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RAPID COMMUNICATION

High serum ferritin levels in newly diagnosed patients with myelodysplastic syndromes are associated with greater symptom severity

Giovanni Caocci[1] · Marco Vignetti[2] · Andrea Patriarca[3] · Massimo Breccia[4] · Uwe Platzbecker[5] · Giuseppe A. Palumbo[6] · Reinhard Stauder[7] · Francesco Cottone[2] · Duska Petranovic[8] · Maria Teresa Voso[9] · Agostino Tafuri[10] · Rosangela Invernizzi[11] · Jo Caers[12] · Mario Luppi[13] · Giorgio La Nasa[1] · Pasquale Niscola[14] · Fabio Efficace[2]

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Abstract
We examined the association between serum ferritin (SF) levels and patient-reported functional aspects and symptoms, as measured by the EORTC QLQ-C30, in newly diagnosed patients with myelodysplastic syndromes (MDS). Analysis was conducted on 497 MDS patients who were classified in two groups based on the SF value of 1000 ng/mL. Clinically relevant differences of patient-reported functional and symptom scales were evaluated and classified as small, medium and large, based on established thresholds. Multivariable linear regression analysis was performed to account for potential confounding factors. Patients with SF of ≥ 1000 ng/mL reported statistically significant and clinically relevant worse outcomes across various health domains. Dyspnea was the symptom indicating the largest difference and mean scores of patients with higher and lower SF levels were 40 and 24.3, respectively ($p = 0.005$), indicating a large clinically relevant difference ($\Delta = 15.7$). Further research is needed to better understand the relationship between SF levels and specific health-related quality of life domains.

Keywords Serum ferritin · Myelodysplastic syndromes · Functional status · Quality of life · Symptoms · Transfusions

Giovanni Caocci and Fabio Efficace contributed equally to this work.

✉ Fabio Efficace
f.efficace@gimema.it

[1] Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy

[2] Data Center and Health Outcomes Research Unit, Italian Group for Adult Haematologic Diseases (GIMEMA), Rome, Italy

[3] Division of Hematology, Department of Translational Medicine, University of Eastern Piedmont, Novara, Italy

[4] Department of Cellular Biotechnologies and Hematology, Division of Hematology, Sapienza University, Rome, Italy

[5] Clinic and Policlinic of Hematology and Cellular Therapy, Oncology and Hemostaseology, University Hospital Leipzig, Leipzig, Germany

[6] Dipartimento di Scienze Mediche, Chirurgiche E Tecnologie Avanzate "G.F. Ingrassia", University of Catania, Catania, Italy

[7] Department of Internal Medicine V (Hematology and Oncology), Innsbruck Medical University, Innsbruck, Austria

[8] Department of Hematology, Clinical Hospital Center Rijeka, Rijeka, Croatia

[9] Department of Biomedicine and Prevention, Università di Roma "Tor Vergata", Rome, Italy

[10] Azienda Ospedaliera Sant' Andrea, Rome, Italy

[11] Department of Internal Medicine, San Matteo IRCCS Policlinic Foundation, University of Pavia, Pavia, Italy

[12] Department of Hematology, CHU de Liège, University of Liege, Liege, Belgium

[13] Department of Medical and Surgical Sciences, Chair of Hematology, AOU Modena, University of Modena and Reggio Emilia, Modena, Italy

[14] Hematology Unit, Sant' Eugenio Hospital, Rome, Italy

Introduction

Myelodysplastic syndromes (MDS) represent a heterogeneous group of hematologic malignancies characterized by peripheral cytopenia, ineffective hematopoiesis as manifested by bone marrow cell dysplasia and risk for progression to acute myeloid leukemia [1].

Patients with MDS may develop iron overload, secondary to blood transfusions and increased intestinal iron absorption and altered distribution/retention (e.g., storing in macrophages) due to inadequate suppression of hepcidin that occurs as a consequence of ineffective erythropoiesis [2]. Accumulation of toxic iron species such as non-transferrin bound iron and labile plasma iron may also occur, resulting in increased levels of reactive oxygen species and subsequent tissue damage, with particular involvement of liver, heart and endocrine system [2, 3]. Recent insights have suggested that iron overload in MDS is not merely a secondary feature, but rather a systemic toxic disease [4].

Iron overload is typically monitored by serum ferritin (SF) concentration and, despite improved availability of advanced imaging techniques, SF remains the most commonly used approach to monitor iron overload and chelation therapy. Serum ferritin measurements are inexpensive and generally correlate with both total body iron stores and clinical outcomes [5]. International guidelines recommend a ferritin-guided chelating approach (at least ≥ 1000 ng/mL) for the treatment of iron overload in MDS patients [6].

Despite international MDS recommendations [6] emphasize the importance of health-related quality of life (HRQOL) as a key goal of therapy, little attention has historically been given to this aspect [7]. For example, while it is known that transfusion dependence and hyperferritinemia are associated with adverse outcomes and shortened survival [8], there is dearth of information with regard to the association between hyperferritinemia, functional status and symptom burden in MDS patients [9].

Therefore, we aimed to examine whether higher pretreatment SF concentration is associated with limitations in functional status or higher symptom severity in a large cohort of newly diagnosed MDS patients.

Materials and methods

Analysis was based on baseline data of an international observational study, which enrolled newly diagnosed adult patients with MDS between 2008 and 2018, across 53 centers [10]. MDS diagnosis was performed by each Institute involved in the study. Out of the 647 patients for whom the SF value was included in case report forms (i.e., after protocol amendment in 2014), the SF data were available for 497 patients. This sample was split in two groups based on the SF value of 1000 ng/mL, with ≥ 1000 ng/mL indicating severe iron overload [6]. All patients completed the validated European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) [11]. This questionnaire includes five functional scales (i.e., physical, role, emotional, cognitive, and social), three symptom scales (i.e., fatigue, nausea/ vomiting, and pain), six single-item scales (i.e., dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a global health status scale/quality of life scale (GHS). However, for the purpose of this analysis, financial difficulties and the GHS scale were not considered. Clinically relevant differences of scales were evaluated and classified as small, medium and large, based on previously published thresholds [12].

The study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent and the study was approved by the ethics committees of each participating center. We used proportions, medians and interquartile range (IQR) to describe the main characteristics and HRQOL profiles of MDS patients, overall and by SF levels (≥ 1000 ng/mL vs. < 1000 ng/mL). For exploratory purposes, additional cut-off values based on median (i.e., 269 ng/mL) and 75th percentile (543 ng/mL) of SF levels in the overall population were also analyzed. We evaluated differences between groups of patients based on ferritin level by chi-square and Wilcoxon Mann–Whitney tests. Multivariable linear regression analysis was also performed to account for potential confounding factors. All tests were bilateral with statistical significance set as $\alpha = 0.05$.

Results

Out of 497 patients with MDS analyzed, at initial diagnosis, 457 reported SF value < 1000 ng/mL (median = 240 ng/mL, IQR = 121–461), and 40 patients reported SF values ≥ 1000 ng/mL (median = 1477 ng/mL; IQR = 1231–1989). The median age of patients was 74 years (IQR = 67–80), and the majority of them were males (59.4%). Overall, the IPSS score was lower (i.e., low or intermediate-1) or higher (i.e., intermediate-2 or high) in 77.5% and 22.5% of patients, respectively. Patients with lower and higher SF level (i.e., < 1000 vs. ≥ 1000 ng/mL) were statistically significant different with respect to sex, ECOG performance status, number of comorbidities, hemoglobin level and transfusion dependency. The distribution of patients according to the IPSS was similar in the two SF groups. Details are reported in (Table 1).

Table 1 Characteristics of 497 patients with myelodysplastic syndromes by serum ferritin concentration

Variable	Serum Ferritin, ng/mL			
	< 1000 (*N* = 457)	≥ 1000 (*N* = 40)	Total (*N* = 497)	*p* value
Age				
Median	73.8	75.6	73.8	0.688
IQR	66.6–79.7	68.1–80.3	66.8–79.7	
Sex, *N* (%)				
Male	265 (58.0)	30 (75.0)	295 (59.4)	0.036
Female	192 (42.0)	10 (25.0)	202 (40.6)	
ECOG performance status, *N* (%)				
0	209 (46.3)	11 (27.5)	220 (44.8)	0.022
≥ 1	242 (53.7)	29 (72.5)	271 (55.2)	
Missing	6	0	6	
Comorbidity, *N* (%)				
0–1	317 (69.7)	17 (42.5)	334 (67.5)	< 0.001
≥ 2	138 (30.3)	23 (57.5)	161 (32.5)	
Missing	2	0	2	
IPSS Risk groups, *N* (%)				
Low and Int.-1	356 (77.9)	29 (72.5)	385 (77.5)	0.433
Int.-2 and High	101 (22.1)	11 (27.5)	112 (22.5)	
Hemoglobin, g/dL				
Median	9.8	8.8	9.7	< 0.001
IQR	8.7–11.4	7.9–9.6	8.6–11.3	
Transfusion dependency[a], *N* (%)				
No	397 (87.6)	19 (48.7)	416 (84.5)	< 0.001
Yes	56 (12.4)	20 (51.3)	76 (15.5)	
Missing	4	1	5	

IQR interquartile range; *IPSS* international prognostic scoring system

[a]Transfusion dependency is defined as having received at least one red blood cell transfusion every 8 weeks over a period of 4 months

Functional status and symptom profile

Small clinically relevant differences favoring patients with SF < 1000 ng/mL were found for the physical and emotional functioning scales (respectively, $\Delta = -9.7$ points, $p = 0.005$ and $\Delta = -10.3$ points, $p = 0.009$). Figure 1 depicts mean scores differences of all functional scales of the EORTC QLQ-C30.

Patients with SF ≥ 1000 ng/mL reported statistically significant and clinically relevant worse outcomes (i.e., higher scores) for the following symptoms: dyspnea, appetite loss, fatigue and pain. Dyspnea was the symptom indicating the largest difference and mean scores of patients with higher and lower SF levels were 40 and 24.3 respectively ($p = 0.005$), indicating a large clinically relevant difference ($\Delta = 15.7$) (Fig. 1). Appetite loss reached a medium clinically meaningful difference ($\Delta = 15.5$), while differences for fatigue and pain were still of clinical relevance ($\Delta = 12.1$ and $\Delta = 9.7$, respectively), albeit of small magnitude (Fig. 1). Multivariable regression analysis controlling for sex, comorbidity, performance status, transfusion dependency and hemoglobin levels, showed that dyspnea, pain, appetite loss, and emotional functioning remained independently associated with SF levels. However, fatigue and physical functioning did not. Results of multivariate analysis of the above-reported symptoms are reported in Table 2.

Further investigation of other SF cut-off values as 269 ng/mL (median) or 543 ng/mL (75 percentile) indicated no significant differences in any of the considered EORTC QLQ-C30 scales (data not shown).

Discussion

We observed that newly diagnosed MDS patients with higher SF levels reported clinically relevant impairments across various functional and symptom domains.

Ferritin is a known marker of inflammation, which has been shown to play a significant role in the pathogenesis of MDS [13], hence the increased inflammation status and the imbalances in cytokine levels may explain the greater symptom burden in patients with higher SF. The largest

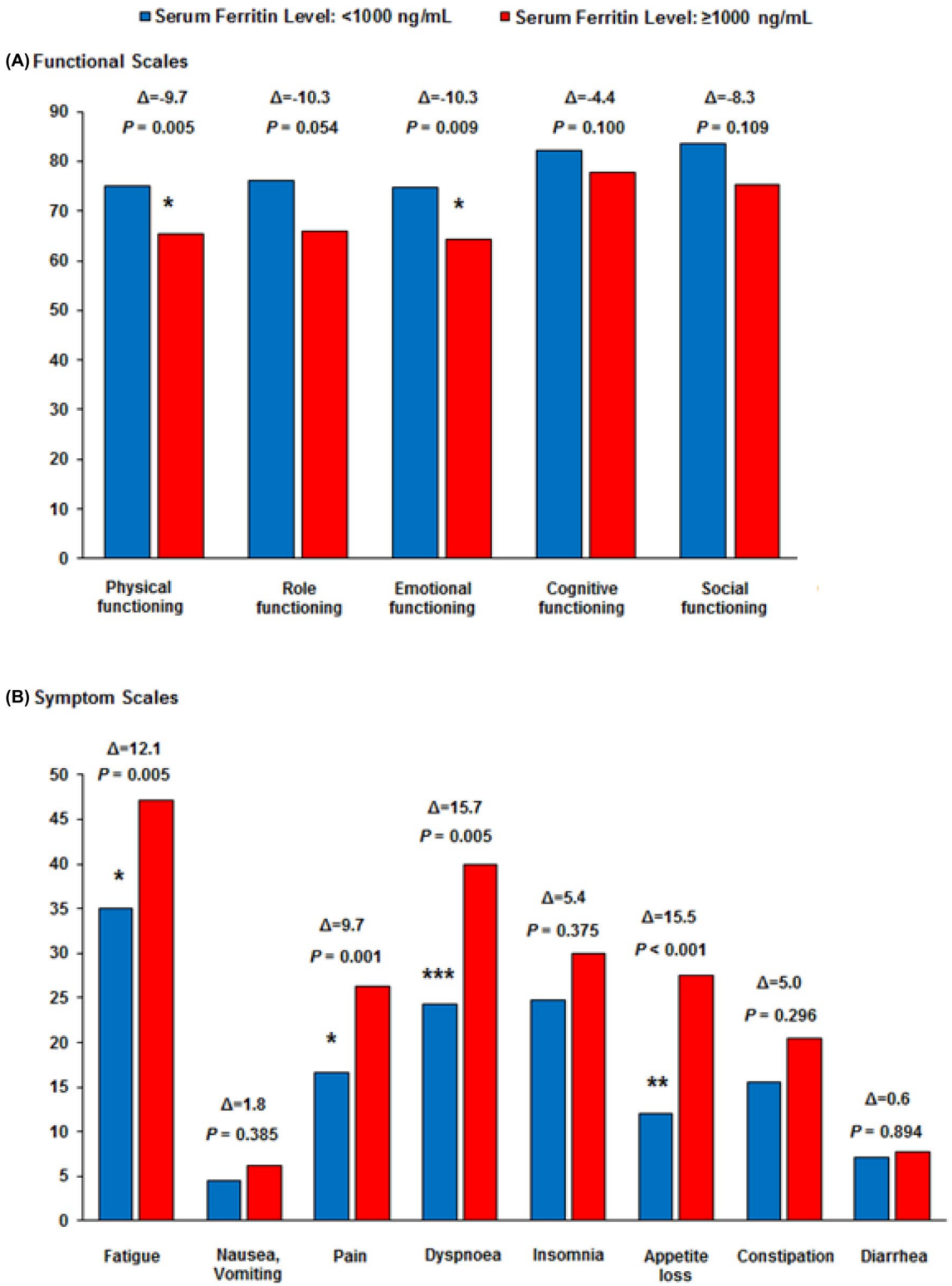

Fig. 1 Functional status and symptom severity by baseline serum ferritin concentration. The figure shows the mean scores for each scale of the EORTC QLQ-C30, by serum ferritin level. For functional scales, a higher score represents a higher level of functioning. For symptom scales, a higher score represents a higher symptom severity. For each scale, the corresponding Δ, represents the difference in mean scores between patients with serum ferritin level ≥ 1000 ng/mL and those with < 1000 ng/mL. *Indicates a small clinically meaningful difference. **Indicates a medium clinically meaningful difference. ***Indicates a large clinically meaningful difference. Clinically important differences were only reported when differences were also statistically significant

Table 2 Results of the multivariable analyses for selected symptom scales of the EORTC QLQ-C30

Variables	Fatigue		Pain		Dyspnea		Appetite Loss	
	β (95% CI)	*P*	*β* (95% CI)	*P*	*β* (95% CI)	*P*	*β* (95% CI)	*P*
Male	−5.3 (−9.8; −0.8)	0.021	−3.0 (−7.3; 1.3)	0.176	−6.8 (−11.9; −1.8)	0.008	−4.5 (−8.8; −0.1)	0.044
ECOG ≥ 1	8.9 (4.0; 13.7)	< 0.001	7.2 (2.5; 11.9)	0.003	8.8 (3.3; 14.3)	0.002	2.0 (−2.6; 6.7)	0.391
Comorbidity ≥ 2	7.1 (2.3; 12.0)	0.004	5.4 (0.7; 10.1)	0.024	6.2 (0.7; 11.7)	0.029	5.0 (0.3; 9.7)	0.036
Hemoglobin level (g/dL)	−1.7 (−2.9; −0.6)	0.003	0.2 (-0.9; 1.4)	0.676	−1.4 (-2.8; −0.1)	0.032	−1.5 (−2.6; −0.4)	0.009
Transfusion dependency*	2.6 (−3.9; 9.1)	0.427	−2.4 (−8.6; 3.9)	0.453	−1.8 (−9.1; 5.6)	0.636	−0.1 (−6.3; 6.2)	0.980
Ferritin level ≥ 1000 ng/mL	5.4 (−3.0; 13.8)	0.204	9.0 (0.9; 17.2)	0.029	12.3 (2.8; 21.7)	0.012	11.9 (3.8; 20.0)	0.004

CI confidence interval

*Transfusion dependency is defined as having received at least one red blood cell transfusion every 8 weeks over a period of 4 months

impairment (i.e., three times the magnitude of a minimal clinically important difference) was found for dyspnea in patients with iron overload compared with those with lower SF concentration. This association remained independent of other key potential confounding factors. Patients with chronic heart failure, a frequent complication in MDS patients, often suffer from dyspnea due to multifactorial mechanisms and, therefore, this finding begs for more research.

Along this line, the association we found between hyperferritinemia and higher pain severity and appetite loss, which still remained independently associated with SF values, could also mirror the disease inflammatory burden. While pain is generally underestimated by physicians treating MDS patients, some recent studies have provided empirical evidence of the burden of this symptom both in lower [14] and higher risk MDS patients [15]. The interpretation of the association between higher fatigue and SF levels, is less clear as it was no longer independently associated with SF while accounting for confounding factors.

Our previous analysis, albeit conducted only in patients with higher risk disease, indicated that female gender, poor performance status and lower hemoglobin levels were independently associated with higher fatigue severity, but SF was not considered [15]. It is possible to speculate that SF might be associated with specific HRQOL domains through different mechanisms of actions, that should be elucidated in future work.

Inspection of lower SF cut-off values (i.e., 269 and 543 ng/mL) in our dataset, revealed no significant differences in any of the domains investigated. Using a higher SF threshold (i.e., 2000 ng/mL) than that used in our analysis, a previous study [9] did not find HRQOL differences between those with higher and lower SF values. However, that study [9] only included transfusion-dependent lower risk MDS patients with a median SF level of 2000 ng/mL, therefore, making it difficult a comparison with current findings.

Although the role of iron chelation in MDS patients is still a matter of debate, especially in those patients with an expected reduced survival (higher IPSS score), a recent study [16] has shown a general benefit of iron chelation on survival in lower risk IPSS patients, and this indication is included in international guidelines [6]. More than half of non-leukemic causes of death are due to cardiac failure secondary to iron overload [6]. However, a study on lower risk transfusion-dependent MDS patients treated with iron chelation therapy, showed no HRQOL benefits over a 1-year period [9]. In our sample, none of the patients with higher SF values received iron chelation therapy before HRQOL assessment. Future studies will have to identify specific subgroups of MDS patients for whom iron chelation therapy may be most beneficial.

In conclusion, our findings suggest to pay special attention to newly diagnosed MDS patients with high SF levels, as they may report clinically relevant impairments in some important symptoms. Further research is needed to better understand the relationship between SF levels and specific HRQOL domains.

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Compliance with ethical standards

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