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Determinants of low health-related quality of life in patients with myelodysplastic syndromes: EUMDS Registry study

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Key Points

- Patients with MDS often experience severe symptom burden resulting with deteriorated health-related quality of life.
- We identified key determinants of low health-related quality of life in MDS to support early clinical evaluation and shared decision making.

Patients with myelodysplastic syndromes (MDS) frequently experience a significant symptom burden, which reduces health-related quality of life (HRQoL). We aimed to identify determinants of low HRQoL in patients recently diagnosed with MDS, for guiding early intervention strategies. We evaluated longitudinal data in 2205 patients with MDS during their first year after diagnosis. Median values of EQ-5D 3-level (EQ-5D-3L) index (0.78) and visual analog scale (VAS) score (0.70) were used as thresholds for low HRQoL. In addition, the 5 dimensions of EQ-5D-3L were analyzed for impairments (any level vs "no problem" category). After multiple imputation of missing values, we used generalized estimating equations (GEE) to estimate odds ratios (OR) for univariable determinant screening ($P < .15$), and to subsequently derive multivariable models for low HRQoL with 95% confidence intervals (CI). Multivariable GEE analysis showed the following independent determinants (OR, 95% CI) for low EQ-5D index: increased age (60-75 years: 1.33, 1.01-1.75; >75: 1.84, 1.39-2.45), female sex (1.70, 1.43-2.03), high serum ferritin level (≥1000 vs ≤300 μg/L: 1.41, 1.06-1.87), comorbidity burden (per unit: 1.11, 1.02-1.20), and reduced Karnofsky performance status (KPS, per 10 units: 0.62, 0.58-0.67). For low VAS

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The full-text version of this article contains a data supplement.

score, additional determinants were transfusion dependence (1.53, 1.03-2.29), low hemoglobin <10 g/dL (1.34, 1.12-1.61), and high body mass index (≥30 vs 23-29.9 kg/m^2: 1.26, 1.02-1.57). Sex, KPS, comorbidity burden, hemoglobin count, and transfusion burden were determinants for all EQ-5D dimensions. Low HRQoL is determined by multiple factors, which should be considered in the management and shared decision making of patients with MDS. This trial was registered at www.clinicaltrials.gov as #NCT00600860.

Introduction

Myelodysplastic syndromes (MDS) are a group of heterogeneous myeloid neoplasms, characterized by cytogenetic abnormalities, dysplastic hematopoiesis, cytopenia, and a high tendency for leukemic transformation.[1] The volatile course of the diseases, advanced age at diagnosis, and the patients' individual health and preferences result in variable treatment modalities, ranging from a watchful waiting strategy to stem cell transplantation as the only potentially curative option. Only a few disease-modifying therapies are available for MDS, and most treatment options are focused on mitigating symptoms of cytopenia and stabilizing or improving health-related quality of life (HRQoL).[2,3] The choice of treatment, including supportive care (eg, blood transfusions, hematopoietic growth factors) or more intensive treatment choices (eg, hypomethylating agents) is usually driven by risk stratification of patients. A commonly used score that combines parameters associated with the biology of the disease for risk assessment is the revised International Prognostic Scoring System (IPSS-R).[4]

Because risk assessment is such an important aspect in determining the course of MDS therapy, a comprehensive evaluation with wider inclusion of patient-reported outcomes (PRO) is essential.[5] Most of the PRO assessments in the past decade were performed in the context of clinical trials and comparative effectiveness studies,[6] likely because of the fact that PROs and especially HRQoL, have been recognized as valuable outcomes in the drug approval process by regulatory authorities.[7-9]

Studies have already provided evidence for the importance of PRO in MDS prediction and therapy planning, adding valuable information on patients' daily functioning and psychosocial status, along with disease and therapy-related symptoms. For instance, fatigue is a frequent and burdensome symptom that can only partly be explained by low hemoglobin (Hb) levels,[10] yet patient-reported fatigue is a relevant MDS prognostic factor.[11,12] Self-reported physical function[13] and frailty[14] were also found to be independent predictors of overall survival in MDS. In addition, the burden of MDS-related comorbidities is associated with poorer expectations for survival and HRQoL in patients.[15-17] HRQoL is also a guideline-based indicator for quality of care in MDS,[18] and was selected as a core outcome by hematologists[19] and patients[20] to be used in future MDS clinical trials and daily practice. With the increased acceptance of PRO into clinical practice and patient monitoring,[21,22] several observational studies also examined the factors associated with HRQoL and/or its domains in MDS.[11,17,23-26]

In contrast to the previous studies, which were focused on specific subgroup analyses,[10,25,26] included limited number of patients or characteristics,[11,17] or provided single time point comparisons,[24] the comprehensive data of the European Myelodysplastic Syndrome (EUMDS) Registry[27] offer a unique opportunity for novel evaluations with an extensive list of potential determinants and for a longitudinal assessment of HRQoL during the MDS course.

Therefore, the aim of this study was to identify significant determinants of low HRQoL in patients with MDS early after diagnosis, using a large, international, prospective data set from the EUMDS Registry.

Methods

Analytic design and ethics

Our analyses aimed to identify determinants of low HRQoL at any specific time point early after diagnosis. We used data from the EUMDS Registry, which has been described earlier.[27] Briefly, EUMDS Registry is a multicenter prospective registry with newly diagnosed patients with MDS who had their diagnosis within 100 days of enrolling in the study.[27] The EUMDS Registry was created by a large group of hematologists from the European LeukemiaNet organization and since early 2008 has been collecting data throughout 17 countries (Austria, Croatia, the Czech Republic, Denmark, France, Germany, Greece, Israel, Italy, The Netherlands, Poland, Portugal, Romania, Serbia, Spain, Sweden, and the United Kingdom) with more than 140 active sites. Currently, the EUMDS Registry has more than 3000 patients with MDS, the majority of whom are lower-risk patients, and includes comprehensive clinical- and patient-related information from baseline (within 100 days after diagnosis) and consequent follow-up visits at 6 month intervals. Treatments are assigned based on local guidelines. Patients are followed until death, loss to follow-up, or study withdrawal. The importance of the EUMDS Registry and the numerous data analyses are described in a recent publication by de Witte et al.[28] Because we aimed to comprehensively analyze recently diagnosed patients with MDS, and the proportion of missing values for HRQoL continuously increased between the 1st and the 18th visit, we restricted the analyses to data from the first 3 time points (ie, baseline, and the 2 follow-up visits at 6 and 12 months).

Country-specific ethical approvals were provided from the enrolled institutions in compliance with the Declaration of Helsinki. Ethical approval for the study was also obtained from the Research Committee for Scientific and Ethical Questions at UMIT - University for Health Sciences, Medical Informatics and Technology, Hall in Tirol, Austria. Additional study details are available at ClinicalTrials.gov (NCT00600860).

Outcome measures

We used the European quality of life 5 dimensions 3 level version (EQ-5D-3L)[29] as a well-established and widely used generic instrument for assessing HRQoL. The EQ-5D-3L instrument

contains the following 2 sections: a descriptive system and a visual analog scale (VAS). Within the descriptive system responders rank their health state by choosing between 3 severity levels (no problems, extreme problems, and some problems) for each of the 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). These rankings were then used to calculate a single summary value (ie, EQ-5D index or "utility") by applying the European value set.[30] The VAS as an additional measure allows the responders to assign a single score of their broader, overall health state on a continuous line from 0 ("worst imaginable health state") to 100 ("best imaginable health state"), without focusing on specific domains or applying further score valuing/weights.[31]

We used the median of the overall distribution for both the EQ-5D index and the VAS score as a cutoff to define "low HRQoL" in the primary analyses. This decision was made because there is no standard threshold for categorizing HRQoL in the MDS setting and the skewed outcome distributions with the third quartile for the EQ-5D being at its maximum value of 1. A similar dichotomization was performed in the MDS prognostic study by Deschler et al.[11] In a secondary explorative analysis, each of the 5 dimensions of EQ-5D was used as outcome contrasting any problems (answer category 1 and 2) vs no problem (answer category 3), to identify potential candidates of domain-specific determinants of low HRQoL.

Statistical analyses

The primary analyses of low EQ-5D index and low VAS score followed a 2-step approach. Firstly, we applied the purposeful variable selection approach,[32] performing univariable determinant screenings with a P value $< .15$ to identify candidate determinants for the multivariable analyses. We also considered potential 2-way interaction terms between each pair of variables with a P value $< .05$. Secondly, we performed multivariable analyses and estimated independent odds ratios (ORs) with 95% confidence intervals (CI). We used generalized estimating equations (GEE) with a logit link function and an exchangeable correlation structure to account for the correlation of repeated measurements per patients along visits. The obtained GEE estimates represent ORs as an overall association measure across the 3 time points, estimated simultaneously. The overall performance of each multivariable model was assessed using the Brier score,[33] and the discrimination ability of the models was validated by computing the area under the receiver operator characteristic curve.

For the secondary explorative analysis identifying potential candidates for domain-specific determinants for HRQoL impairments, we used univariable GEE logistic regression models (P value $< .15$).

Missing values were imputed by multiple imputation using the chained equation (MICE) method.[34,35] We also performed several sensitivity analyses including univariable and multivariable analyses without imputations, multivariable analyses on the 1506 patients with MDS consistently participating in all 3 time points, and sensitivity analyses for a more parsimonious model after backward variable selection ($P < .05$).

All analyses were conducted using Stata software version 15 (StataCorp, College Station, TX). Figures were prepared in R Statistical Software (version 3.5.3; R Foundation for Statistical Computing, Vienna, Austria). Further details on the statistical analyses are available in supplemental Methods.

Results

General characteristics

At baseline, 2205 patients were included in the study, followed by 1861 (83.9%) and 1506 (68.2%) observations in the following 2 visits. After the baseline visit, 209 patients were lost to follow-up, 83 patients died, and 52 patients withdrew from the study. After the second visit, 166 patients were lost to follow-up, 125 patients died, and 64 patients withdrew. Before the imputation process, we observed 1827 (82.9%), 1199 (64.4%), and 957 (63.5%) EQ-5D measures and 1800 (81.6%), 1196 (64.3%), and 951 (63.2%) VAS measures at each of the 3 time points. Median age at baseline was 74 years (interquartile range, 67-80) with 61.5% male population. Most patients (ie, >60%) were classified within "very low" and "low" IPSS-R risk groups at baseline, with red blood cell (RBC) transfusions, erythropoiesis stimulating agents (ESA), and iron chelators being the 3 most frequently observed therapies.

The EQ-5D index value and the VAS score had skewed distribution with median cutoff points for "low HRQoL" of 0.779 and 0.700 respectively. These values are comparable with those from other MDS studies that used EQ-5D and resulted in mean utilities ranging from 0.67 to 0.95, depending on MDS risk stratification.[36] Overall, several MDS studies reported lower HRQoL than reference populations,[23] including the study by Stauder et al[24] with matched European populations for lower-risk patients, which showed mean EQ-5D index and VAS scores of 0.76 and 71.8 respectively. At baseline, low HRQoL was reported by 46.4% of the patients for EQ-5D and by 41.5% of patients for VAS. For the 5 dimensions of EQ-5D, patients reported similar percentages of impairments ranging around 30%. An exception was observed for the "self-care" dimension with 10% to 11% reporting impairments along the 3 visits. A detailed summary of the patients' characteristics is shown in Table 1. Missing value percentages and number of patients per country are presented in supplemental Tables 1 and 2.

Univariable selection of potential determinants

In the univariable analyses of EQ-5D and VAS, the majority of tested variables were included as potential determinants of low HRQoL (P value $< .15$). These included age, sex, IPSS-R, serum ferritin (SF) levels, Hb and neutrophil counts, receiving ESA, RBC transfusions or iron chelators, Sorror and MDS-specific comorbidity indexes (MDS-CI), Karnofsky performance status (KPS), and body mass index (BMI). Time since diagnosis and platelets level were not significantly associated with low EQ-5D, but the lowest category of platelet count was associated with low VAS. Erythropoietin level, neutrophil count below 1×10^9/L, and ESA treatment given below Hb value of 10 g/dL showed no relevant association with any of the 2 outcomes. Figure 1 shows the univariable (ie, crude) ORs and 95% CIs for all variables and both EQ-5D and VAS.

Multivariable analyses

The multivariable analyses yielded age >75 years, female sex, SF $\geq$ 1000 μg/L, high MDS-CI, and reduced KPS as significant determinants of low EQ-5D and low VAS (Table 2). Transfusion dependence, Hb value of <10 g/dL, and a high BMI of >30 kg/m^2 were additional significant determinants of low VAS. Two interaction terms of transfusion dependence with Hb $\leq$10 g/dL and ESA were included after the univariable determinant screening. The

Table 1. Patient characteristics

Variable	Baseline n = 2205 Median (IQR)/n (%)	First visit n = 1861 Median (IQR)/n (%)	Second visit n = 1506 Median (IQR)/n (%)
Age, y	74 (67-80)	74 (67-80)	74 (67-80)
Age, y (categorical)			
<60	228 (10)	181 (10)	134 (9)
60-75	893 (41)	763 (41)	621 (41)
≥75	1084 (49)	917 (49)	751 (50)
Female	849 (38.5)	734 (39)	610 (40)
Time since diagnosis, months	1.4 (0.7-2.3)	6.5 (5.9-7.6)	12.8 (11.8-14.4)
EQ-5D index value	0.8 (0.6-1.0)	0.8 (0.6-1.0)	0.8 (0.6-1.0)
Low EQ-5D index value (<0.779)	1022 (46)	643 (35)	541 (36)
Visual analog score	70 (58-85)	70 (60-85)	70 (60-80)
Low visual analog score (<0.7)	914 (42)	618 (33)	485 (32)
Impaired EQ-5D – mobility*	750 (34)	484 (26)	414 (28)
Impaired EQ-5D – self-care*	243 (11)	192 (10)	166 (11)
Impaired EQ-5D – usual activities*	659 (30)	465 (25)	402 (27)
Impaired EQ-5D – pain/discomfort*	908 (41)	569 (31)	479 (32)
Impaired EQ-5D – anxiety/depression*	688 (31)	435 (23)	346 (23)
WHO subtypes			
RA	381 (17)	204 (11)	167 (11)
RARS	345 (16)	234 (13)	209 (14)
RCMD	854 (39)	506 (27)	398 (26)
RCMD-RS	127 (6)	60 (3)	48 (3)
RAEB-1	264 (12)	154 (8)	114 (8)
RAEB-2	9 (0)	36 (2)	32 (2)
MDS-U	94 (4.3)	51 (3)	36 (2)
Del 5q	130 (6)	88 (5)	76 (5)
IPSS-R (continuous, score unit)	2 (1.5-3.0)	2 (1.0-3.0)	2 (1.0-3.0)
IPSS-R, (categorical)			
Very low	559 (25)	505 (27)	430 (29)
Low	900 (41)	675 (36)	546 (36)
Intermediate	327 (15)	235 (13)	199 (13)
High	80 (4)	78 (4)	55 (4)
Very high	6 (0)	17 (1)	19 (1)
Hb, g/dL	10.2 (9.0-11.4)	10.6 (9.3-11.8)	10.5 (9.2-11.9)
Hb, g/dL (categorical)			
≥10	1197 (54)	1140 (61)	890 (59)
8-10	791 (36)	520 (28)	438 (29)
<8	202 (9)	156 (8)	136 (9)
Ferritin, µg/L (categorical)			
≥1000	164 (7)	181 (10)	167 (11)
300-1000	624 (28)	337 (18)	247 (16)
≤300	726 (33)	409 (22)	339 (23)
Erythropoietin, IU/L (categorical)			
>500	75 (3)	36 (2)	21 (1)

The numbers represent the observed, nonmissing values for the patient characteristics at each time point. Reported percentages relate to all patients (including those with missing values). The complementary missing values are represented detail in supplemental Table 1.

Del 5q, MDS associated with isolated del(5q); EQ-5D, EQ-5D 3-Levels questionnaire; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; IQR, interquartile range; MDS-U, MDS-unclassified; RA, refractory anemia; RAEB, refractory anemia with excess blasts; RARS, refractory anemia with ringed sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RCMD-RS, refractory cytopenia with multilineage dysplasia and ringed sideroblasts.

*Any problems (answer category 1 and 2) versus no problems (answer category 3).

†At least 1 unit RBC transfusion for a surveillance time of 8 weeks before the HRQoL assessment.

‡Average number of RBC transfusions per month since the last visit or up to 8 weeks before MDS diagnose.

§Progression to higher IPSS-R risk group.

Table 1 (continued)

Variable	Baseline n = 2205 Median (IQR)/n (%)	First visit n = 1861 Median (IQR)/n (%)	Second visit n = 1506 Median (IQR)/n (%)
100-500	253 (12)	112 (6)	82 (5)
<100	680 (31)	303 (16)	221 (15)
Platelets, $\times 10^9$/L (categorical)			
≥100	1634 (74)	1293 (70)	1074 (71)
50-100	375 (17)	321 (17)	220 (15)
<50	171 (8)	186 (10)	162 (11)
Neutrophils, $\times 10^9$/L	2.4 (1.0-3.8)	2.4 (1.3-3.8)	2.3 (1.3-3.7)
Neutrophils, $\leq 1 \times 10^9$/L	335 (15)	298 (16)	235 (16)
Therapies received			
ESA	331 (15)	514 (28)	424 (23)
ESA with Hb ≤ 10 g/dL	258 (12)	239 (13)	184 (12)
Granulocyte colony-stimulating factor	27 (1)	54 (3)	55 (4)
Iron chelation	17 (1)	59 (3)	83 (6)
Immunosuppressive therapy	7 (0)	15 (1)	17 (1)
Demethylating agent	2 (0)	28 (2)	30 (2)
Lenalidomide	7 (0)	38 (2)	45 (3)
Transfusion dependence†	500 (23)	455 (25)	332 (22)
Transfusion density‡	0 (0.0-0.5)	0 (0.0-0.5)	0 (0.0-0.5)
Cumulative number of transfusions	0 (0.0-1.0)	0 (0.0-2.0)	0 (0.0-2.0)
MDS progression§	-	200 (11)	186 (12)
KPS (continuous)	90 (80-100)	90 (80-100)	90 (80-100)
KPS (categorical)			
Able to work (80-100)	1428 (65)	1110 (60)	874 (58)
Unable to work (50-80)	392 (18)	329 (18)	248 (17)
Unable to care for self (<50)	28 (1)	26 (1)	26 (2)
MDS-CI (continuous)	0 (0.0-2.0)	0 (0.0-0.0)	0 (0.0-1.0)
MDS-CI (categorical)			
Low risk (0)	1355 (62)	1399 (75)	1091 (72)
Intermediate risk (1-2)	716 (33)	398 (21)	352 (23)
High risk (≥3)	126 (6)	46 (3)	46 (3)
HCT-CI (continuous)	1 (0.0-3.0)	0 (0.0-2.0)	0 (0.0-2.0)
HCT-CI (categorical)			
Low risk (0)	771 (35)	1009 (54)	759 (50)
Intermediate risk (1-2)	799 (36)	545 (29)	461 (31)
High risk (≥3)	635 (29)	307 (17)	286 (19)
BMI, kg/m^2	26 (23.8-29.0)	26 (23.8-29.1)	26 (23.5-29.1)
BMI, kg/m^2 (categorical)			
Underweight <23	311 (14)	268 (14)	242 (16)
Weight range (23-29.9)	1084 (50)	911 (49)	733 (49)
Overweight ≥30	320 (15)	282 (15)	231 (15)

The numbers represent the observed, nonmissing values for the patient characteristics at each time point. Reported percentages relate to all patients (including those with missing values). The complementary missing values are represented detail in supplemental Table 1.

Del 5q, MDS associated with isolated del(5q); EQ-5D, EQ-5D 3-Levels questionnaire; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; IQR, interquartile range; MDS-U, MDS-unclassified; RA, refractory anemia; RAEB, refractory anemia with excess blasts; RARS, refractory anemia with ringed sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RCMD-RS, refractory cytopenia with multilineage dysplasia and ringed sideroblasts.

*Any problems (answer category 1 and 2) versus no problems (answer category 3).

†At least 1 unit RBC transfusion for a surveillance time of 8 weeks before the HRQoL assessment.

‡Average number of RBC transfusions per month since the last visit or up to 8 weeks before MDS diagnose.

§Progression to higher IPSS-R risk group.

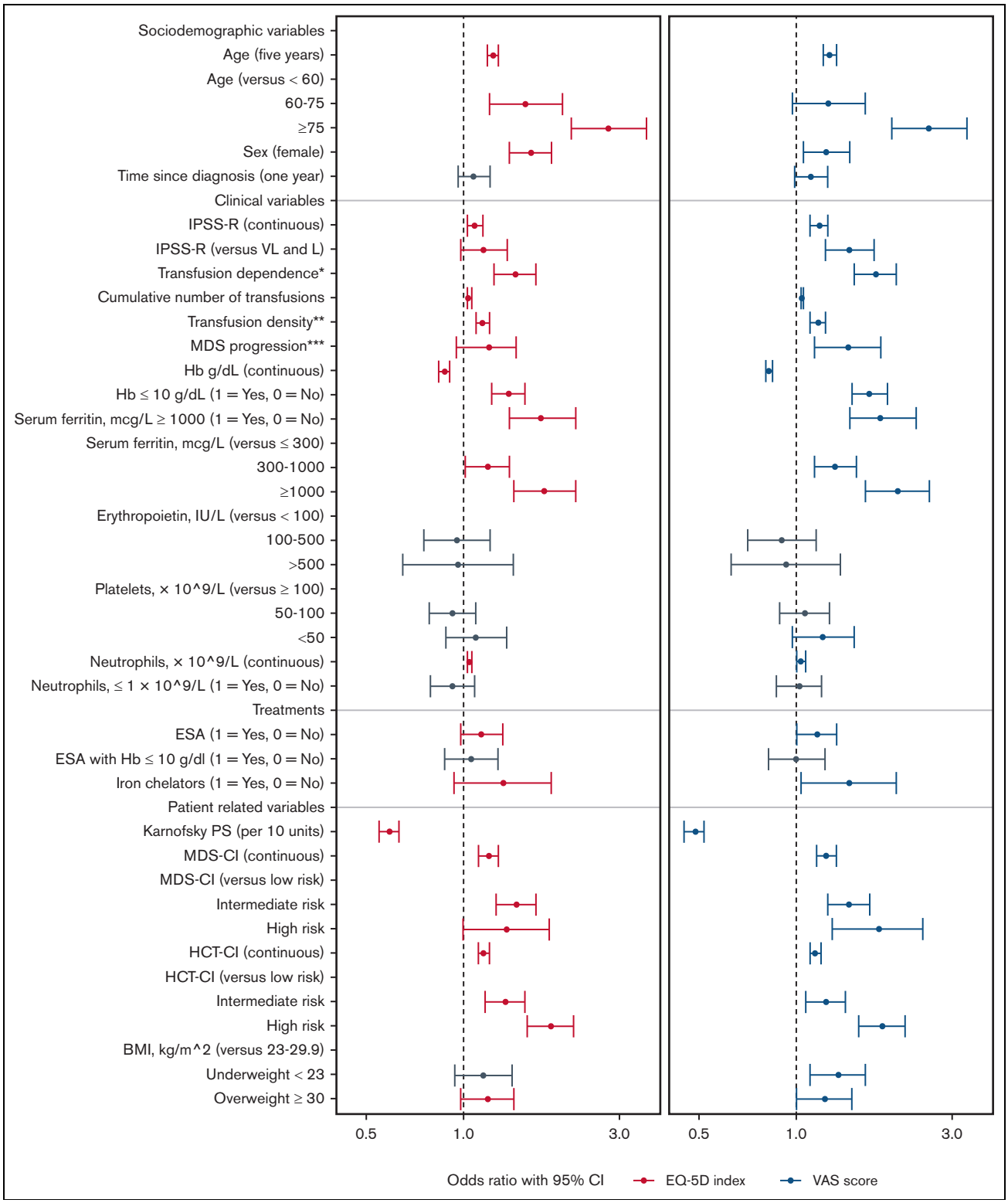

Figure 1. Determinants of low HRQoL – univariable analyses. Presented are the univariable analyses of the determinants of low EQ-5D index value and of low EQ-5D VAS score. ORs are colored if *P* value < .15 and gray if *P* value > .15. *At least 1 unit RBC transfusion for a surveillance time of 8 weeks before the HRQoL assessment; **Average number of RBC transfusions per month since the last visit or since the MDS diagnosis; ***Progression to higher IPSS-R risk group. HCT-CI, hematopoietic cell transplantation-specific comorbidity index; IPSS-R (vs VL/L), all remaining IPSS-R groups vs very low/low risk.

Table 2. Determinants of low HRQoL - multivariable analyses based on multiple imputation

	Multivariable model EQ-5D index N = 5522 observations; Brier score: 0.20; ROC area: 0.76		Multivariable model VAS score N = 5522 observations; Brier score: 0.18; ROC area: 0.80	
Independent variable	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Sociodemographic variables				
Age (vs <60)				
60-75	1.33 (1.01-1.75)	**.045**	0.96 (0.72-1.26)	.758
≥75	1.84 (1.39-2.45)	**.000**	1.44 (1.07-1.92)	**.015**
Sex (female)	1.70 (1.43-2.03)	**.000**	1.22 (1.02-1.46)	**.032**
Clinical variables				
Transfusion dependence*	1.34 (0.92-1.95)	.127	1.53 (1.03-2.29)	**.037**
Hb ≤ 10 g/dL	1.14 (0.97-1.36)	.120	1.34 (1.12-1.61)	**.001**
Transfusion dependence AND Hb ≤ 10	0.75 (0.50-1.12)	.161	0.79 (0.51-1.23)	.303
SF, µg/L (vs ≤300)				
300-1000	1.10 (0.92-1.32)	.306	1.14 (0.95-1.37)	.167
≥1000	1.41 (1.06-1.87)	**.018**	1.37 (1.02-1.84)	**.034**
Neutrophils, $\times 10^9$/L (continuous)	1.02 (1.00-1.05)	.098	1.01 (0.99-1.04)	.275
Treatments				
ESA (1 = yes, 0 = no)	1.04 (0.86-1.27)	.672	1.13 (0.92-1.39)	.229
ESA AND transfusion dependence	0.91 (0.63-1.29)	.586	0.72 (0.50-1.05)	.092
Use of iron chelators	1.15 (0.77-1.73)	.487	1.18 (0.78-1.79)	.424
Patient-related variables				
KPS (per 10 units)	0.62 (0.58-0.67)	**.000**	0.53 (0.49-0.57)	**.000**
MDS-CI (continuous)	1.11 (1.02-1.20)	**.011**	1.14 (1.05-1.25)	**.002**
BMI, kg/m^2 (vs 23-29.9)				
Underweight <23	0.97 (0.78-1.21)	.772	1.14 (0.91-1.42)	.249
Overweight ≥30	1.21 (0.99-1.50)	.068	1.26 (1.02-1.57)	**.033**

Bold *P* values < .05.
EQ-5D, EQ-5D 3-levels questionnaire; ROC, receiver operating characteristic curve; VAS, EQ-5D VAS.
*At least 1 unit RBC transfusion for a surveillance time of 8 weeks before the HRQoL assessment.

validity assessment showed that the Brier score for the overall model performance was good with 0.20 for the EQ-5D and 0.18 for the VAS. The discrimination ability was reasonable to excellent with an area under the receiver operator characteristic curve of 0.76 for EQ-5D and 0.80 for VAS in the multivariable analyses. Table 2 shows the adjusted ORs and 95% CI for all variables and both outcomes derived from the multivariable analyses.

Secondary analyses – EQ-5D dimensions

The results of the exploratory univariable analyses for the 5 dimensions of EQ-5D are presented in Figure 2. Female sex, reduced KPS, high Sorror comorbidity index, low Hb count, and transfusion related variables (transfusion dependence, cumulative number of RBC transfusions, and transfusion density) are potential determinants of low HRQoL among all the dimensions. Increased age was also a potential determinant for low HRQoL, particularly for the dimensions "mobility" and "self-care."

An overall shorter list of relevant determinants was identified for impairments in the "anxiety/depression" dimension. The variables age, SF level, neutrophil count, and MDS-CI, which were found relevant for the other dimensions, were not relevant for the "anxiety/depression" dimension. In addition, IPSS-R and sex were not relevant for the "pain/discomfort" dimension.

Sensitivity analyses

The univariable and multivariable ORs were similar before and after imputations. Differences in the statistical significance ($P < .15$) within the univariable analyses concerned mainly the following variables: SF level from 300 to 1000 µg/L, BMI < 23 kg/m^2, erythropoietin from 100 to 500 IU/L, age from 60 to 75 years, and MDS progression (supplemental Figures 1 and 2). In the multivariable analyses we observed changes in the statistical significance ($P < .05$) for SF level ≥1000 µg/L, MDS-CI, and BMI ≥ 30 kg/m^2 for the EQ-5D model, as well as changes in the variables sex, transfusion dependence, and age category ≥75 years for the VAS model (for detailed results refer to supplemental Table 3). Overall, the imputation process did not influence the univariable selection process nor significantly affected the final multivariable estimates. In the sensitivity analyses on the 1506 consistent patients along the 3 visits, the multivariable models remained stable (supplemental Table 4). The sensitivity analysis using the parsimonious model for EQ-5D revealed the same statistically significant determinants, and all ORs differed by <10% compared with the full model. In the

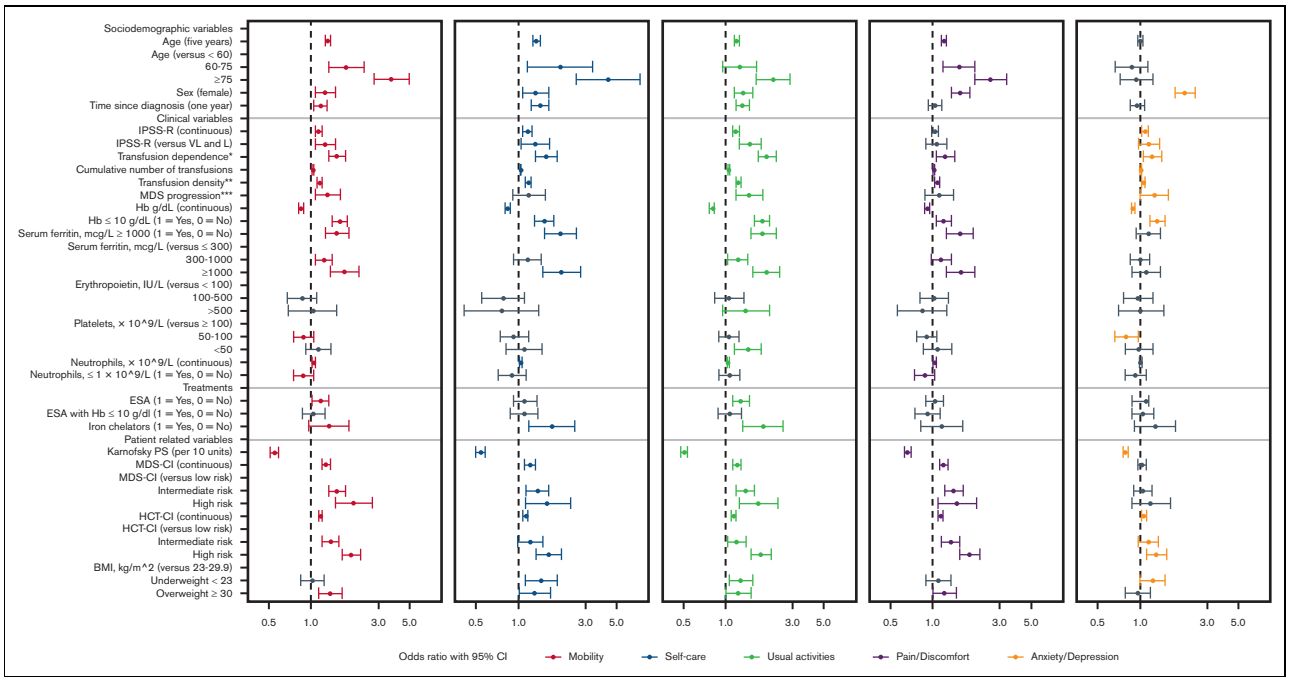

Figure 2. Determinants of impaired EQ-5D-3L dimensions - univariable analyses. Presented are the univariable analyses of the determinants of impaired dimensions of the EQ-5D questionnaire. ORs are colored if *P* value < .15 and gray if *P* value > .15. *At least 1 unit RBC transfusion for a surveillance time of 8 weeks before the HRQoL assessment; **Average number of RBC transfusions per month since the last visit or since the MDS diagnosis; ***Progression to higher IPSS-R risk group. HCT-CI, hematopoietic cell transplantation-specific comorbidity index; IPSS-R (vs VL/L), all remaining IPSS-R groups vs very low/low risk.

sensitivity analysis using the parsimonious model for VAS, all statistically significant variables of the full model remained with minor changes in the OR estimates, except transfusion dependence, which was removed in the parsimonious model.

Discussion

We performed a prospective longitudinal study to assess a wide range of potentially relevant determinants of low HRQoL as measured by the generic EQ-5D-3L instrument, in a uniquely large cohort of recently diagnosed patients with MDS.

The multivariable analyses for EQ-5D and VAS showed that advanced age, female sex, high SF level, low Hb count, high comorbidity index, high BMI, reduced KPS, and transfusion dependence are relevant key determinants of low HRQoL in MDS.

Blood transfusions are an important element of supportive therapy and symptom management, particularly for patients with lower-risk MDS.[1] However, optimal transfusion schedules and trigger points are still being explored, especially for asymptomatic anemic patients. An individual benefit-harm assessment is required because using RBC transfusions to treat anemia symptoms (eg, fatigue, dyspnea) carries the risk of iron overload, allergic or autoimmune reactions, infections, organ dysfunctions, and other complications.[37] SF is a regularly used indicator of iron overload. Although SF appears to be primarily linked to the frequent RBC transfusions in MDS, it can also be increased by inflammations/autoimmune conditions, malignant comorbidities, as well as by the intrinsic MDS pathology of ineffective erythropoiesis and/or deregulated iron absorption (eg, MDS with ringed sideroblasts).[38]

Our multivariable analyses have shown that patients with SF ≥ 1000 µg/L are at particular risk for deteriorated HRQoL. This determinant was relevant for both low EQ-5D and low VAS, indicating additional health implication and independent effect beyond the transfusion dependence. In patients with MDS, hyperferritinemia was also associated with dyspnea, pain, and loss of appetite.[39] Overall, regular RBC transfusions and iron overload are associated with both worse prognosis and lower HRQoL.[23] Even at low transfusion rates of <0.75 units per month, there was a negative effect of RBC transfusions on MDS progression.[40] Therefore, the frequency of transfusions, SF level, and symptoms of organ failure (liver, heart, pancreas) should all be closely evaluated in patients receiving chronic RBC transfusion support. Iron chelation treatment and lowering SF < 1000 µg/L may be beneficial for improving clinical outcomes and HRQoL.[41] Other therapy options, such as ESA or luspatercept, have been shown to postpone the initiation of RBC transfusions or reduce transfusion needs, although their influence on HRQoL should be further evaluated.[23,37]

In MDS, KPS can be used as an outcome parameter to compare treatment efficacy to estimate patient prognosis (eg, pretransplant risk assessment), and to supplement important clinical characteristics (eg, chronological age, comorbidities) and markers (eg, blood cell counts) for treatment decision making.[11,42] Unlike some earlier MDS studies,[17,43] which could not prove a relevant association of performance status and HRQoL, our multivariable analyses showed an independent effect of KPS as a determinant of low HRQoL. The differences between the study results can partly be explained by the varying performance measures, different types of performance status variable (ie, ordinal vs dichotomized) and by the

number of studied patients. Our results support and extend the findings from Efficace et al[10] on the correlation of poor performance status and worse HRQoL in patients with higher-risk MDS. The information from KPS could be used among other prognostic factors including age, mutations, SF level, or lactate dehydrogenase levels in planning treatment modalities, which may be particularly valuable for patients with intermediate-risk MDS.[3] Interventions such as exercise programs that improve physical capabilities and perhaps avoiding high BMI should be considered, because obesity is associated with several comorbidities and poor HRQoL, as shown in our analyses.[44] Furthermore, the burden of preexisting comorbidities has negative impact on patients' HRQoL and was a relevant determinant of low HRQoL. Because of its relevance for HRQoL, applicability across all patients with MDS, additional risk classification, and prognostic capabilities, MDS-CI should be broadly used, well beyond the pretransplantation assessment.[16,45] Of note, effect estimates derived from the multivariable analyses were generally smaller than those from the univariable analyses, indicating a biological dependence between factors influencing the course of MDS. For example, the lower effect estimates for low Hb levels, transfusion dependence, and SF in the multivariable analyses may be because of reasons other than the assessed independent effects (Table 2). Furthermore, including KPS in the multivariable models reduced the effect of age, likely because without adjustment for KPS, age may act in part as a proxy for performance status. Controlling for KPS helped reveal the independent effect of age.

Focusing on the results of the EQ-5D dimensions, we observed one-third (11%) of impairments for the dimension "self-care" as compared with restrictions in other dimensions. This phenomenon was also observed in other cancer subtypes[46,47] and can be explained by the retained "self-care" capabilities of the patients with MDS or by reporting more problems in the "usual activities" dimension.[24] For the "anxiety/depression" dimension we observed less relevant determinants, like in other hematological cancers.[48] Particularly, female patients with lower Hb levels, impaired performance, and higher IPSS-R seem to be affected more than others.

Overall, the identified determinants associated with low HRQoL early after the MDS diagnosis could help physicians target specific patients at risk, facilitate an effective patient-physician communication to address patients' needs, promote continuous assessment and monitoring of symptoms, support maintaining or improving HRQoL, and initiate healthy lifestyle adjustments or coping mechanisms including support groups, professional counselors, and prescription alternatives. Patients with higher risk of low HRQoL may benefit from an early psychological counseling, physical therapy, different pain management approaches, etc. All these aspects are particularly important because patients with MDS, compared with population-referenced groups, may experience impaired physical, emotional, social, and role functioning, as well as issues related to fatigue and dyspnea.[23]

A significant strength of our study was the availability of the large prospective cohort group of 2205 newly diagnosed patients with MDS that enabled us to analyze and identify multiple potential determinants of HRQoL. Including multiple time points during the first year allowed us to: (1) increase power and estimation precision, (2) apply a solid imputation approach, and (3) generate a more stable result that is applicable to patients during the initial phase after diagnosis. Therefore, our analyses provided more valid and reliable estimates than those of cross-sectional analyses restricted to baseline data.

Our study also has several limitations. First, the binary split of outcomes comes with the potential risk of reducing information and may lead to the underestimation of variation or concealing nonlinear relation between determinants and outcomes.[49] In contrast, as seen in the study by Schünemann et al[50] the categorization of PROs into 2 groups can strengthen clinical understanding and interpretation in MDS trials and improve the usability of our results in daily practice. Further research is needed to determine the optimal cutoff points for HRQoL in MDS. Second, categorization of the determinant variables is also a limitation, therefore we presented the association of the continuous and categorical type of determinants in the univariable analyses for all variables that were available. We observed only minor differences for the neutrophil count significance. This is not a surprise because the neutrophil counts are not prognostic in the most recent IPSS score, which also includes molecular aberrations.[51] Third, other potential determinants of HRQoL that were not assessed in this study, including social determinants of health (eg, socioeconomic status, education quality, housing, health care access, marital status) may be relevant. Moreover, we had to impute a considerable portion of missing data for the other variables that were available to us in the registry. However, we were able to account for the missingness conditional on the extensively available data using the MICE procedure, and therefore we were not forced to assume missingness completely at random. Our sensitivity analysis without imputing any data showed similar estimates, indicating robustness of our results (refer to supplemental Figures 1 and 2; supplemental Table 3). Fourth, we restricted the follow-up period to 1 year to specifically analyze the effects at a time early after MDS diagnosis. We were not able to investigate any later time points because of a higher percentage of missing data. Therefore, we are not able to infer effect beyond the defined study period. Fifth, our study used the generic HRQoL measures of EQ-5D and VAS, which—although widely used in MDS research[6]—are not tailored to the specific symptoms that patients with MDS may encounter. MDS-specific HRQoL measures such as QoL-E[52] and QUALMS[53] could offer a more pertinent insight into the patients' experience with their condition.[23] Although the EUMDS Registry has been implementing QUALMS in a number of countries and sites since December 2016, the number of completed assessments were still, too limited to be included in our analyses. Last, although we used multivariable analyses to derive adjusted effect estimates representing independent effect sizes of all our determinants of HRQoL, caution is warranted when interpreting these effects causally. Particularly when interpreting treatment effects (eg, blood transfusions) in observational MDS studies, time-dependent confounding by indication must be appropriately addressed and further analyzed using more sophisticated causal inference methods (eg, g-methods).[54] Such causal-effect estimates could then be combined with decision-analytic modeling to assess the long-term benefit-harm balance and cost-effectiveness of personalized treatment strategies in MDS.[55,56] Future research should also address the mechanisms through which determinants affect HRQoL. For example, Wouters et al[57] showed that MDS has an effect on HRQoL because of low Hb level, but there was also an independent effect not mediated by anemia.

In conclusion, we identified increased age, female sex, high SF level, low Hb count, reduced KPS, high MDS-CI, high BMI, and transfusion dependence as significant independent determinants of low HRQoL in MDS, assessed by EQ-5D or VAS. Our analyses minimized the potential missing-data bias and made use of the repeated measurements of an extensive array of variables in the EUMDS Registry. Knowing and considering the determinants of low HRQoL is expected to provide improved patient-oriented quality of care, increase patients' participation in the MDS disease management, and guide patient-shared decision making. Patients with a higher chance for early deterioration of HRQoL might be the primary candidates for early clinical evaluations and interventions that aspire to deliver systematic, multidisciplinary, and timely health care to fragile patients.

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Authorship

Contribution: A.C.-F., I.S., K.A.K., R.S., and U.S. designed the research; A.G.B., A.S., D.B., D.J.C., F.E., G.F.S., I.K., J.M., K.M., L.M., L.S., M.M., P.F., R.S., S.L., T.d.W., and U.G. collected the data; A.C.-F., D.S., I.S., K.A.K., M.S., R.S., S.P., U.R., and U.S. analyzed and interpreted the data; I.S., M.A., and M.S. performed statistical analyses; A.C.-F., I.S., K.A.K., R.S., U.R., and U.S. wrote the manuscript; A.C.-F., A.G.B., A.S., C.V.M., D.B., D.J.C., D.S., F.E., G.F.S., I.K., I.S., J.M., K.A.K., K.M., L.M., L.S., M.A., M.M., M.S., P.F., R.S., S.L., S.P., T.d.W., U.G., U.R., and U.S. performed research; and all authors reviewed the manuscript.

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