pearson's correlation coefficient of 0.25 between Hb levels and various QOL indexes previously reported [25]. Assuming that 20% of the subjects enrolled would be excluded from the analyses of association, the sample size was rounded to 150 patients.

The subjects withdrawn after enrolment because of a major violation of entry criteria were excluded from all analyses. Categorical data were reported as frequencies and proportions. Continuous variables were summarized by interquartile ranges, medians, and means with standard deviation (SD) as appropriate.

Baseline characteristics were separately reported for transfusion-free (TF) and transfusion-dependent (TD) subjects, and comparisons between these two groups were performed using Fisher's exact test, the Mantel-Haenszel chi-square test or Wilcoxon's two-sample test as appropriate, and Student's two-sample t test for normal continuous variables.

For all QOL measures, the data within the time windows for each visit were used and missing data were not estimated. QOL indexes were analyzed over time using mixed linear regression models to allow for missing data; model-derived means and CIs were calculated at each visit, and means with CIs and corresponding p-values were calculated for pairwise differences between visits.

The consistency of the QOL-E items is described through Cronbach's alpha coefficient. Correlation coefficients were calculated between the VAS measures and the QOL-E indexes and between each LASA and the EQ-5D VAS.

To compare the physician-assessed QOL scores with patients' scores, the weighted kappa coefficient for QOL-E scores and Pearson's coefficient for LASA scores were determined at each visit. The mean difference between physician- and patient-assessed scores was calculated using Wilcoxon's one-sample test for QOL-E scores and Student's one-sample t test for LASA scores.

Univariate and multivariate regression analyses were performed for the QOL indexes using all observations and including visit time as a covariate using linear repeated-measure mixed-effect models with candidate predictors as fixed effects and subjects as random effect. Dependent variables were subjected to angular (arc sine of square-root) transformation and then rescaled from 0 to 100. Based on the log-likelihood criterion, a Toeplitz covariance structure was chosen, whereby correlation between repeated measures of the same subject depends only on the time lag [26].

Conventionally, $p \leq 0.05$ has been considered statistically significant. Statistical analyses were carried out using the SASâ system, PC release 9.2.

Results

Baseline characteristics

One hundred and sixty patients entered the study from March 12, 2007 to May 14, 2008. Twelve subjects were withdrawn due to major violation of inclusion criteria: 4 for lack of significant cytopenias, 3 for history of other neoplastic disease, and 5 because of excessive time span between MDS diagnosis and the baseline visit.

The remaining 148 subjects (males 83) were of mean age 72.0 ± 10.7). Thirty-nine (26.4%) were TD (35 subjects (23.6%) required ≥2 RBC units/month before enrolment) and were comparable for gender, age, education, marital status and home care. One hundred and fifteen cases (77.7%) had Hb <12 g/dL, of which 82 (55.4%) with Hb <10 g/dL. **Table 1** illustrates clinical features at diagnosis. Charlson's comorbidity index was >1 in 33 subjects (22.3%). Cytogenetic information, thus IPSS score, was unavailable in 14 cases (9.5%) who continued the study because of a bone marrow blast count <10% and a single cytopenia.

Patient disposition and therapies

Eighty-nine patients (60.1%) completed the study. Thirteen (8.8%) died during the study (4

Table 1. Clinical features at diagnosis

		All Patients (N=148)	Transfusion-free Patients (N=109)	Transfusion-dependent Patients (N=39)	P-value
WHO classification	RA	48 (40.3)	41 (48.2)	7 (20.6)	
	RARS	4 (3.4)	2 (2.4)	2 (5.9)	
	5q- syndrome	6 (5.0)	6 (7.1)	0 (0.0)	
	RCMD	29 (24.4)	17 (20.0)	12 (35.3)	
	RCMD/RS	1 (0.8)	1 (1.2)	0 (0.0)	
	RAEB-1	21 (17.6)	11 (12.9)	10 (29.4)	
	RAEB-2	7 (5.9)	5 (5.9)	2 (5.9)	
	CMML	3 (2.5)	2 (2.4)	1 (2.9)	
	MDS-Unknown	29	24	5	
Hb g/dL	mean ± SD	10.30 ± 2.06	10.88 ± 1.99	8.70 ± 1.25	<0.0001*
Platelets 103/µL	median (Q1 - Q3)	120 (70 - 216)	122 (79 - 223)	108 (37 - 186)	0.10†
Neutrophils 103/µL	median (Q1 - Q3)	1.76 (0.97 - 2.99)	1.92 (1.04 - 3.30)	1.55 (0.76 - 2.64)	0.18†
Cytopenias, N (%)	1	85 (57.4)	74 (67.9)	11 (28.2)	0.0002‡
	2	49 (33.1)	28 (25.7)	21 (53.8)	
	3	14 (9.5)	7 (6.4)	7 (17.9)	
Bone marrow blasts, N (%)	<5%	120 (81.1)	95 (87.2)	25 (64.1)	0.0034§
	5-10%	22 (14.9)	10 (9.2)	12 (30.8)	
	>10%‖	6 (4.1)	4 (3.7)	2 (5.1)	
Karyotype¶, N (%)	Good	108 (80.6)	81 (82.7)	27 (75.0)	0.46§
	Intermediate	22 (16.4)	15 (15.3)	7 (19.4)	
	Poor‖	4 (3.0)	2 (2.0)	2 (5.6)	
	Not reported	14	11	3	
IPSS degree, N (%)	Low	56 (41.8)	50 (51.0)	6 (16.7)	0.0004‡
	Intermediate-1	64 (47.8)	42 (42.9)	22 (61.1)	
	Intermediate-2	14 (10.4)	6 (5.5)	8 (22.2)	
	Not available	14	11	3	
Charlson's index, N (%)	0	78 (52.7)	58 (53.2)	20 (51.3)	0.69†
	1	37 (25.0)	24 (22.0)	13 (33.3)	
	2	19 (12.8)	14 (12.8)	5 (12.8)	
	3	8 (5.4)	8 (7.3)	0 (0.0)	
	4	5 (3.4)	4 (3.7)	1 (2.6)	
	5	1 (0.7)	1 (0.9)	0 (0.0)	
ECOG PS, N (%)	0	94 (63.5)	77 (70.6)	17 (43.6)	0.038†
	1	44 (29.7)	26 (23.9)	18 (46.2)	
	2	10 (6.8)	6 (5.5)	4 (10.3)	

*Student's two-sample t test between transfusion groups; †Wilcoxon's two-sample test between transfusion groups; ‡Mantel-Haenszel chi-square test between transfusion groups; §Fisher's exact test between transfusion groups; ¶good: normal, del(5q) only, del(20q) only, -Y only; poor: complex (ie, ≥3 abnormalities) or chromosome 7 abnormalities; intermediate: other abnormalities; ‖pooled with nearest level for test calculation.

TF and 9 TD), while 17 (11.5%) discontinued the study for medical reasons, and 21 (14.2%) were lost to follow-up.

During the study, 93 (62.8%) patients received ESAs (mainly epoetin alfa), 18 (12.2%) received azacitidine and 3 (2.0%) received lenalidomide.

Changes in hematological parameters during the study

Table 2. Baseline QOL scores

QOL domain	QOL index		All Patients (N=148)	Transfusion-free Patients (N=109)	Transfusion-dependent Patients (N=39)	P-value
QOL-E	Physical*	median (Q1 - Q3)	63 (38-75)	63 (50-75)	50 (38-63)	0.0096†
	Functional*	median (Q1 - Q3)	56 (22-100)	67 (33-100)	33 (22-89)	0.044†
	Social*	median (Q1 - Q3)	67 (33-100)	75 (44-100)	56 (33-88)	0.14†
	Fatigue*	median (Q1 - Q3)	81 (71-86)	81 (71-90)	78 (67-86)	0.18†
	MDS-specific*	median (Q1 - Q3)	81 (71-90)	83 (74-93)	74 (63-86)	0.0011†
LASA	Energy*	mean ± SD	48 ± 25	50 ± 25	42 ± 25	0.066‡
	Activity*	mean ± SD	53 ± 27	55 ± 27	49 ± 29	0.21‡
	General*	mean ± SD	53 ± 27	56 ± 27	43 ± 24	0.0077‡
EQ-5D	VAS Health State*	mean ± SD	60 ± 20	63 ± 19	53 ± 20	0.0043‡
	Summary index§	median (Q1 - Q3)	0.74 (0.62-0.85)	0.74 (0.62-0.85)	0.74 (0.52-0.85)	0.75†

*scaled from 0 (worst possible value) to 100 (best possible value); †Wilcoxon's two-sample test between transfusion groups; ‡Student's two-sample t test between transfusion groups; §scaled from -0.594 (worst possible value) to 1 (best possible value).

Fifty-two patients (35.1%) received transfusions during the study. Within three months from diagnosis, 75% of all previously TD patients and 9% of all previously TF patients were transfused. Overall mean Hb values increased by 0.37 g/dL (95%CI 0.10-0.64, p=0.0075), from 10.32 (median 9.8, IQR 8.8-11.8) at baseline to 10.69 (median 10.7, IQR 9.1-12.0) at end of study.

QOL instrument validity and scores

Cronbach's alpha, calculated at each visit, varied for QOL-E domains between 0.54 and 0.85 with most values ranging from 0.6 to 0.8; for the EQ-5D dimensions it ranged from 0.7 to 0.8. Most Spearman's correlation coefficients between each QOL-E domain score and VAS measures (the three LASA and the EQ-5D VAS) ranged from 0.4 to 0.65, and Pearson's correlation coefficients between each LASA and the EQ -5D VAS were mostly in the 0.55-0.65 range.

The scores of all scales at baseline are reported in **Table 2**. Fatigue was not prevalent; however, average energy levels were low and physical function was poor. TD patients had a significantly poorer QOL than TF patients in QOL-E physical, functional, and MDS-specific, in LASA general, and EQ-5D VAS health state scores. There was no difference between the mean EQ-5D summary index in TD and TF patients.

In general, changes in QOL in time did not achieve statistical significance once adjusted for the multiplicity of comparisons. However, there was significant worsening in the QOL-E MDS-specific domain (**Figure 1A**) with a mean change in score of -7.4 (95%CI, -12.9 to -1.9, p=0.0024) after 12 months, persisting at the end of the study. LASA energy scores increased significantly only during the first 6 months (**Figure 1B**), the mean change being +8.7 (95% CI, +1.1 to +16.3, p=0.017), and decreased thereafter.

Very limited changes over time were observed in the EQ-5D summary index. Similarly, the ECOG PS through time did not change in most patients.

Predictive factors of quality of life

Univariate and multivariate analyses of the effects of candidate predictors of QOL, including: age, gender, marital status, education, family/ home care, Charlson's comorbidity index, Hb levels, platelet count, neutrophil count, transfusions and time from baseline (disease duration), were performed for each QOL scale (**Tables 3** and **4**).

At univariate analysis, better QOL-E physical, functional, social and fatigue scores, LASA and EQ-5D VAS scores were associated with younger age, Charlson's index ≤1 (except LASA energy), higher Hb levels and transfusion independence.

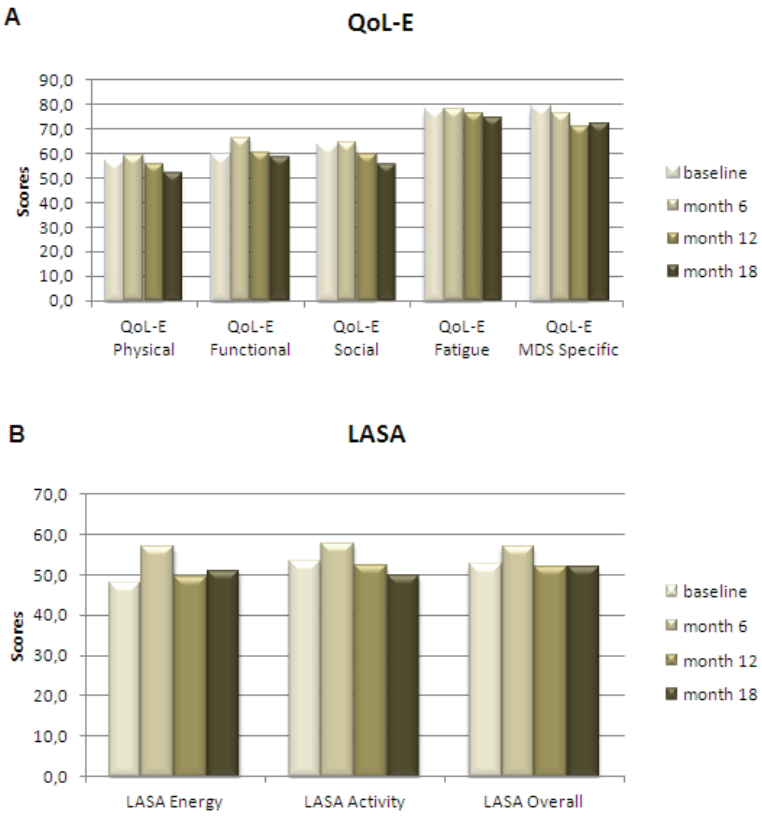

Figure 1. A. QOL-E score patient (Physical, Functional, Social, Fatigue, MDS-specific) in time; B. QOL LASA score patient (energy, activity, overall) in time.

QOL-E social scores were also associated with marital status (married subjects had worse scores) and inversely with duration of disease. QOL-E MDS-specific scores were associated with Charlson's index, Hb levels and transfusion independence and inversely with time from diagnosis.

At multivariate analysis, Hb concentration was the most important independent predictor, higher values being significantly associated with better QOL scores. After adjustment for other factors, transfusions were still significantly associated with worse QOL-E physical, QOL-E functional, QOL-E social, QOL-E MDS-specific, LASA activity and EQ-5D VAS scores. With the exception of the LASA energy score, Charlson's comorbidity index was a significant independent predictor of all QOL indexes, multiple comorbidity being associated with a poorer QOL. The effect of age achieved statistical significance only for the QOL-E physical score (younger age predicted better scores). Marriage was still significantly associated with worse social scores, while male gendere was significantly associated with better fatigue scores in multivariate analysis.

No independent predictive effect was found for thrombocytopenia or neutropenia. There was a significant worsening in QOL-E physical, social and MDS -specific scores in time.

Physician's assessment of QOL compared to patients' self-assessment

Physician- and patient-assessed QOL-E scores were significantly correlated with most kappa correlation coefficients ranging from 0.2 to 0.6. Exceptions were observed at baseline for the item "Does inability to travel disturb your daily life?", at baseline and after 12 months for the item "Does depending on hospital, physicians and nurse staff disturb your daily life?", and for an item regarding sexual life after 6 and 12 months.

Relevant differences between physician- and patient-assessed mean scores were observed for 3 QOL-E items: item 1 (a general statement of health state perception); "Has climbing stairs been limited by your health state over the last week?"; "Has lowering yourself been limited by your health state over the last week?". The physicians' score rating was always higher than the patients' own scores.

Correlations between patient and physician LASA scores were initially weak (Pearson's coefficients 0.31-0.33) and increased considerably at later visits (0.53-0.74). Physicians' ratings for LASA energy were significantly higher than the patients' scores. Physicians' scores for LASA activity and LASA general were significantly higher at 6 and 12 months.

The relationship between patient-assessed QOL-E physical and ECOG PS is shown in **Figures 2A**,

Table 3. Predictive factors of QOL-E scores

QOL index*	Factor	Univariate analysis		Multivariate analysis†	
		Effect (95% CI)‡	p value	Effect (95% CI)‡	p value
QOL-E, Physical	Age (1 year)	-0.73 (-1.00, -0.46)	<0.0001	-0.48 (-0.74, -0.22)	0.0003
	Charlson's index (2-5 vs 0-1)§	-16.3 (-23.0, -9.5)	<0.0001	-14.2 (-20.4, -8.0)	<0.0001
	Hb (1 g/dL)‖	+2.48 (+1.50, +3.45)	<0.0001	+1.69 (+0.71, +2.67)	0.0008
	Transfusions (yes vs no)¶	-9.1 (-13.6, -4.7)	0.0002	-7.2 (-11.7, -2.6)	0.0029
	Time from baseline (1 month)	-0.22 (-0.45, +0.01)	0.061	-0.29 (-0.52, -0.06)	0.014
QOL-E, Functional	Age (1 year)	-0.34 (-0.66, -0.01)	0.042	-0.01 (-0.33, +0.30)	0.93
	Charlson's index (2-5 vs 0-1)§	-14.8 (-22.6, -7.1)	0.0002	-15.5 (-22.9, -8.1)	<0.0001
	Hb (1 g/dL)‖	+3.79 (+2.49, +5.09)	<0.0001	+2.99 (+1.61, +4.36)	<0.0001
	Transfusions (yes vs no)¶	-13.0 (-19.3, -6.6)	0.0002	-8.3 (-15.1, -1.6)	0.017
	Time from baseline (1 month)	-0.10 (-0.47, +0.27)	0.60	-0.21 (-0.59, +0.16)	0.26
QOL-E, Social	Age (1 year)	-0.46 (-0.83, -0.08)	0.017	-0.26 (-0.63, +0.11)	0.17
	Charlson's index (2-5 vs 0-1)§	-15.3 (-24.4, -6.3)	0.0011	-15.6 (-24.3, -6.9)	0.0005
	Hb (1 g/dL)‖	+2.42 (+1.10, +3.74)	0.0003	+2.15 (+0.79, +3.52)	0.0021
	Transfusions (yes vs no)¶	-8.1 (-14.2, -2.1)	0.0098	-6.7 (-12.9, -0.4)	0.037
	Marital status (married vs single)	-9.3 (-17.9, -0.6)	0.036	-9.8 (-18.0, -1.6)	0.019
	Time from baseline (1 month)	-0.37 (-0.72, -0.02)	0.037	-0.42 (-0.76, -0.08)	0.014
QOL-E, Fatigue	Age (1 year)	-0.17 (-0.33, -0.00)	0.046	-0.04 (-0.20, +0.11)	0.57
	Charlson's index (2-5 vs 0-1)§	-7.8 (-11.6, -3.9)	0.0001	-8.6 (-12.3, -4.8)	<0.0001
	Hb (1 g/dL)‖	+1.50 (+0.92, +2.07)	<0.0001	+1.45 (+0.89, +2.01)	<0.0001
	Transfusions (yes vs no)¶	-3.8 (-6.5, -1.2)	0.0063	-2.6 (-5.4, +0.2)	0.064
	Gender (male vs female)	+2.0 (-1.4, +5.4)	0.24	+3.3 (+0.2, +6.4)	0.038
	Time from baseline (1 month)	-0.08 (-0.23, +0.07)	0.28	-0.11 (-0.25, +0.04)	0.16
QOL-E, MDS specific	Age (1 year)	-0.21 (-0.42, +0.00)	0.053	-0.03 (-0.23, +0.17)	0.80
	Charlson's index (2-5 vs 0-1)§	-8.0 (-13.1, -3.0)	0.0021	-8.8 (-13.5, -4.1)	0.0003
	Hb (1 g/dL)‖	+1.94 (+1.23, +2.65)	<0.0001	+1.53 (+0.81, +2.26)	<0.0001
	Transfusions (yes vs no)¶	-7.9 (-11.2, -4.6)	<0.0001	-6.8 (-10.2, -3.5)	0.0002
	Time from baseline (1 month)	-0.33 (-0.50, -0.16)	0.0002	-0.38 (-0.55, -0.22)	<0.0001

*scaled from 0 (worst possible value) to 100 (best possible value); †variables with $p<0.05$ are included in the basic model, for other factors the reported p-value tests the addition to this model; ‡mean difference of predicted dependent variable between levels (first - second) of binomial factors or for each 1-unit increase of quantitative factors; §at baseline; ‖ at each visit; ¶any transfusion within 3 months before the day of visit.

2B and 2C. There were significant mismatches since about half of patients with ECOG PS = 0 (judged as being fully active and with excellent functioning) experienced poor QOL-E physical scores.

Discussion

This study confirms that Hb levels are correlated with QOL in MDS. Hb was in fact the most important independent predictor of QOL consistently throughout the QOL-E, LASA and EQ-5D tools analyzed. On the contrary, no significant effect was observed for either thrombocytopenia or neutropenia.

The independent role of transfusion-dependence is difficult to establish since Hb levels and transfusion status are confounded. The univariate difference related to transfusion,

Table 4. Predictive factors of LASA and EQ-5D VAS

QOL index*	Factor	Univariate analysis		Multivariate analysis†	
		Effect (95% CI)‡	p value	Effect (95% CI)‡	p value
LASA, Energy	Age (1 year)	-0.34 (-0.55, -0.13)	0.0017	-0.20 (-0.41, +0.01)	0.059
	Charlson's index (2-5 vs 0-1)§	-5.2 (-10.4, +0.1)	0.056	-4.8 (-9.8, +0.2)	0.060
	Hb (1 g/dL)‖	+3.12 (+2.24, +3.99)	<0.0001	+3.12 (+2.24, +3.99)	<0.0001
	Transfusions (yes vs no)¶	-8.2 (-12.4, -3.9)	0.0005	-2.4 (-7.1, +2.2)	0.29
	Time from baseline (1 month)	+0.04 (-0.21, +0.29)	0.78	-0.02 (-0.26, +0.22)	0.87
LASA, Activity	Age (1 year)	-0.40 (-0.63, -0.17)	0.0008	-0.18 (-0.41, +0.04)	0.11
	Charlson's index (2-5 vs 0-1)§	-9.2 (-15.0, -3.4)	0.0019	-9.2 (-14.6, -3.9)	0.0009
	Hb (1 g/dL)‖	+3.02 (+2.09, +3.94)	<0.0001	+2.48 (+1.48, +3.47)	<0.0001
	Transfusions (yes vs no)¶	-9.8 (-14.2, -5.3)	<0.0001	-5.5 (-10.3, -0.8)	0.023
	Time from baseline (1 month)	-0.15 (-0.39, +0.10)	0.25	-0.22 (-0.46, +0.02)	0.074
LASA, General	Age (1 year)	-0.36 (-0.58, -0.14)	0.0015	-0.16 (-0.38, +0.05)	0.14
	Charlson's index (2-5 vs 0-1)§	-7.0 (-12.5, -1.4)	0.014	-6.7 (-11.9, -1.5)	0.011
	Hb (1 g/dL)‖	+3.16 (+2.27, +4.04)	<0.0001	+3.13 (+2.26, +4.01)	<0.0001
	Transfusions (yes vs no)¶	-9.1 (-13.4, -4.8)	<0.0001	-4.4 (-9.0, +0.2)	0.060
	Time from baseline (1 month)	-0.04 (-0.28, +0.21)	0.78	-0.10 (-0.34, +0.14)	0.41
EQ-5D, Health state VAS	Age (1 year)	-0.33 (-0.52, -0.15)	0.0004	-0.15 (-0.32, +0.03)	0.099
	Charlson's index (2-5 vs 0-1)§	-9.6 (-14.0, -5.2)	<0.0001	-9.9 (-14.1, -5.7)	<0.0001
	Hb (1 g/dL)‖	+2.13 (+1.49, +2.77)	<0.0001	+1.77 (+1.12, +2.43)	<0.0001
	Transfusions (yes vs no)¶	-6.4 (-9.5, -3.3)	0.0002	-4.4 (-7.5, -1.3)	0.0062
	Time from baseline (1 month)	-0.12 (-0.30, +0.06)	0.19	-0.17 (-0.35, +0.01)	0.057

*scaled from 0 (worst possible value) to 100 (best possible value); †variables with $p<0.05$ are included in the basic model, for other factors the reported p-value tests the addition to this model; ‡mean difference of predicted dependent variable between levels (first - second) of binomial factors or for each 1-unit increase of quantitative factors; §at baseline; ‖at each visit; ¶any transfusion within 3 months before the day of visit.

which was statistically significant in all models, may actually be due in part to the fact that average Hb levels measured at visits in transfused patients were considerably lower than in patients not given transfusions. However, the multivariate effect of transfusion, after adjustment for Hb, was generally reduced although remaining above statistical significance in most models. This multivariate effect may be viewed as the effect of transfusion per se, i.e. the impact of undergoing this disturbing procedure, rather than of the anemia associated with the need of transfusions.

The presence of more than one co-morbid condition was also strongly associated with poor QOL, independent of Hb levels or transfusion need. Co-morbidities represent a prognostic factor for numerous disease states and were shown to be a major determinant of QOL in our patient sample. Unlike transfusion status, the size of the univariate and multivariate effects of co-morbidity were similar, suggesting that this variable and Hb were largely not confounded.

Age was inversely associated only with the QOL-E physical score in multivariate analysis. Marital status maintained an importance in determining QOL-E social scores in this elderly patient population at multivariate analysis.

The proportion of drop-outs in the study was larger than expected, attrition being caused more often by death or medical reasons in patients who were transfusion-dependent at baseline and more often by loss to follow-up in patients who were transfusion-free at baseline. The main analyses of QOL were conducted using likelihood-based mixed-effect linear regression models for repeated measures that allow the inclusion of subjects with missing data. This method provides adjustment to the extent that the probability of missing a value is related to measured data (earlier measures of the same variable and subject characteristics included in analysis models), yielding unbiased estimates

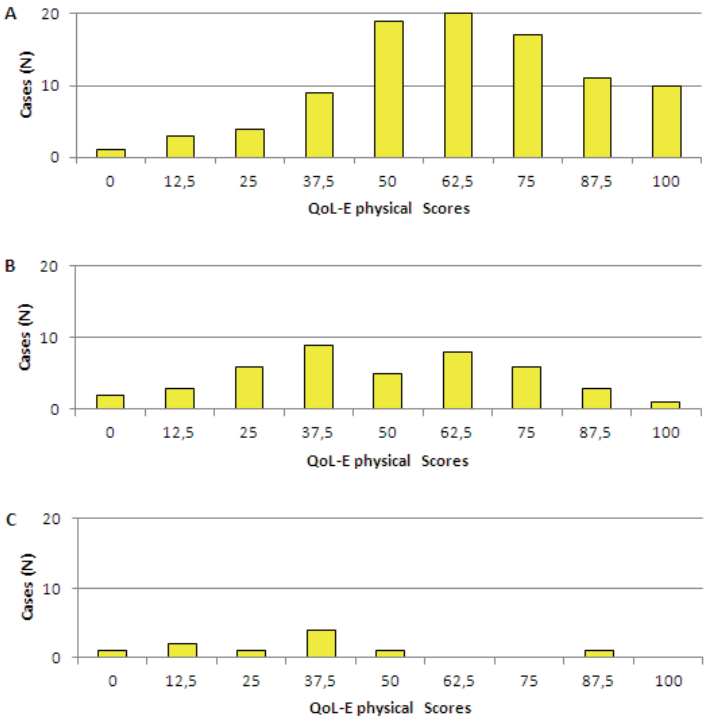

Figure 2. A. Distribution of QOL-E physical scores in patients (n=94) with ECOG PS = 0 at baseline; B. Distribution of QOL-E physical scores in patients (n=44) with ECOG PS = 1 at baseline; C. Distribution of QOL-E physical scores in patients (n=10) with ECOG PS = 2 at baseline.

when the data are missing at random [27, 28], i.e. the probability of missing a value is related only to measured data, and is superior to other methods in accounting for drop-outs [29]. However, as can be judged from the reasons of study discontinuation, the QOL data in our study were likely not missing at random. In the oncological setting, where a substantial amount of missing data is caused by patient withdrawal, the estimates of QOL changes over time were consistently more pessimistic than those obtained assuming that the data were missing at random [30, 31] However, the main purpose of QOL data analysis in this study was to show the association of QOL with various demographic and clinical characteristics measured during observation. This association was essentially independent of time from diagnosis. Therefore it can reasonably be assumed that losses due to attrition did not appreciably alter the estimate of the effects that demographic and clinical characteristics have on patient QOL.

Both general-purpose VAS measures and QOL-E, were used to assess QOL in this study. The consistency and validity of the instruments were verified and confirmed.

The patients' self-assessed QOL generally agreed with scores generated by their physicians using the QOL-E and LASA instruments. When a significant difference existed, especially for the LASA measures, the physicians were more inclined to produce systematic optimistic errors. The error persisted, suggesting that physicians did not seem to improve their understanding of their patients over time. Furthermore, patients were frequently allocated in a good ECOG PS group, though experiencing poor QOL, which has been recently described in the elderly AML patient population [32]. A similar phenomenon has been observed when physicians estimate prognosis for patients in palliative care programs, the number of overoptimistic predictions outnumbering overpessimistic predictions of survival by a factor of 2- to 4-fold [33, 34]. The peril may arise when such patients are included in clinical trials in which the enrolment criteria includes ECOG PS scores.

For MDS patients, the disturbance caused by protocol-derived frequent hospital visits was revealed in a recent report [35]. In the present study, the same disturbance was underestimated by clinicians. It is thus recommended that this particular problem be properly assessed before entering patients into trials.

In conclusion, the assessment of PROs is mandatory in patient care. When offering experimental drugs or palliative therapy, defined by the World Health Organization as "an approach which improves QOL of patients and their families facing life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual [36], an attentive evaluation of QOL would improve patient well-being particularly in the palliative care setting".

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Disclosures of potential conflicts of interest

Esther Natalie Oliva received honoraria from Celgene and Novartis; Valeria Santini received honoraria from Celgene, Janssen-Cilag and Novartis; Pellegrino Musto disclosed advisory relationship and honoraria for Janssen-Cilag. All the other authors indicated no potential conflicts of interest.

Address correspondence to: Dr. Esther Oliva, Azienda Ospedaliera "Bianchi-Melacrino-Morelli", Divisione Ematologia, Reggio Calabria, Italy. Tel: +39 0965-397222. E-mail: estheroliva@hotmail.com

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