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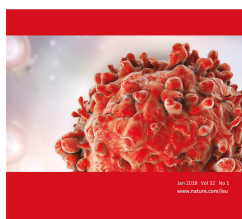
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## Health-related quality of life in lower-risk MDS patients compared with age- and sex-matched reference populations: a European LeukemiaNet study

Reinhard Stauder, Ge Yu, Karin A. Koinig, Tim Bagguley, Pierre Fenaux, Argiris Symeonidis, Guillermo Sanz, Jaroslav Cermak, Moshe Mittelman, Eva Hellström-Lindberg, Saskia Langemeijer, Mette Skov Holm, Krzysztof Mądry, Luca Malcovati, Aurelia Tatic, Ulrich Germing, Aleksandar Savic, Corine van Marrewijk, Agnès Guerci-Bresler, Elisa Luño, Jackie Droste, Fabio Efficace, Alex Smith, David Bowen, Theo de Witte

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1 **Health-related quality of life in lower-risk MDS patients compared with age- and sex-matched**  
 2 **reference populations: a European LeukemiaNet study**

3  
 4 Reinhard Stauder\* <sup>1</sup>, Ge Yu<sup>2</sup>, Karin A. Koinig<sup>1</sup>, Tim Bagguley<sup>2</sup>, Pierre Fenaux<sup>3</sup>, Argiris Symeonidis<sup>4</sup>,  
 5 Guillermo Sanz<sup>5</sup>, Jaroslav Cermak<sup>6</sup>, Moshe Mittelman<sup>7</sup>, Eva Hellström-Lindberg<sup>8</sup>, Saskia  
 6 Langemeijer<sup>9</sup>, Mette Skov Holm<sup>10</sup>, Krzysztof Mądry<sup>11</sup>, Luca Malcovati<sup>12</sup>, Aurelia Tatic<sup>13</sup>, Ulrich  
 7 Germing<sup>14</sup>, Aleksandar Savic<sup>15</sup>, Corine van Marrewijk<sup>9</sup>, Agnès Guerci-Bresler<sup>16</sup>, Elisa Luño<sup>17</sup>, Jackie  
 8 Droste<sup>9</sup>, Fabio Efficace<sup>18</sup>, Alex Smith<sup>2</sup>, David Bowen<sup>19</sup>, Theo de Witte<sup>20</sup>

9  
 10 1 Dep. of Internal Medicine V (Hematology and Oncology), Medical University Innsbruck, Innsbruck, Austria

11 2 Epidemiology and Cancer Statistics Group, Department of Health Sciences, University of York, York, United Kingdom

12 3 Service d'Hématologie, Hôpital Saint-Louis, Assistance Publique des Hôpitaux de Paris (AP-HP) and Université Paris 7, Paris, France

13 4 Dep. of Medicine, Div. Hematology, University of Patras Medical School, Patras, Greece,

14 5 Dep. Of Hematology, Hospital Universitario y Politécnico La Fe, Valencia, Spain

15 6 Dep. of Clinical Hematology, Inst. Of Hematology & Blood Transfusion, Praha, Czech Republic

16 7 Dep. of Medicine A, Tel Aviv Sourasky (Ichilov) Medical Center and Sackler Medical Faculty, Tel Aviv University, Tel Aviv, Israel

17 8 Dep. of Medicine, Div. Hematology, Karolinska Institutet, Stockholm, Sweden

18 9 Dep. Of Hematology, Radboud University Medical Center, Nijmegen, Netherlands

19 10 Dep. of Hematology, Aarhus University Hospital, Aarhus, Denmark

20 11 Dep. of Hematology, Oncology and Internal Medicine, Warszawa Medical University, Warszawa, Poland

21 12 Dep. of Hematology Oncology, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy

22 13 Center of Hematology and Bone Marrow Transplantation, Fundeni Clinical Institute, Bucharest, Romania

23 14 Dep. of Hematology, Oncology and Clinical Immunology, Universitätsklinik Düsseldorf, Düsseldorf, Germany

24 15 Clinic of Hematology - Clinical Center of Vojvodina, University of Novi Sad, Novi Sad, Serbia

25 16 Service d'Hématologie, Center Hospitalier Universitaire Brabois Vandoeuvre, Nancy, France

26 17 Servicio d'Hematología, Servicio de Salud del Principado de Asturias Oviedo, Oviedo, Spain

27 18 Fondazione GIMEMA Onlus, Rome, Italy

28 19 St. James's Institute of Oncology, Leeds Teaching Hospitals, Leeds, United Kingdom

29 20 Dep. of Tumor Immunology - Nijmegen Center for Molecular Life Sciences, Radboud University Medical Center, Nijmegen,  
 30 Netherlands

31 \* corresponding author

32 **Corresponding Author**

33 Reinhard STAUDER MD, MSc, Associate Professor

34 Department of Internal Medicine V (Hematology and Oncology)

35 Innsbruck Medical University, Anichstraße 35, 6020 Innsbruck, Austria

36 [reinhard.stauder@i-med.ac.at](mailto:reinhard.stauder@i-med.ac.at), Tel: 0043 512 504 27302; FAX: 0043 512 504 25615

37 **Running Head: HRQoL in low-risk MDS**

38 **Keywords:** HRQoL, MDS, EQ-5D, European norms, patient-reported outcome (PRO)

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46 In myelodysplastic syndromes (MDS) health-related quality of life (HRQoL) represents a relevant  
47 patient-reported outcome, which is essential in individualized therapy planning. Prospective data  
48 on HRQoL in lower-risk MDS remain rare. We assessed HRQoL by EQ-5D-questionnaire at initial  
49 diagnosis in 1690 consecutive IPSS-Low/Int-1 MDS-patients from the European LeukemiaNet  
50 Registry. Impairments were compared with age- and sex-matched EuroQol Group norms. A  
51 significant proportion of MDS-patients reported moderate/severe problems in the dimensions  
52 pain/discomfort (49.5%), mobility (41.0%), anxiety/depression (37.9%), and usual activities  
53 (36.1%). Limitations in mobility, self-care, usual activities, pain/discomfort and EQ-VAS were  
54 significantly more frequent in the old, in females, and in those with high co-morbidity burden, low  
55 haemoglobin-levels, or red blood cells transfusion-need ( $p < 0.001$ ). In comparison to age- and sex-  
56 matched peers, the proportion of problems in usual activities and anxiety/depression was  
57 significantly higher in MDS-patients ( $p < 0.001$ ). MDS-related restrictions in the dimension mobility  
58 were most prominent in males, and in older people ( $p < 0.001$ ); in anxiety/depression in female and  
59 in younger people ( $p < 0.001$ ); and in EQ-VAS in women and in persons older than 75 years  
60 ( $p < 0.05$ ). Patients newly diagnosed with IPSS lower-risk MDS experience a pronounced reduction  
61 in HRQoL and a clustering of restrictions in distinct dimensions of HRQoL as compared with  
62 reference populations.

63

65 Myelodysplastic syndromes (MDS) represent challenging hematopoietic disorders characterized by  
66 cytopenias, functional blood defects and clonal hematopoiesis. The clinical course is characterized  
67 by an impaired health-related quality of life (HRQoL), the risk of transformation to acute myeloid  
68 leukaemia (AML) and reduced survival in the majority of patients.<sup>1</sup> Based on biological parameters,  
69 patients are classified into different risk groups to predict overall survival (OS) and the risk of AML  
70 transformation. The international prognostic scoring system (IPSS)<sup>2</sup> and more recently, the revised  
71 IPSS (IPSS-R)<sup>3</sup> represent the gold standard in prognostication of MDS. Based on these scoring  
72 systems, IPSS low/intermediate-1 risk and IPSS-R (very) low/intermediate risk are classified as  
73 lower-risk MDS with a low propensity to transform to AML.<sup>2,3</sup> The treatment goals in this cohort of  
74 patients are an improvement in cytopenias, prolongation of survival, and improvement and  
75 maintenance of HRQoL and functional capacities. IPSS intermediate-2/high and IPSS-R high/very  
76 high risk are classified as higher-risk MDS, which are characterized by an increased risk of AML  
77 transformation and a short median survival of less than two years.<sup>1</sup>

78  
79 Patients with MDS often suffer from a high symptom burden, resulting in restrictions in HRQoL.  
80 Assessment of HRQoL provides information on the patient's perspective and perception, thus  
81 representing a relevant patient-reported outcome (PRO).<sup>1,4,5</sup> The study of HRQoL has become an  
82 increasingly critical area of research,<sup>6</sup> as limitations in HRQoL are frequently observed in MDS and  
83 are only partially explained by anaemia.<sup>7,8</sup> Moreover, restrictions in HRQoL may predict an  
84 unfavourable clinical outcome.<sup>9-12</sup> In addition HRQoL represents a parameter of response  
85 evaluation.<sup>1,13,14</sup> Thus, the integration of assessment of HRQoL in MDS has been propagated by  
86 clinicians, stakeholders and authorities.<sup>1,13-15</sup> However, definitive data on HRQoL in low-risk MDS  
87 at initial diagnosis are limited by small sample size,<sup>16,17</sup> selection bias,<sup>7,16,17</sup> and assessment later

88 after initial diagnosis.<sup>7, 11, 16, 18, 19</sup> In addition, most studies have included patients with higher-risk  
89 MDS,<sup>9-12, 16, 18-20</sup> AML,<sup>10, 11</sup> or CMML,<sup>11, 16</sup> which precludes precise interpretation. Lower-risk  
90 patients with MDS are typically of advanced age with a median of 74 years at diagnosis.<sup>21</sup> The  
91 dissection between age-associated restrictions in HRQoL and the incremental impact of MDS in  
92 these patients is relevant, yet has not been analysed at all.

93

94 The main objective of this international prospective cohort observational study is to investigate  
95 the HRQoL-profile of patients with lower-risk MDS at time of diagnosis, as compared with the  
96 general population matched on age and sex. The incremental impact of MDS on symptom burden  
97 is dissected by comparing features in MDS with the general population. A secondary objective is to  
98 examine clinical factors associated with HRQoL of these patients.

99

## 100 **MATERIALS / METHODS**

### 101 *Participants*

102 The EUMDS Registry is a prospective, non-interventional longitudinal study, enrolling newly  
103 diagnosed patients with IPSS low or intermediate-1 MDS from 145 haematology centres in 17  
104 European countries and Israel. Patients with an IPSS risk intermediate-2 or high, or with therapy-  
105 related MDS were excluded. Patients without cytogenetic information were only included if the  
106 diagnosis of MDS was morphologically proven, with <5% bone marrow blasts and at most a single  
107 cytopenia according to the IPSS. Based on these criteria, exclusively IPPS low or intermediate-1  
108 patients were included in EUMDS.

109

110 Therapy is given according to local guidelines.<sup>21</sup> Enrolment was within 100 days of the diagnostic  
111 bone marrow aspirate. The average time from date of diagnosis to inclusion was 44 days (standard  
112 deviation 28 days). Details on design and data collection have been published elsewhere.<sup>21</sup>  
113 As EQ-5D was not licensed in two countries, 15 countries were included in this analysis. EUMDS  
114 (ClinicalTrials.gov: NCT00600860) has been approved by the ethics committees of all participating  
115 centres and is performed in accordance with the Declaration of Helsinki. Written informed consent  
116 was obtained from all patients.

### 117 *HRQoL Measurement*

118 Patient reported HRQoL was measured by the European Quality of Life five Dimensions (EQ-5D), at  
119 the time of study enrolment. EQ-5D is a validated, generic, HRQoL-questionnaire,<sup>22</sup> consisting of  
120 the EQ-5D descriptive system with five dimensions related to daily activities (mobility, self-care,  
121 usual activities, pain/discomfort, anxiety/depression), with three-level answers (no problem, some  
122 problems, severe problems), and a visual analogue scale (EQ-VAS). The five dimensions were  
123 converted into a single summary index (EQ-5D index) by applying the European value set (EVS).<sup>23</sup>  
124 EQ-VAS<sup>22</sup> is a global evaluation of 'own health today' using a health state scale ranging from 0  
125 (worst imaginable) to 100 (best imaginable).

### 126 *Measures of Population Norms*

127 The main objective of this paper was to compare the QoL of patients with MDS with general  
128 population with a similar age and gender distribution. Therefore population norms were used as  
129 reference values to assess the relative HRQoL of patients in comparison to that of an average  
130 person.<sup>24</sup> Population norms are based on descriptions of current health status from population  
131 surveys. Nine European countries in this study (Denmark, France, Germany, Greece, Italy,  
132 Netherlands, Spain, Sweden, and the UK) have reported a series of tables of age/sex population  
133 norms for the EQ-5D for both, profile data and VAS scores.<sup>25</sup> For the five European countries and

134 Israel for which there are no published EQ-5D population norms, we replaced the missing data on  
135 the probabilities of being in a given level for each EQ-5D dimension with the mean of the available  
136 European countries by matching the combination of age group and gender.

#### 137 *Demographic and Clinical Parameters*

138 Information on patients' demographics (age and gender), IPSS-R, co-morbidity index (MDS-CI),  
139 haemoglobin (Hb)-level at the time of diagnosis, and red blood cell transfusions (RBCT) in the year  
140 prior the diagnosis were recorded.<sup>3, 21, 26</sup> Due to the small number of young adult patients, age was  
141 categorised into three groups (<60, 60–75, and 75+ years) to compare HRQoL of different age  
142 groups.

#### 143 *Statistical Analysis*

144 Differences in response between the five EQ-5D dimensions in patients with MDS and European  
145 norms were evaluated using chi-square tests. For both EQ-5D index and EQ-VAS, the mean score  
146 with standard deviation was calculated. Wilcoxon's signed ranks tests were conducted to identify  
147 any major difference between the MDS patient baseline values and European norms. The  
148 relationship between HRQoL and demographic/clinical factors was examined using multilevel  
149 linear regression (additional information is available in Supplementary Materials); univariate  
150 analysis was performed for age at diagnosis, gender, IPSS-R, MDS-CI, Hb and RBCT status, and a  
151 multivariate analysis was performed adjusting for all other variables. We assessed the  
152 discriminative ability of HRQoL not only by a significant difference, but also by a minimally  
153 important difference (MID).<sup>27</sup> The MID is viewed as the smallest difference in score in the domain  
154 of interest that is perceived by patients as beneficial or that would result in a change in treatment.

155 *See supplementary material for more detail.*

156

157 All analyses were undertaken in Stata 14 (StataCorp, College Station, TX).



**159 Characteristics of patients**

160 Based on IPSS-scoring, i.e. the gold-standard in classification at the time at the start of the registry,  
161 1985 patients were included between December 2007 and January 2016, among which 961  
162 (48.4%) were IPSS low-risk and 912 (45.9%) were IPSS Int-1. IPSS score could not be calculated in  
163 5.6% of patients where cytogenetic testing was not available or had failed. Based on inclusion  
164 criteria, exclusively IPSS low or int-1 patients were included. Retrospective classification by IPSS-R  
165 revealed a (very) low risk in 24.8% and 37.6%, an intermediate risk in 21. 2%, high/very high risk in  
166 6.1% and classification was unknown in 10.3% of patients. In total 1690 patients (85.1%)  
167 completed both EQ-5D descriptive system and EQ-VAS. Thirty-three patients (1.7%) completed EQ-  
168 5D description only, and 7 patients (0.3%) completed EQ-VAS only (Table 1.). The majority of  
169 patients had advanced age (median age: 74 years), and a male preponderance was observed.  
170 Nearly half of patients were characterized by Hb-levels <10g/dL at baseline, and more than 30% of  
171 patients had received RBCT within one year prior to diagnosis. Demographic characteristics of the  
172 patients who completed EQ-5D did not differ substantially from the total cohort, showing a similar  
173 age distribution and a slightly higher proportion of men. Overall, the HRQoL data in our sample  
174 were likely missing at random (Table 1).

**175 Patients with MDS reveal profound impairments in HRQoL**

176 The MDS-cohort was characterized by a mean EQ-5D index-score of 0.74 and a mean EQ-VAS of  
177 69.6. A significant proportion of MDS-patients reported moderate or severe problems in the  
178 dimensions pain/discomfort (49.5%), mobility (41.0%), anxiety/depression (37.9%), and usual  
179 activities (36.1%), respectively. The dimension with the lowest proportion of restrictions was self-  
180 care (13.3%) (Table 2). Clinically meaningful restrictions in the dimensions mobility, self-care, usual  
181 activities, and pain/discomfort as well as in EQ-VAS and EQ-5D index were observed significantly

182 more often in older patients and in those with a high co-morbidity burden, low Hb-levels, or RBCT  
183 need ( $p < 0.001$ ). Increased problems with anxiety/depression were significantly more frequent in  
184 women ( $p < 0.001$ ) and in patients with lower Hb-levels ( $p < 0.01$ ). The impact both of IPSS and IPSS-  
185 R on EQ-5D scoring was only marginal. In general, restrictions in all parameters of EQ-5D were  
186 significantly more often reported in female patients ( $p < 0.05$ , Table 2).

### 187 **Association of restrictions in HRQoL and demographic and disease factors**

188 To assess possible associations between clinical parameters and HRQoL, univariate and  
189 multivariate linear analyses were performed. It was estimated that patients in the reference group  
190 of each of demographic and clinical parameters would have a mean score of 0.85 on the EQ-5D  
191 index, and 80.85 on the EQ-VAS (Table 3). Relative to these scores, there was a significant loss in  
192 HRQL for groups who were older (e.g. 75+ vs <60 years; index: -0.08; VAS: -7.33), female, or had  
193 increased comorbidities, low Hb-levels or transfusion dependence (Table 3.). These differences  
194 exceeded the MID on each of the two HRQL measures ( $> 0.03$  on the EQ-5D index and  $> 3.0$  on the  
195 EQ-VAS). In summary HRQoL as defined by EQ-5D index and EQ-VAS was more often significantly  
196 impaired in older and in female patients and in persons with advanced comorbidities, low Hb-  
197 levels and increased transfusion need both in uni- and in multivariate analyses.

198

### 199 **Comparison of HRQoL in MDS and in age- and sex-matched reference populations**

200 We compared subgroups of MDS-patients with age- and sex-matched reference norms. Overall,  
201 patients with MDS were characterized by a small, but significantly lower EQ-5D index (0.74 vs  
202 0.76) and lower EQ-VAS (69.6 vs 71.8) than European norms ( $p < 0.05$ )(Table 4). However, these  
203 differences were too small to fulfil the criteria of MID. In contrast distinct differences which  
204 fulfilled the criteria of a MID were seen in individual components of EQ-5D: a significantly higher

205 proportion of MDS-patients reported moderate/severe problems in the dimensions mobility, usual  
206 activities and anxiety/depression compared to the reference populations ( $p < 0.001$ )(Table 4).

207

208 Analyses stratified by sex and age depicted most pronounced differences in the dimensions  
209 anxiety/depression, and usual activities, in all age groups, and in both sexes ( $p < 0.001$ ). Compared  
210 to peers, prevalence of problems in anxiety/depression was most prominent in female (16.7 vs.  
211 50.3%; Fig. 1B), and in younger patients (9.8 vs. 40.8%,  $p < 0.001$ ; Fig. 2A). Restrictions in mobility  
212 were most pronounced in male (Fig. 1A), and in older patients (60+ years;  $p < 0.01$ ; Fig. 2C). The  
213 dimensions self-care and pain/discomfort were not different between the cohorts (Table 2; Figure  
214 1 & 2). Differences in EQ-5D index were most pronounced in younger MDS-patients (<60yrs). EQ-  
215 VAS was more often diminished at advanced age (75+ yrs) as compared to peers ( $p < 0.001$ ; Table  
216 2). These differences fulfilled the criteria of a MID.

217

## 218 **DISCUSSION**

219 This prospective cohort observational study adds substantial information on the prevalence and  
220 clustering of restrictions in HRQoL in lower-risk Patients with MDS at diagnosis. In a cross-sectional  
221 analysis, we observed profound restrictions in distinct dimensions of the EQ-5D when compared  
222 with European reference populations. Moreover, we identified demographic and clinical factors,  
223 which are associated with restrictions in HRQoL.

### 224 **Prevalence of restrictions in HRQoL in MDS at initial diagnosis / Factors associated with** 225 **decreased HRQoL**

226 Data on symptom burden in lower-risk MDS at initial presentation are rare, and limited by small  
227 sample size,<sup>16, 17</sup> selection bias,<sup>7, 16, 17</sup> and analyses performed later after initial diagnosis.<sup>7, 11, 16, 18,</sup>

228 <sup>19</sup> In addition, most studies have included patients with higher risk MDS,<sup>9-11 9-11, 16, 18-20</sup> AML<sup>10, 11</sup> or  
229 CMML<sup>11, 16</sup>, which precludes precise interpretation. The strength of our study is the large number  
230 of observations at initial diagnosis and the parallel analysis of the different parameters of the  
231 validated score EQ-5D including EQ-5D VAS, EQ-5D index as well as the different EQ-5D  
232 dimensions in a homogenous cohort of lower-risk patients. This is the first report to present  
233 details on restrictions in the distinct domains of EQ-5D in MDS, which reveals huge differences in  
234 HRQoL-profile in daily activities. These findings are particularly relevant, as studies from the  
235 literature reported exclusively EQ-5D summary scores and EQ-5D VAS,<sup>16, 20</sup> but lacked a  
236 presentation of EQ-5D daily activities.

237

238 Our study shows a pronounced symptom burden in many patients with MDS, predominantly in the  
239 dimensions pain/discomfort, mobility, anxiety/depression, and usual activities. Moreover, a  
240 clustering of symptoms in distinct subgroups of patients is revealed. The low percentage of self-  
241 reported problems in the dimension self-care, particularly in elderly is remarkable. This  
242 phenomenon has been observed across different cancer types<sup>28</sup> and may be explained by focusing  
243 on “washing and dressing” in the definition of self-care, whereas functional capacities like “work,  
244 housework, family or leisure activities” are assessed in the dimension “usual activities”.

245

246 We demonstrated that advanced age, pronounced co-morbidities, low Hb-levels, RBCT need, and  
247 female sex, were significantly associated both with a decreased EQ-5D index, and decreased EQ-  
248 VAS after adjustment for co-variables. These observations extend data from the literature<sup>7, 8, 18, 20</sup>  
249 and define cohorts of patients which are at high risk of decreased HRQoL. Hb-levels<sup>7, 18, 20</sup> and  
250 transfusion dependence<sup>20</sup> are important predictors of HRQoL, both in this study and in the  
251 literature. Effective treatment for anemia and reduction of transfusion need might thus contribute

252 to improvement and maintenance of HRQoL.<sup>17</sup> Future studies will focus on the prediction of  
253 deterioration of HRQoL, and focus on early prevention.

254

255 A relevant aspect of our work is the significant difference in symptom burden in patients with MDS  
256 as compared to age- and sex matched European reference populations. Thus, dissection of  
257 features which are MDS-specific from symptoms which are present in matched general  
258 populations is possible. This study reveals an incremental symptom burden in MDS characterized  
259 by pronounced age- and sex-dependent differences in the distinct EQ-5D dimensions. Both young  
260 and old patients suffer from troublesome MDS-related symptoms. Data from the literature are  
261 rare and have been characterized by a small sample size and were restricted to one country.<sup>16, 17</sup>  
262 The study of Hellstrom evaluated HRQoL at later time points after diagnosis, and was focused on  
263 selecting anaemic patients with a high probability for response to ESAs for a clinical study.<sup>17</sup> The  
264 study of Jansen<sup>16</sup> reported exclusively EQ-5D VAS but lacked a presentation of EQ-5D daily  
265 activities for which we show strong differences. Moreover, patients in Jansen's study were  
266 entered at variable time points after diagnosis, and included patients with higher risk MDS and  
267 CMML.<sup>16</sup>

268

269 The high prevalence of anxiety/depression and of limitations in usual activities is more  
270 pronounced in women in our study. These observations form the basis to appreciate the relevance  
271 of MDS on individual health in a given patient and the opportunity to assist health care providers  
272 in managing the relevant symptoms.<sup>8</sup> Thus, patient-centred care will be improved by special  
273 attention to patient subgroups.<sup>29, 30</sup> The finding of the difference of depression between our MDS  
274 patients and the general population is corroborated by similar evidence in other hematologic  
275 conditions. For example, Efficace et al.<sup>31</sup> observed that depression was one of the most impaired  
276 psychological domains in a sample of chronic myeloid leukemia patients as compared to their

277 peers in the general population; and, similar to our findings, this impairment was most  
278 pronounced in female patients. In agreement with other studies,<sup>8, 32, 33</sup> differences by gender were  
279 observed with lower HRQoL being more pronounced in females. Although the discussion of causes  
280 of disparity in gender-based distribution is beyond the scope of this manuscript, gender-specific  
281 evaluations and interventions should be discussed or suggested in patients with MDS.

282

283 The relevance of anxiety/depression in patients with MDS is supported by the fact that 9.5% of EU-  
284 MDS patients receive antidepressants at baseline,<sup>21</sup> and that impairments in depression screening  
285 by geriatric depression scale (GDS) are observed in 24% of patients with MDS<sup>34</sup>. Likewise  
286 “emotional health” and “uncertainty/sense of control” have been highly ranked by patients and  
287 caregivers in a recent study.<sup>35</sup> To address the individual needs of patients with MDS, the novel,  
288 disease specific score for MDS, QUALMS,<sup>18, 35</sup> is currently applied and validated in the EUMDS-  
289 cohort. Our study also confirms that age- and sex-dependent baseline values in HRQoL should be  
290 considered when interpreting the results of clinical studies in MDS that use HRQoL as an endpoint,  
291 as suggested recently.<sup>4, 8</sup>

292

293 **Strengths** of this work are the large number of observations, the well-defined inclusion criteria in a  
294 non-interventional registry, the enclosure of newly diagnosed MDS-patients within 100 days of the  
295 date of the diagnostic bone marrow aspirate, and the parallel analysis of the different parameters  
296 of the validated generic score EQ-5D.<sup>21</sup> Based on the use of a generic questionnaire, comparisons  
297 with reference populations are possible.

298 **Limitations:** Disease-specific scores may more accurately reflect the spectrum in a given disease.  
299 To address this aspect, the MDS-specific score QUALMS has been developed recently.<sup>18, 35</sup>  
300 QUALMS has been integrated in EUMDS in a recently amended version of the protocol. Based on  
301 objectives of this study and the EUMDS-registry, analyses have been restricted to IPSS lower-risk

302 MDS. Therefore, this study does not allow conclusions on MDS in general. However, the recently  
303 introduced new protocol of the registry will register all subtypes of MDS. Other aspects of HRQoL,  
304 which might be relevant for the outcome of patients e.g. the deterioration of HRQoL over time,  
305 have not yet been analysed. These investigations are currently performed in several studies  
306 focusing on the impact of specific interventions on HRQoL.

### 307 **In summary**

308 This is the first study to analyse prospectively the patient reported outcome HRQoL in IPSS lower-  
309 risk MDS at diagnosis, and to compare patients with MDS with age- and sex matched healthy  
310 populations. Patients experience profound age- and sex-dependent restrictions in different  
311 HRQoL-dimensions. Distinct demographic and disease parameters are associated with reduced  
312 HRQoL. These observations should form the basis for individualized treatment directed at relief of  
313 distinct symptoms. In addition, these results may provide a benchmark in the evaluation of new  
314 interventional options aimed at improving HRQoL outcomes.

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316

317 **Supplementary information** is available at Leukemia ([www.nature.com/leu](http://www.nature.com/leu)) providing additional  
318 information regarding (i) EQ-5D index and EVS; (ii) on the comparison of patients with MDS and  
319 the reference population; (iii) on multivariate analysis; and (iiii) on minimally important difference  
320 (MID)

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331

### 332 **Authorship Contributions**

333 Explanation of author contributions: Conception and design: TdW, DB, SL, ASi, RS, JC, PF, UG, MSH,  
334 AG, LM, KM, ASa, GS, EH, CvM; Collection and assembly of data: all co-authors; Data analysis  
335 and/or interpretation: RS, KK, CvM, GY, AS, TDW; Manuscript writing: all co-authors; Final approval  
336 of manuscript: all co-authors

337

### 338 **Disclosure of Conflicts of Interest**

339 Conflict of interest disclosure: This study was carried out within the EUMDS Registry which is  
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**Fig 1: Proportion of moderate/severe problems in male (A) and female (B) patients with MDS (blue bars) as compared to European age- and sex matched standard population (dark grey). Standard errors indicated as lines. Differences ( $\Delta$ ) of patients with MDS to sex-matched reference group shown when significant (\*\*\*)  $p < 0.001$ ; \*\*  $p < 0.01$ ; \*  $p < 0.05$ ; as assessed by Wilcoxon signed rank tests).**

**Fig 2: Proportion of moderate/severe problems by age group (<60 (A), 60-75 (B) or >75 (C) years old) in patients with MDS (blue bars) as compared to European age- and sex matched standard population (dark grey). Standard errors indicated as lines. Differences ( $\Delta$ ) of patients with MDS to sex-matched reference group shown when significant (\*\*\*)  $p < 0.001$ ; \*\*  $p < 0.01$ ; \*  $p < 0.05$ ; as assessed by Wilcoxon signed rank tests).**

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**Table 1. Demographic and clinical characteristics of MDS-patients - entire cohort and EQ-5D respondents**

Characteristic	Total		EQ-5D Completed ♦		EQ-5D Not completed	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Entire Cohort	1 985	100.0	1 690	85.1	295	14.9
Age, years						
<60	214	10.8	187	11.1	27	9.2
60-75	818	41.2	707	41.8	111	37.6
75+	953	48.0	796	47.1	157	53.2
Gender						
Male	1 202	60.6	1 039	61.5	163	55.3
Female	783	39.4	651	38.5	132	44.7
Diagnosis (WHO 2001)						
RA	355	17.9	283	16.7	72	24.4
RARS	310	15.6	276	16.3	34	11.5
RCMD	755	38.0	651	38.5	104	35.3
RCMD-RS	118	5.9	102	6.0	16	5.4
RAEB-1	239	12.0	207	12.2	32	10.8
RAEB-2	9	0.5	8	0.5	1	0.3
MDS-U	81	4.1	68	4.0	13	4.4
5q-Syndrome	118	5.9	95	5.6	23	7.8
IPSS						
Low risk	961	48.4	813	48.1	148	50.3
Intermediate-1	912	45.9	782	46.3	130	43.9
Low/int-1 no cytogenetics*	112	5.6	95	5.6	17	5.7
IPSS-R						
Very low risk	493	24.8	433	25.6	60	20.3
Low risk	746	37.6	646	38.2	100	33.9
Intermediate risk	420	21.2	341	20.2	79	26.8
High/very high risk	121	6.1	110	6.5	11	3.7
Unknown	205	10.3	160	9.5	45	15.3
MDS-CI						
Low risk	1 276	64.3	1 076	63.7	200	67.8
Intermediate risk	606	30.5	525	31.1	81	27.5
High risk	103	5.2	89	5.3	14	4.7
Hemoglobin (g/dL)						
≥10	1 076	54.2	913	54.0	163	55.3
<10	884	44.5	768	45.4	116	39.3
Unknown	25	1.3	9	0.5	16	5.4
Red Blood Cell Transfusion #						
No	1 390	70.0	1 163	68.8	227	76.9
Yes	595	30.0	527	31.2	68	23.1

Abbreviations: WHO, World Health Organization; IPSS International Prognostic Scoring System, IPSS-R, Revised International Prognostic Scoring System; MDS-CI, Myelodysplastic Syndrome-Comorbidity Index; HCT-CI, Hematopoietic Cell Transplant-Comorbidity Index.

◆ Includes EQ-5D completed only, EQ VAS completed only and both completed.

\* Patients with cytogenetics failed or not available were included if the diagnosis of MDS was morphologically proven, with <5% bone marrow blasts and at most a single cytopenia according to the IPSS. Based on these criteria exclusively IPSS low or int-1 patients were included in this cohort.

# as assessed in the year prior to initial diagnosis

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**Table 2. Prevalence of problems in distinct dimensions of EQ-5D, in EQ-5D index and in EQ**

	Mobility Problem*		Self-care Problem*		Usual Activities Problem*		Pain/Discomfort Problem*		Anxiety/Depression Problem*		mean
	%	<i>p</i>	%	<i>p</i>	%	<i>p</i>	%	<i>p</i>	%	<i>p</i>	
	Total	41.0		13.3		36.1		49.5		37.9	
Sex		<b>0.007</b>		<b>0.030</b>		<b>0.021</b>		<b>&lt;0.001</b>		<b>&lt;0.001</b>	
Male	39.1		11.6		33.6		45.5		30.1		0.77
Female	44.0		16.0		40.0		55.9		50.3		0.69
Age Group (years)		<b>&lt;0.001</b>		<b>&lt;0.001</b>		<b>&lt;0.001</b>		<b>&lt;0.001</b>		0.581	
<60	18.5		2.7		26.6		31.5		40.8		0.80
60-75	33.0		8.5		29.1		43.5		35.9		0.78
75+	53.3		20.0		44.5		58.9		39.0		0.69
IPSS		0.083		0.057		0.899		<b>0.005</b>		0.884	
Low risk	42.4		13.2		49.6		53.1		39.2		0.74
Intermediate risk	38.2		13.1		47.7		49.3		36.8		0.75
Low/int-1 no cytogenetics*	51.6		16.1		64.5		44.7		36.6		0.70
IPSS-R		0.656		0.907		0.899		<b>0.023</b>		0.119	
Very low risk	40.6		11.9		32.4		53.1		33.8		0.75
Low risk	40.8		13.0		36.6		49.3		38.9		0.73
Intermediate risk	42.4		14.4		36.5		44.7		42.9		0.73
High/very high risk	40.4		14.7		35.8		52.3		36.7		0.76
Unknown	40.6		15.0		43.1		48.8		35.0		0.74
MDS-CI		<b>&lt;0.001</b>		<b>&lt;0.001</b>		<b>&lt;0.001</b>		<b>&lt;0.001</b>		0.493	
Low risk	33.9		10.1		31.6		44.5		37.3		0.76
Intermediate risk	51.8		18.4		42.8		57.2		38.4		0.70
High risk	63.6		22.7		50.0		64.8		42.0		0.67
Haemoglobin (g/dL)		<b>&lt;0.001</b>		<b>&lt;0.001</b>		<b>&lt;0.001</b>		<b>0.026</b>		<b>0.002</b>	
>=10	34.5		9.2		28.9		46.9		34.3		0.77
<10	49.2		18.3		45.0		53.2		42.4		0.70
Unknown	0.0		0.0		0.0		0.0		22.2		0.95
Red Blood Cell Transfusion #		<b>&lt;0.001</b>		<b>&lt;0.001</b>		<b>&lt;0.001</b>		<b>0.049</b>		0.070	
No	35.9		9.8		30.9		47.5		36.2		0.76
Yes	52.2		21.0		47.4		53.9		41.7		0.69

Abbreviations: IPSS-R, Revised International Prognostic Scoring System; MDS-CI, Myelodysplastic Syndrome-Comorbidity Index; ♦ Problem: moderate or severe  
 \* Patients with cytogenetics failed or not available were included if the diagnosis of MDS was morphologically proven, with <5% bone marrow blasts and at most 1% exclusively IPSS low or int-1 patients were included in EUMDS.

**Table 3. Association of HRQL and demographic and disease characteristics in MDS-patients based on univariate and multivariate analyses**

Variable	EQ-5D Index (n = 1,681 patients)									
	Univariate				Multivariate *				Univariate	
	coef.	95% CI		<i>p</i>	coef.	95% CI	<i>p</i>		coef.	95% CI
Constant	0.74	0.73	0.76	<b>&lt;0.001</b>	0.85	0.81	0.89	<b>&lt;0.001</b>	70.71	67.98
Age Group										
<60										
60-75	-0.03	-0.06	0.01	0.144	-0.02	-0.05	0.02	0.287	-3.12	-6.23
75+	-0.11	-0.14	-0.07	<b>&lt;0.001</b>	-0.08	-0.12	-0.05	<b>&lt;0.001</b>	-10.06	-13.19
Sex										
Male										
Female	-0.07	-0.09	-0.05	<b>&lt;0.001</b>	-0.08	-0.10	-0.06	<b>&lt;0.001</b>	-3.24	-5.17
IPSS-R										
Very low risk										
Low risk	-0.01	-0.04	0.02	0.414	0.03	0.00	0.06	<b>0.045</b>	-2.19	-4.59
Intermediate/high risk	-0.01	-0.04	0.03	0.750	0.04	0.01	0.07	<b>0.022</b>	-2.68	-5.42
Unknown	0.00	-0.04	0.04	0.909	0.02	-0.02	0.07	0.254	-0.01	-3.69
MDS-CI										
Low risk										
Intermediate/high risk	-0.07	-0.09	-0.04	<b>&lt;0.001</b>	-0.06	-0.08	-0.04	<b>&lt;0.001</b>	-7.33	-9.26
Hemoglobin (g/dL)										
>=10										
<10	-0.07	-0.09	-0.04	<b>&lt;0.001</b>	-0.05	-0.08	-0.03	<b>&lt;0.001</b>	-7.12	-8.99
Red Blood Cell Transfusion #										
No										
Yes	-0.07	-0.10	-0.05	<b>&lt;0.001</b>	-0.04	-0.07	-0.02	<b>&lt;0.001</b>	-7.14	-9.14

Abbreviations: IPSS-R, Revised International Prognostic Scoring System; MDS-CI, Myelodysplastic Syndrome-Comorbidity Index. # as assessed in the year prior to initial diagnosis; \* adjusted for all other variables



**Table 4. Comparison of HRQL in MDS-patients and age and sex matched European ref**

	Mobility		Self-care		Usual Activities		Pain/Discomfort		Anxiety/Depression		EQ mean
	Problem*		Problem*		Problem*		Problem*		Problem*		
	%	<i>p</i>	%	<i>p</i>	%	<i>p</i>	%	<i>p</i>	%	<i>p</i>	
Entire Cohort		<b>&lt;0.001</b>		0.438		<b>&lt;0.001</b>		0.919		<b>&lt;0.001</b>	
European Norm	33.5		12.4		26.0		48.8		14.9		0.76
EUMDS	41.0		13.3		36.1		49.5		37.9		0.74
Male		<b>&lt;0.001</b>		0.409		<b>&lt;0.001</b>		0.371		<b>&lt;0.001</b>	
European Norm	29.4		10.7		23.4		43.9		13.7		0.79
EUMDS	39.1		11.6		33.6		45.5		30.1		0.77
Female		0.142		0.820		<b>&lt;0.001</b>		0.355		<b>&lt;0.001</b>	
European Norm	40.0		15.0		30.1		56.8		16.7		0.72
EUMDS	44.0		16.0		40.0		55.9		50.3		0.69
Age Group, <60		0.202		0.288		<b>&lt;0.001</b>		0.645		<b>&lt;0.001</b>	
European Norm	13.6		4.9		11.4		28.3		9.8		0.86
EUMDS	18.5		2.7		26.6		31.5		40.8		0.80
Age Group, 60-75		<b>0.002</b>		0.179		<b>&lt;0.001</b>		0.606		<b>&lt;0.001</b>	
European Norm	25.4		6.7		20.0		44.5		14.9		0.79
EUMDS	33.0		8.5		29.1		43.5		35.9		0.78
Age Group, 75+		<b>&lt;0.001</b>		0.711		<b>&lt;0.001</b>		0.671		<b>&lt;0.001</b>	
European Norm	45.2		19.1		34.6		57.4		16.0		0.71
EUMDS	53.3		20.0		44.5		58.9		39.0		0.69

◆ Problem: moderate or severe problems

Figure 1

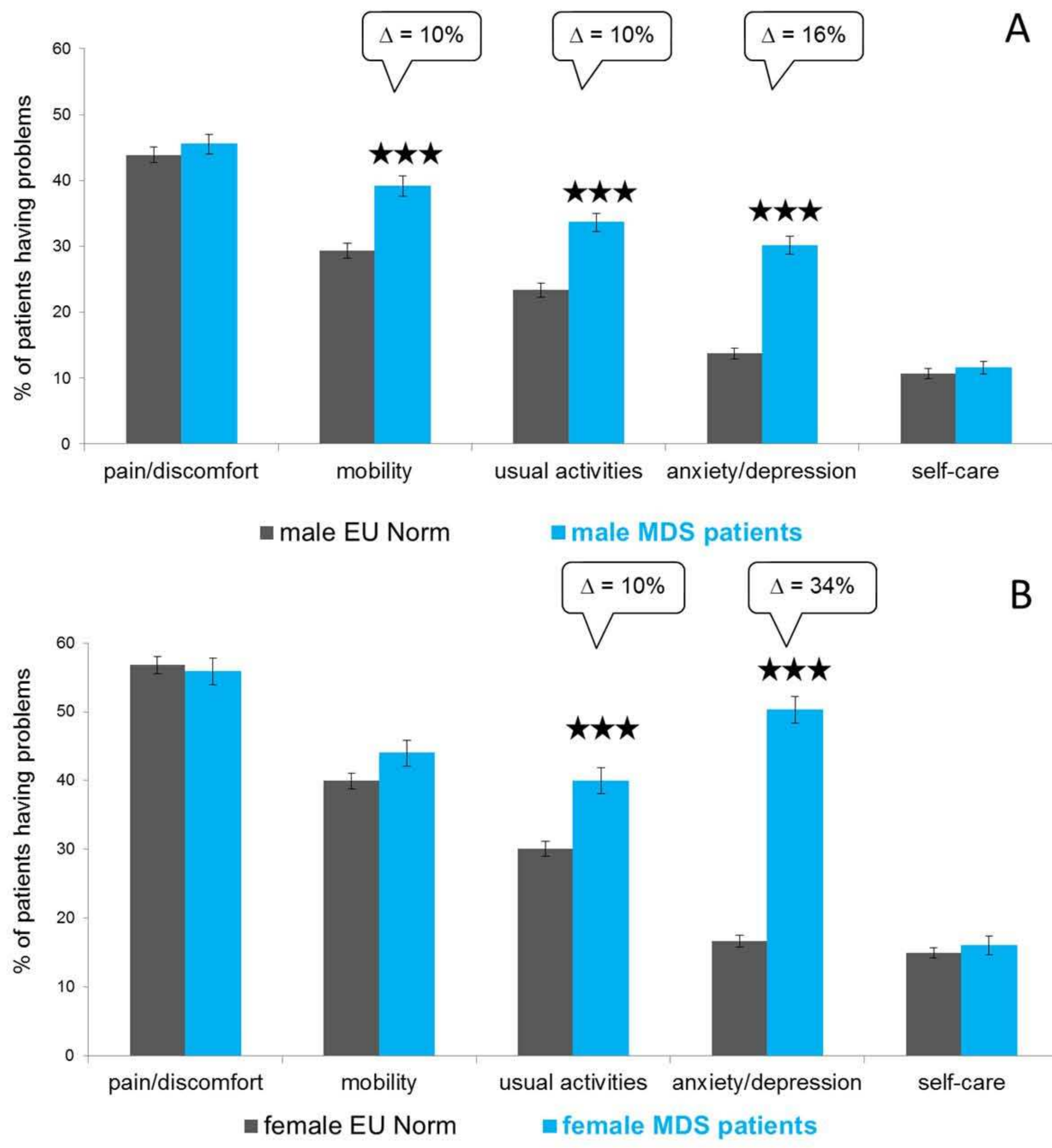


Figure 2

