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Prevalence, severity and correlates of fatigue in newly diagnosed patients with myelodysplastic syndromes

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Summary

The primary objective of this study was to investigate factors associated with fatigue severity in newly diagnosed patients with higher-risk myelodysplastic syndromes (MDS). The secondary objectives were to assess symptom prevalence and to examine the relationships between fatigue, quality of life (QoL) and overall symptom burden in these patients. The analyses were conducted in 280 higher-risk MDS patients. Pre-treatment patient-reported fatigue was evaluated with the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale and QoL was assessed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). Female gender ($P = 0{\cdot}018$), poor performance status (i.e., ECOG of 2–4) ($P < 0{\cdot}001$) and lower levels of haemoglobin (Hb) ($P = 0{\cdot}026$) were independently associated with higher fatigue severity. The three most prevalent symptoms were as follows: fatigue (92%), dyspnoea (63%) and pain (55%). Patients with higher levels of fatigue also had greater overall symptom burdens. The mean global QoL scores of patients with the highest versus those with the lowest levels of fatigue were 29·2 [standard deviation (SD), 18·3] and 69·0 (SD, 18·8), respectively and this difference was four times the magnitude of a clinically meaningful difference. Patient-reported fatigue severity revealed the effects of disease burden on overall QoL more accurately than did degree of anaemia. Special attention should be given to the female patients in the management of fatigue.

Keywords: myelodysplastic syndromes, fatigue, anaemia, quality of life, haemoglobin.

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The myelodysplastic syndromes (MDS) are clonal disorders of haematopoietic stem cells that are characterized by ineffective haematopoiesis that results in blood cytopenias and a high risk of progression to acute myeloid leukaemia (AML). The prognosis of MDS is typically evaluated with the International Prognostic Scoring System (IPSS) that distinguishes between four subgroups of patients; i.e., low, intermediate-1, intermediate-2 and high-risk patients (Greenberg *et al*, 1997). Intermediate-2 and high-IPSS risk patients (i.e., higher risk patients) have poor prognoses (Greenberg *et al*, 1997).

In 2000, quality of life (QoL) was included in the International Working Group Standard Response Criteria for the evaluation of MDS therapies (Cheson *et al*, 2000). However, despite the long-standing general consensus regarding the importance of QoL in this patient population (Greenberg *et al*, 2011; Malcovati *et al*, 2013), empirically based information remains scarce (Caocci *et al*, 2009; Thomas *et al*, 2012).

While anaemia is the most common objective manifestation of the disease at the time of diagnosis (Greenberg *et al*, 2009), the extent to which subjective fatigue can be explained by haemoglobin (Hb) levels is not well understood (Jansen *et al*, 2003; Steensma *et al*, 2008). Patient self-reports are the gold standard for the assessment of fatigue severity (National Comprehensive Cancer Network, 2012) but very few studies of MDS patients have used patient-reported outcome measures (Jansen *et al*, 2003). Fatigue severity has important clinical implications in cancer patients as it might substantially impair the patient's QoL and daily functioning and might correlate with other symptoms (Stone *et al*, 2000; Wang *et al*, 2002; National Comprehensive Cancer Network, 2012; Efficace *et al*, 2013). Preliminary evidence in MDS has also revealed that greater pretreatment fatigue is associated with a shorter survival time (Deschler *et al*, 2013). However, in addition to fatigue, newly diagnosed MDS patients might suffer from a wide range of other cancer symptoms, but data on the prevalence of such symptoms is lacking.

The early identification of patients who might experience greater fatigue and a better understanding of the identities of the most predominant symptoms prior to the initiation of active therapy can be critical for informing the development of more personalized treatment approaches.

Based on previous literature (Stone *et al*, 2000; Wang *et al*, 2002; Miaskowski, 2004; National Comprehensive Cancer Network, 2012; Bejar, 2013), a core set of disease and patient-related factors were selected to examine the associations of these factors with pretreatment fatigue.

The primary objective of this study was to investigate the factors associated with fatigue severity in newly diagnosed patients with higher-risk MDS. The secondary objectives were to assess the prevalence of other cancer-specific symptoms and to examine the relationships between fatigue, QoL and overall symptom burden.

Patients and methods

Study design and population

This was an international prospective cohort observational study that consecutively enrolled patients from 37 centres in nine countries. The patients were eligible if they had been diagnosed with MDS and had an IPSS risk level of intermediate-2 or high-risk within 6 months before the date of registration. The patients were classified according to the World Health Organization (WHO) classification (Vardiman *et al*, 2002). Exclusion criteria included the following: having received any type of therapy [other than red blood cell (RBC) or platelet transfusions] and the presence of any type of psychiatric disorder or major cognitive dysfunction that would hamper a self-reported evaluation. Additional details have been reported previously (Efficace *et al*, 2014).

The study was approved by the ethical committee of each participating centre and all patients provided written informed consent.

Patient-reported outcome assessment

The patients were invited to participate by their treating physician in the hospital, and all patients completed questionnaires prior to treatment initiation for higher-risk MDS.

Fatigue was evaluated with the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale (Yellen *et al*, 1997). The FACIT-Fatigue scale is a 13-item questionnaire that assesses self-reported tiredness, weakness and difficulty conducting typical activities due to fatigue. This scale ranges from 0 to 52, and higher scores indicate lower levels of fatigue. This scale has undergone a rigorous validation process that revealed excellent psychometric properties (Yellen *et al*, 1997). This scale has also been used in several studies of patients with haematological malignancies, which demonstrated that the sensitivity of this measure discriminated these patients from the general population and other cancer patients with different grades of anaemia (Cella *et al*, 2002a). The mean time between the fatigue assessment and haemoglobin (Hb) evaluation was 5 d (25th and 75th percentiles, 0 and 6 d, respectively). The QoL was assessed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). This is a well validated questionnaire that consists of 30 items, including five functional scales (physical, role, emotional, social and cognitive), three symptoms (fatigue, nausea and vomiting and pain), a global health status/QoL scale and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties) (Aaronson *et al*, 1993). The standardized scores for this questionnaire range from 0 to 100, and higher scores indicate greater levels of functioning or more severe symptoms.

Selection and definition of variables examined for their associations with pre-treatment fatigue severity

The selection of disease-related variables was based on the key factors that have been previously included in MDS prognostic indices in the literature (Bejar, 2013). The following variables were examined: Hb level, serum lactate dehydrogenase (LDH), absolute neutrophil count (ANC), bone marrow blasts, karyotype (based on IPSS classification) (Greenberg *et al*, 1997), white blood cell count (WBC), platelet count and transfusion dependency (i.e., defined by the receipt of at least one RBC transfusion every 8 weeks over a period of 4 months) (Malcovati *et al*, 2007). Moreover, whether the patients had evolved from a lower IPSS risk group category was also considered.

The patient-related variables that were investigated in terms of their possible relationships with fatigue severity were also selected based on previous literature (Miaskowski, 2004; Wang *et al*, 2010; National Comprehensive Cancer Network, 2012) and clinical relevance. The following factors were considered: age at study entry, gender, living arrangements (living alone *versus* living with others) and education level (low *versus* intermediate/high). The Eastern Cooperative Oncology Group (ECOG) good performance status (0–1) *versus* poor status (2–4) and comorbidity, as assessed with the Haematopoietic Cell Transplantation (HCT)-specific comorbidity index, were also investigated (Sorror *et al*, 2005). The potential impact of comorbidity was also explored using the MDS-specific comorbidity index (Della Porta *et al*, 2011).

Statistical analyses

Multivariate linear regression (MLR) analysis was used to identify the factors associated with fatigue. The first model explored the relationship between fatigue and disease-related variables and the second model explored the relationship between fatigue and patient-related variables. In each model, univariate regression analyses were performed to select candidates for the stepwise selection procedure that was used to identify the MLR model after examining the variables for possible multi-colinearity using the variance inflation factor. The variables included in the disease- and patient-related MLR models were used to run the same stepwise procedure to select a final overall model. Sensitivity analysis was performed by a bootstrap resampling procedure to investigate the replication stability of the final overall model and the importance of each single variable that was included in the model (Sauerbrei, 1999). The same stepwise selection procedure was performed in a MLR model for each of 5000 bootstrap-generated samples using the initial set of variables after examining them for multi-colinearity. Symptoms were assessed with the EORTC QLQ-C30 and classified as 'not at all', 'mild' and 'moderate to severe' based on previous work (Johnsen *et al*, 2009), and the proportions of these classifications were reported. The patients were divided into four

subgroups that were defined as having low, low-medium, medium-high and high levels of fatigue based on the FACIT-Fatigue scores quartiles, and the symptom proportions were summarized according to fatigue levels. The patients' self-reported overall health status/QoL (EORTC QLQ-C30) were summarized according to both fatigue and Hb levels, which were also defined as low, low-medium, medium-high and high based on the quartiles of the Hb distribution. All analyses were performed with SAS Version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Overall, 280 patients with a median age of 71 years (range: 32–89 years) were consecutively enrolled and included in the analysis. The patient participation compliance per centre was 91% and 31 patients overall refused to participate. There were 176 men (63%) and 104 (37%) women and the mean Hb level was 93 g/l (range 41–158). Fifty-six patients (20%) were transfusion-dependent at the time of enrolment. There were no statistically significant differences with regard to gender, Hb level or IPSS risk categories at study entry between the patients (n = 68, 24%) who evolved from lower IPSS risk categories (i.e., low or intermediate-1) and those who did not. For example, the mean Hb levels at the time of study entry were 95 g/l (range, 44–142; g/l) and 93 g/l (range, 41–158) for the patients who evolved from a lower risk and those who did not, respectively (P = 0·993). Further details of the study sample are provided in Table I.

Table I. Socio-demographic and clinical characteristics of the MDS study population.

Variable	Total (N = 280)
Age (years)	
Mean (SD)	70·02 (10·51)
Median	71·25
Range	31·67–88·58
Gender, n (%)	
Male	176 (62·86)
Female	104 (37·14)
Education level, n (%)	
Intermediate/High (high school and university degree)	168 (60·22)
Low (compulsory school)	111 (39·78)
Living arrangements, n (%)	
Living alone	38 (13·62)
Living with spouse/partner only	191 (68·46)
Living with a child, child-in-law or grandchild	39 (13·97)
Living with another relative (other than a spouse/partner or child/grandchild)	8 (2·87)
Living with unrelated people only, apart from the person's spouse/partner	3 (1·08)
ECOG performance status, n (%)	
0–1	221 (78·93)
2–4	59 (21·07)
HCT comorbidity index	
Mean (SD)	1·46 (2·63)
Median	0
Range	0·00–29·00
IPSS risk score	
Intermediate 2	206 (73·57)
High risk	74 (26·43)
Karyotype (IPSS classification)	
Poor	102 (36·43)
Intermediate	60 (21·43)
Good	118 (42·14)
Haemoglobin level (g/l)	
Mean (SD)	93·2 (18·2)
Median	90·5
Range	41·0–158
Previous MDS, n (%)*	
No	212 (75·71)
Yes	68 (24·3)

MDS, myelodysplastic syndrome; ECOG, Eastern Cooperative Oncology Group; HCT, Haematopoietic Cell Transplantation; IPSS, International Prognostic Scoring System; SD, standard deviation.
*Patients that evolved from a lower IPSS risk category.

Disease- and patient-related factors associated with fatigue severity

Out of all of the candidate disease-related variables considered in the univariate analyses, only a higher degree of anaemia (P < 0·001) was associated with greater fatigue in the multivariate analysis (Table II).

In the model that considered only the patient-related factors, female gender (P = 0·005), having a low level of education (P = 0·038) and poor ECOG performance status (P < 0·001) were retained as independent factors that were associated with a greater fatigue in the multivariate analysis (Table II). The mean scores on the FACIT-fatigue scale were 30·6 [standard deviation (SD) 13·1] and 34·9 (SD, 11·3) for the women and men, respectively which corresponded to a clinically meaningful difference (i.e., this difference exceeded the 3-point threshold) (Cella *et al*, 2002b).

Final multivariate model predicting fatigue severity

Poor performance status (P < 0·001), female gender (P = 0·018) and lower Hb levels (P = 0·026) were independently associated with greater fatigue severity (Table III). An additional analysis based on the 5000 bootstrap-generated simulation datasets confirmed that these factors were the top three most included with respective inclusion percentages of 100%, 79·5% and 63·6% (Table III). It should be noted that the inclusion frequency provides an indication of the importance of the inclusion of single variables as independent factors in the final model. This model was also the top ranking model of the 5000 simulated multivariate models, which provides supportive evidence for the results obtained from the standard regression analyses.

Table II. Linear regression analyses of fatigue, based on disease and patient-related factors.

	Univariate analysis		Multivariate analysis	
Variables	β (95%, CI)	*P* value	β (95%, CI)	*P* value
Disease-related model				
Haemoglobin (g/l)	0·136 (0·059; 0·213)	<0·001	0·136 (0·059; 0·213)	<0·001
Bone marrow blasts (%)	0·157 (−0·160; 0·475)	0·331	NA	NA
White blood cells ($\times 10^9$/l)	−0·218 (−0·461; 0·025)	0·079	NA	NA
Platelet count ($\times 10^9$/l)	0·009 (−0·006; 0·024)	0·257	NA	NA
Absolute neutrophil count ($\times 10^9$/l)*	−0·341 (−0·753; 0·071)	0·105	NA	NA
Poor karyotype	−1·554 (−4·523; 1·416)	0·304	NA	NA
Serum lactate dehydrogenase (u/l)	0·015 (−0·481; 0·511)	0·953	NA	NA
Evolving from lower IPSS risk group	−1·398 (−4·732; 1·937)	0·410	NA	NA
Transfusion dependency†	−4·154 (−7·699; −0·608)	0·022	NA	NA
Patient-related model				
Age (years)	−0·033 (−0·169; 0·103)	0·634	NA	NA
Female gender	−4·277 (−7·197; −1·357)	0·004	−3·868 (−6·566; −1·170)	0·005
Low education level	−4·039 (−6·920; −1·157)	0·006	−2·851 (−5·541; −0·161)	0·038
Living alone	−0·118 (−4·306; 4·071)	0·956	NA	NA
HCT comorbidity index‡	−0·394 (−0·936; 0·149)	0·154	NA	NA
ECOG ≥2	−11·141 (−14·396; −7·886)	<0·001	−10·388 (−13·619; −7·157)	<0·001

CI, Confidence Interval; NA, Not Applicable; ECOG, Eastern Cooperative Oncology Group; HCT, Haematopoietic Cell Transplantation.
According to the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale, the higher the score the lower is the reported level of fatigue.
*Neutrophils were not included in any stepwise selection procedure because of high colinearity with white blood cells;
†Defined as having received at least one red blood cell (RBC) transfusion every 8 weeks over a period of 4 months.
‡Impact of comorbidity was also explored with the myelodysplastic syndrome Comorbidity Index and was not statistically significant in univariate analysis.

Table III. Final multivariate model of factors associated with fatigue severity.

	Multivariate analysis		Bootstrap analysis
Variables	β (95%, CI)	*P* value	Inclusion frequency (%)*
Haemoglobin (g/l)	0·0832 (0·001; 0·157)	0·026	63·6
Female gender	−3·295 (−6·016; −0·575)	0·018	79·5
ECOG ≥2	−10·147 (−13·410; −6·884)	<0·001	100

CI, Confidence Interval; ECOG, Eastern Cooperative Oncology Group.
According to the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale, the higher the score the lower is the reported level of fatigue.
*This percentage refers to the number of times a single variable was selected as an independent factor in multivariate analysis out of the 5000 bootstrap-generated samples.

We also investigated the possible differential effects of Hb levels on fatigue in the men and women and included an interaction term in the final multivariate regression model; however, this term was not statistically significant ($P = 0·505$). Additional analyses of the relationships between gender and Hb levels revealed that, given the same levels of Hb, the women reported higher average levels of fatigue (data not shown).

Pre-treatment symptom prevalence

Fatigue was by far the most prevalent symptom; 92% of the patients reported fatigue at any level of concern. The two other most prevalent symptoms were dyspnoea (63%) and pain (55%). At least one-fifth of the patients also reported moderate to severe fatigue, dyspnoea, appetite loss and insomnia (Fig 1).

Fatigue and its relationship to the other symptoms

A greater overall symptom burden was found among the patients who reported higher levels of fatigue. For example, among the patients who reported high levels of fatigue, 54% and 53% also reported moderate to severe appetite loss and dyspnoea, respectively while among the group who reported low levels of fatigue, only 1% and 3% reported moderate to

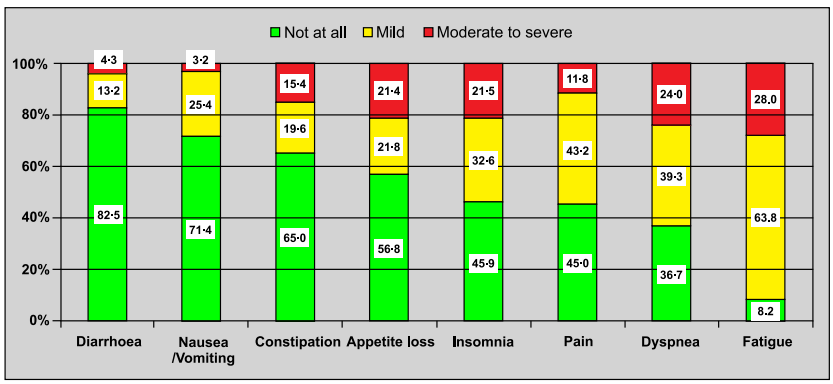

Fig 1. Pre-treatment Symptom Prevalence. Each symptom scale of the EORTC QLQ-C30 has been scored on a (0–100) range (where a higher score means a worse outcome) and then rated as 'Not at all' (if score = 0), 'Mild' (if score >0 and <66) and 'Moderate to severe' (if score ≥66).

severe appetite loss and dyspnoea, respectively. This pattern was consistent across all symptoms investigated, although the percentages varied (Fig 2).

Accuracy of haemoglobin levels and fatigue severity in explaining quality of life impairments

Figure 3 depicts the mean scores on the global QoL scale of the EORTC QLQ-C30 by quartiles of Hb and FACIT-Fatigue scores. The mean QoL scores of the patients with the lowest (i.e., <81 g/l) versus those with the highest levels of Hb (i.e., ≥101 g/l) were 46·6 (SD, 21·6) and 60·5 (SD, 20·3) respectively (Δ = 13·9 points) and this difference was clinically meaningful (i.e., at least 10 points) (Osoba *et al*, 1998). However, the mean QoL scores of the patients with the highest versus the lowest levels of fatigue were 29·2 (SD, 18·3) and 69·0 (SD, 18·8), respectively (Δ = 39·8 points). This latter difference was markedly larger than that found for the Hb levels and was four times the magnitude of a clinically meaningful difference. Additional analyses revealed a stronger correlation (Spearman's coefficient) between fatigue and QoL (r_s = 0·670) than between Hb levels and QoL (r_s = 0·220). Moreover, the strength of the correlations between Hb levels and all of the functional scales of the EORTC QLQ-C30 (i.e., social, emotional, cognitive, role and physical functioning) were weaker than those found between the functional scales and fatigue (data not shown).

Discussion

The main finding of this study was the identification of gender differences in newly diagnosed higher-risk MDS patients, with women reporting greater fatigue severity than men.

This novel data from this population might have important clinical implications as they suggest that, at the time of diagnosis, physicians should pay special attention to female patients regarding the management of fatigue. In our study, the female patients also reported worse outcomes on all scales of the EORTC QLQ-C30 (data not shown). Worse baseline fatigue and QoLs in female patients should be considered when interpreting the results of MDS studies that use the QoL as an endpoint. Our findings might be supported by recent preliminary data from lower-risk MDS patients, which revealed that female patients reported significantly more pain/discomfort and anxiety/depression than males (Stauder *et al*, 2010). In a pooled analysis of a large cohort of cancer patients with various diagnoses, Wang *et al* (2010) found that women reported significantly more severe fatigue than men. Higher levels of fatigue in women have also been reported in patients with various haematological malignancies that are treated with targeted therapies or those who have received allogeneic bone marrow transplantation (Heinonen *et al*, 2001; Efficace *et al*, 2011). The gender difference in symptom reporting in our MDS population might have several psychosocial explanations (van Wijk & Kolk, 1997) that remain to be clarified in future studies.

The degree of anaemia was found to be an important factor in our analysis, but this factor *per se* could not fully explain the subjective perception of fatigue. An internet-based survey found no relationship between Hb and fatigue in MDS patients (Steensma *et al*, 2008). However, because 66% of the patients had undergone treatments beyond transfusions at the time of this survey, it is difficult to compare these findings with our own. Conversely, in a smaller study of 50 patients, Jansen *et al* (2003) found a significant correlation between fatigue and Hb level.

Another finding was that Hb levels provided little insight into the overall burden of the disease from the patients' perspectives. The difference between the patients with highest versus those with lowest levels of fatigue on the global QoL EORTC QLQ-C30 scale was four times the magnitude of a clinically meaningful difference. Conversely, changes in Hb values were not associated with such large variation in global QoL scores (Fig 3). This finding might have important implications because Hb level at disease onset is an important factor on which treatment decisions can be made. Our data indicate that patient-reported fatigue severity, rather than the degree of anaemia, more accurately revealed the effects of disease burden on the patients' wellbeing and daily functioning. This finding empirically substantiates the recent European LeukaemiaNet recommendation (Malcovati *et al*, 2013) that patient-reported outcome assessment be included in the standard diagnostic work-ups of individual MDS patients.

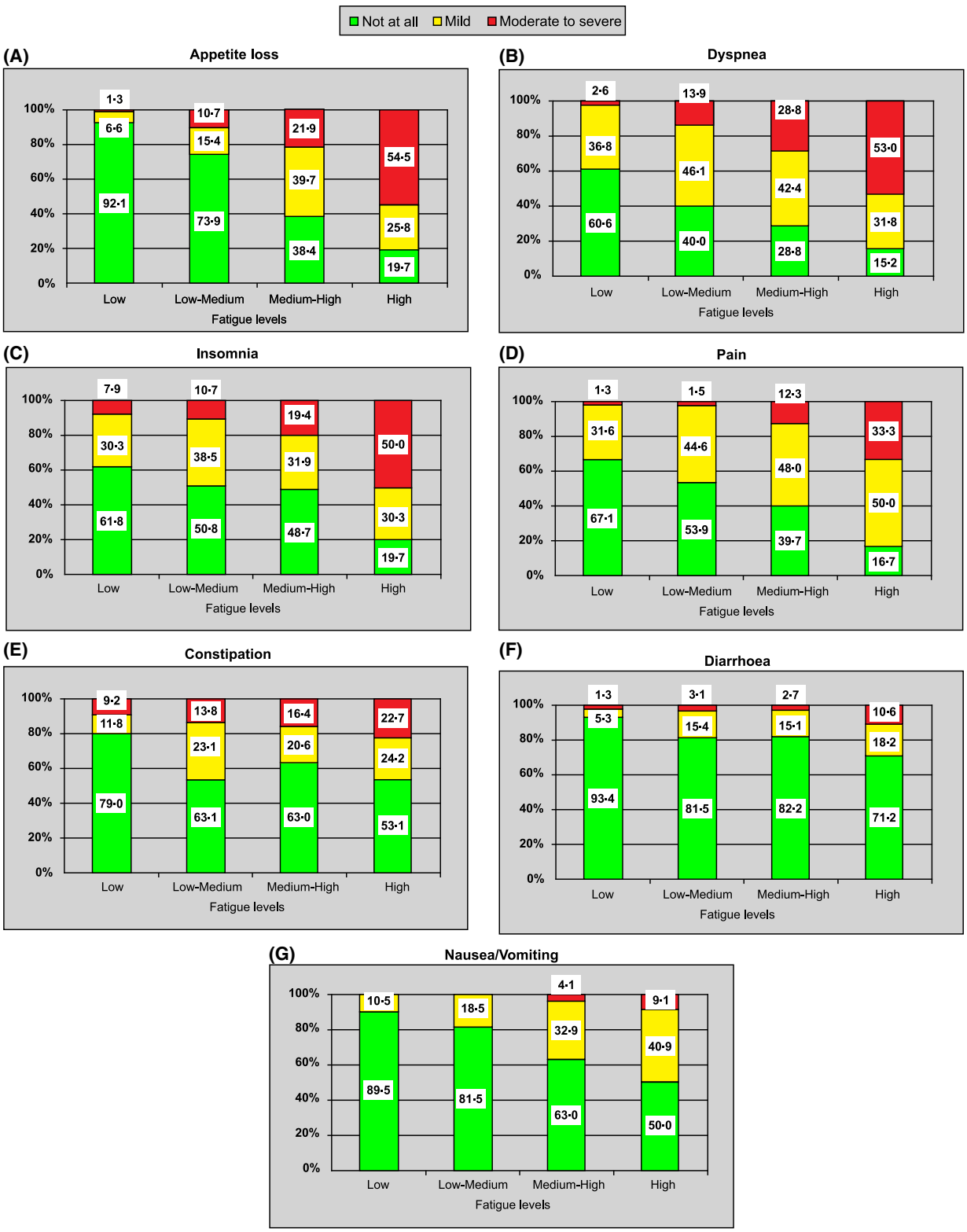

Fig 2. Prevalence of patient-reported symptoms by fatigue severity. This figure reports the prevalence of symptom burden by levels of fatigue. Each symptom scale of the EORTC QLQ-C30 has been scored on a (0–100) range (where a higher score means a worse outcome). In order to summarize the severity of symptom burden, each scale was then rated as 'Not at all' (if score = 0), 'Mild' (if score >0 and <66) and 'Moderate to severe' (if score ≥66). Low, low-medium, medium-high and high fatigue correspond respectively to the 4th (75th to 100th percentile), 3rd, 2nd and 1st (0th to 25th percentile) quartile of FACIT-Fatigue scale. On this scale, the higher the score the lower is the reported level of fatigue.

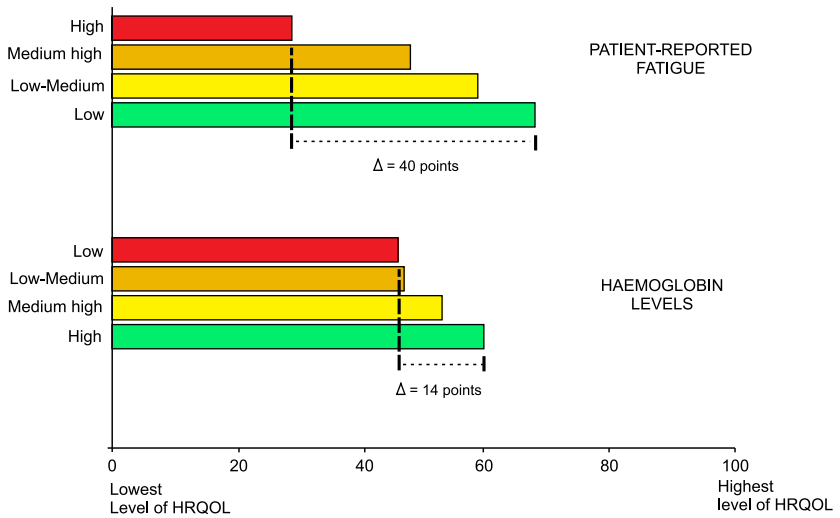

Fig 3. Quality of Life Mean Scores of the EORTC QLQ-C30 by levels of Fatigue and Haemoglobin. The upper panel reports mean scores of the global health status/quality of life (QoL) scale of the EORTC QLQ-C30 by levels of fatigue, defined by quartiles of the FACIT Fatigue scale distribution. This scale ranges from 0 to 52, with higher scores indicating lower levels of fatigue. 'Low' fatigue corresponds to 4th quartile, score range (43–52) points, 'low-medium' to 3rd quartile, score range (36–42) points, 'medium-high' to 2nd quartile, score range (25–35) points and 'high' fatigue to 1st quartile score range (2–24) points. The lower panel reports mean scores of the global health status/QoL scale of the EORTC QLQ-C30 by levels of haemoglobin (Hb) values (g/l), defined by quartiles of Hb distribution. 'Low' level of Hb corresponds to 1st quartile, range (41·0–80·9) g/l, 'low-medium' to 2nd quartile, range (81·0–90·4) g/l, 'medium-high' to 3rd quartile, range (90·5–100·4) g/l, and 'high' to 4th quartile, range (100·5–158·0) g/l. HRQOL, health-related quality of life.

Analysis of symptom prevalence revealed that these patients reported a wide range of symptoms at the time of disease onset; more than half of the patients not only reported fatigue but also reported dyspnoea, pain and insomnia (Fig 1). These symptoms have rarely been documented in clinical research of patients with MDS, and the early recognition of these symptoms might help physicians to improve symptom management. It is important that future studies focus on improved understanding of the factors underlying these symptoms. For example, studies investigating the origin of pain and the factors associated with pain severity might help to further improve symptom management in this high-risk MDS population.

A related finding was the relationship between fatigue and overall symptom burden. Greater levels of fatigue were associated with greater symptom severity, particularly appetite loss, dyspnoea, insomnia and pain (Fig 2). The associations of fatigue severity with pain and dyspnoea have been reported in patients with solid tumours that include breast, colorectal, lung, ovarian and prostate cancers (Stone *et al*, 2000; Holzner *et al*, 2002). Our data revealed that fatigue was not the only burdensome symptom at the time of diagnosis and support the need for studies examining whether reductions in overall symptom burden can contribute to reducing the severity of fatigue.

The present study has limitations. As the analyses were cross-sectional, we were unable to investigate the persistence of fatigue over time or to examine its relationships with various treatments. We plan to report this additional data in our prospective cohort study after all follow-up data are acquired. Moreover, although we analysed a comprehensive set of key clinical, laboratory and patient-related factors, some other laboratory variables, such as serum albumin, creatinine and bilirubin were not considered.

Our study also has key strengths. As recommended by international guidelines (National Comprehensive Cancer Network, 2012), fatigue was reported by the patients themselves using a well-validated questionnaire. Moreover, 80% of the patients underwent a blood test within 1 week of completion of the fatigue assessments, which increases the confidence in the generalizability of the findings. Finally, our study was conducted in a large inception cohort of patients who were accrued from many centres, and the results were supported by state of the art sensitivity analysis.

In conclusion, the routine assessment of pre-treatment patient-reported fatigue is recommended to better understand the effects of disease burden on patients' QoL. The current data could also lay the groundwork for the development and testing of gender-specific interventions in order to more effectively address fatigue in higher-risk MDS patients.

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Authors' contributions

Conception and design: FE, FM. Collection and assembly of data: FE, GG, MB, MC, FC, GC, DB, ML, EA, RS, DS, UP, GrS, AJ, FB, GS, GAP, PN, CW, SF, VK, KN. Statistical analysis: FC, FE. Manuscript writing: FE, FC, FM. Final approval of manuscript: FE, GG, MB, MC, FC, GC, DB, ML, EA, RS, DS, UP, GrS, AJ, FB, GS, GAP, PN, CW, SF, VK, KN, FM.

Conflict of interest

The authors have declared no conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. List of participating centers.

References

Aaronson, N.K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N.J., Filiberti, A., Flechtner, H., Fleishman, S.B., de Haes, J.C.J.M., Kaasa, S., Klee, M.C., Osoba, D., Razavi, D., Rofe, P.B., Schraub, S., Sneeuw, K.C.A., Sullivan, M. & Takeda, F. (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute*, **85**, 365–376.

Bejar, R. (2013) Prognostic models in myelodysplastic syndromes. *Hematology/the Education Program of the American Society of Hematology*, **2013**, 504–510.

Caocci, G., La Nasa, G. & Efficace, F. (2009) Health-related quality of life and symptom assessment in patients with myelodysplastic syndromes. *Expert Review of Hematology*, **2**, 69–80.

Cella, D., Lai, J.S., Chang, C.H., Peterman, A. & Slavin, M. (2002a) Fatigue in cancer patients compared with fatigue in the general United States population. *Cancer*, **94**, 528–538.

Cella, D., Eton, D.T., Lai, J.S., Peterman, A.H. & Merkel, D.E. (2002b) Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. *Journal of Pain and Symptom Management*, **24**, 547–561.

Cheson, B.D., Bennett, J.M., Kantarjian, H., Pinto, A., Schiffer, C.A., Nimer, S.D., Lowenberg, B., Beran, M., de Witte, T.M., Stone, R.M., Mittelman, M., Sanz, G.F., Wijermans, P.W., Gore, S. & Greenberg, P.L. (2000) Report of an international working group to standardize response criteria for myelodysplastic syndromes. *Blood*, **96**, 3671–3674.

Della Porta, M.G., Malcovati, L., Strupp, C., Ambaglio, I., Kuendgen, A., Zipperer, E., Travaglino, E., Invernizzi, R., Pascutto, C., Lazzarino, M., Germing, U. & Cazzola, M. (2011) Risk stratification based on both disease status and extra-hematologic comorbidities in patients with myelodysplastic syndrome. *Haematologica*, **96**, 441–449.

Deschler, B., Ihorst, G., Platzbecker, U., Germing, U., Marz, E., de Figuerido, M., Fritzsche, K., Haas, P., Salih, H.R., Giagounidis, A., Selleslag, D., Labar, B., de Witte, T., Wijermans, P. & Lubbert, M. (2013) Parameters detected by geriatric and quality of life assessment in 195 older patients with myelodysplastic syndromes and acute myeloid leukemia are highly predictive for outcome. *Haematologica*, **98**, 208–216.

Efficace, F., Baccarani, M., Breccia, M., Alimena, G., Rosti, G., Cottone, F., Deliliers, G.L., Barate, C., Rossi, A.R., Fioritoni, G., Luciano, L., Turri, D., Martino, B., Di Raimondo, F., Dabusti, M., Bergamaschi, M., Leoni, P., Simula, M.P., Levato, L., Ulisciani, S., Veneri, D., Sica, S., Rambaldi, A., Vignetti, M. & Mandelli, F. (2011) Health-related quality of life in chronic myeloid leukemia patients receiving long-term therapy with imatinib compared with the general population. *Blood*, **118**, 4554–4560.

Efficace, F., Baccarani, M., Breccia, M., Cottone, F., Alimena, G., Deliliers, G.L., Barate, C., Specchia, G., Di Lorenzo, R., Luciano, L., Turri, D., Martino, B., Stagno, F., Dabusti, M., Bergamaschi, M., Leoni, P., Simula, M.P., Levato, L., Fava, C., Veneri, D., Sica, S., Rambaldi, A., Rosti, G., Vignetti, M. & Mandelli, F. (2013) Chronic fatigue is the most important factor limiting health-related quality of life of chronic myeloid leukemia patients treated with imatinib. *Leukemia*, **27**, 1511–1519.

Efficace, F., Gaidano, G., Sprangers, M., Cottone, F., Breccia, M., Voso, M.T., Caocci, G., Stauder, R., Di Tucci, A.A., Sanpaolo, G., Selleslag, D., Angelucci, E., Platzbecker, U. & Mandelli, F. (2014) Preference for involvement in treatment decisions and request for prognostic information in newly diagnosed patients with higher-risk myelodysplastic syndromes. *Annals of Oncology*, **25**, 447–454.

Greenberg, P., Cox, C., LeBeau, M.M., Fenaux, P., Morel, P., Sanz, G., Sanz, M., Vallespi, T., Hamblin, T., Oscier, D., Ohyashiki, K., Toyama, K., Aul, C., Mufti, G. & Bennett, J. (1997) International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood*, **89**, 2079–2088.

Greenberg, P.L., Rigsby, C.K., Stone, R.M., Deeg, H.J., Gore, S.D., Millenson, M.M., Nimer, S.D., O'Donnell, M.R., Shami, P.J. & Kumar, R. (2009) NCCN Task Force: transfusion and iron overload in patients with myelodysplastic syndromes. *Journal of the National Comprehensive Cancer Network*, **7**(Suppl. 9), S1–S16.

Greenberg, P.L., Attar, E., Bennett, J.M., Bloomfield, C.D., De Castro, C.M., Deeg, H.J., Foran, J.M., Gaensler, K., Garcia-Manero, G., Gore, S.D., Head, D., Komrokji, R., Maness, L.J., Millenson, M., Nimer, S.D., O'Donnell, M.R., Schroeder, M.A., Shami, P.J., Stone, R.M., Thompson, J.E. & Westervelt, P. (2011) NCCN Clinical Practice Guidelines in Oncology: myelodysplastic syndromes. *Journal of the National Comprehensive Cancer Network*, **9**, 30–56.

Heinonen, H., Volin, L., Uutela, A., Zevon, M., Barrick, C. & Ruutu, T. (2001) Gender-associated differences in the quality of life after allogeneic BMT. *Bone Marrow Transplantation*, **28**, 503–509.

Holzner, B., Kemmler, G., Greil, R., Kopp, M., Zeimet, A., Raderer, M., Hejna, M., Zochbauer, S., Krajnik, G., Huber, H., Fleischhacker, W.W. & Sperner-Unterweger, B. (2002) The impact of hemoglobin levels on fatigue and quality of life in cancer patients. *Annals of Oncology*, **13**, 965–973.

Jansen, A.J., Essink-Bot, M.L., Beckers, E.A., Hop, W.C., Schipperus, M.R. & Van Rhenen, D.J. (2003) Quality of life measurement in patients with transfusion-dependent myelodysplastic syndromes. *British Journal of Haematology*, **121**, 270–274.

Johnsen, A.T., Tholstrup, D., Petersen, M.A., Pedersen, L. & Groenvold, M. (2009) Health related quality of life in a nationally representative sample of haematological patients. *European Journal of Haematology*, **83**, 139–148.

Malcovati, L., Germing, U., Kuendgen, A., Della Porta, M.G., Pascutto, C., Invernizzi, R., Giagounidis, A., Hildebrandt, B., Bernasconi, P., Knipp, S., Strupp, C., Lazzarino, M., Aul, C. & Cazzola, M. (2007) Time-dependent prognostic scoring system for predicting survival and leuke-

mic evolution in myelodysplastic syndromes. *Journal of Clinical Oncology*, **25**, 3503–3510.

Malcovati, L., Hellstrom-Lindberg, E., Bowen, D., Ades, L., Cermak, J., Del Canizo, C., Della Porta, M.G., Fenaux, P., Gattermann, N., Germing, U., Jansen, J.H., Mittelman, M., Mufti, G., Platzbecker, U., Sanz, G.F., Selleslag, D., Skov-Holm, M., Stauder, R., Symeonidis, A., van de Loosdrecht, A.A., de Witte, T. & Cazzola, M. (2013) Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. *Blood*, **122**, 2943–2964.

Miaskowski, C. (2004) Gender differences in pain, fatigue, and depression in patients with cancer. *Journal of the National Cancer Institute. Monographs*, **32**, 139–143.

National Comprehensive Cancer Network, NCCN (2012) Clinical Practice Guidelines in Oncology: Cancer-Related Fatigue. Version 1.2014. National Comprehensive Cancer Network, Fort Washington, PA. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp – Accessed August 2014.

Osoba, D., Rodrigues, G., Myles, J., Zee, B. & Pater, J. (1998) Interpreting the significance of changes in health-related quality-of-life scores. *Journal of Clinical Oncology*, **16**, 139–144.

Sauerbrei, W. (1999) The use of resampling methods to simplify regression models in medical statistics. *Journal of the Royal Statistical Society: Series C (Applied Statistics)*, **48**, 313–329.

Sorror, M.L., Maris, M.B., Storb, R., Baron, F., Sandmaier, B.M., Maloney, D.G. & Storer, B. (2005) Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood*, **106**, 2912–2919.

Stauder, R., Smith, A., De Witte, T., Droste, J., Fenaux, P., Symeonidis, A., Hellstrom-Lindberg, E., Sanz, G., Cermak, J., Georgescu, O., Germing, U., MacKenzie, M., Beyne-Rauzy, O., Malcovati, L. & Bowen, D. (2010) Health-related quality of life in newly diagnosed low risk and intermediate-1 risk MDS: report on the first 683 patients from the European LeukemiaNet registry. *Blood* (ASH Annual Meeting Abstracts), **116**, Abstract 3999.

Steensma, D.P., Heptinstall, K.V., Johnson, V.M., Novotny, P.J., Sloan, J.A., Camoriano, J.K., Niblack, J., Bennett, J.M. & Mesa, R.A. (2008) Common troublesome symptoms and their impact on quality of life in patients with myelodysplastic syndromes (MDS): results of a large internet-based survey. *Leukemia Research*, **32**, 691–698.

Stone, P., Richards, M., A'Hern, R. & Hardy, J. (2000) A study to investigate the prevalence, severity and correlates of fatigue among patients with cancer in comparison with a control group of volunteers without cancer. *Annals of Oncology*, **11**, 561–567.

Thomas, M.L., Crisp, N. & Campbell, K. (2012) The importance of quality of life for patients living with myelodysplastic syndromes. *Clinical Journal of Oncology Nursing*, **16**(Suppl.), 47–57.

Vardiman, J.W., Harris, N.L. & Brunning, R.D. (2002) The World Health Organization (WHO) classification of the myeloid neoplasms. *Blood*, **100**, 2292–2302.

Wang, X.S., Giralt, S.A., Mendoza, T.R., Engstrom, M.C., Johnson, B.A., Peterson, N., Broemeling, L.D. & Cleeland, C.S. (2002) Clinical factors associated with cancer-related fatigue in patients being treated for leukemia and non-Hodgkin's lymphoma. *Journal of Clinical Oncology*, **20**, 1319–1328.

Wang, X.S., Cleeland, C.S., Mendoza, T.R., Yun, Y.H., Wang, Y., Okuyama, T. & Johnson, V.E. (2010) Impact of cultural and linguistic factors on symptom reporting by patients with cancer. *Journal of the National Cancer Institute*, **102**, 732–738.

van Wijk, C.M. & Kolk, A.M. (1997) Sex differences in physical symptoms: the contribution of symptom perception theory. *Social Science and Medicine*, **45**, 231–246.

Yellen, S.B., Cella, D.F., Webster, K., Blendowski, C. & Kaplan, E. (1997) Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *Journal of Pain and Symptom Management*, **13**, 63–74.