



Aalborg Universitet

AALBORG UNIVERSITY
DENMARK

Toxic iron species in lower-risk myelodysplastic syndrome patients

course of disease and effects on outcome

Hoeks, Marlijn; Bagguley, Tim; van Marrewijk, Corine; Smith, Alex; Bowen, David; Culligan, Dominic; Kolade, Seye; Symeonidis, Argiris; Garelius, Hege; Spanoudakis, Michail; Langemeijer, Saskia; Roelofs, Rian; Wiegerinck, Erwin; Tatic, Aurelia; Killick, Sally; Panagiotidis, Panagiotis; Stanca, Oana; Hellström-Lindberg, Eva; Cermak, Jaroslav; van der Klauw, Melanie; Wouters, Hanneke; van Kraaij, Marian; Blijlevens, Nicole; Swinkels, Dorine W.; de Witte, Theo; Stauder, R.; Walder, A.; Pfeilstöcker, M.; Schoenmetzler-Makrai, A.; Burgstaller, S.; Thaler, J.; Mandac Rogulj, I.; Krejci, M.; Voglova, J.; Rohon, P.; Jonasova, A.; Cermak, J.; Mikulenková, D.; Hochova, I.; Jensen, P. D.; Holm, M. S.; Kjeldsen, L.; Dufva, I. H.; Vestergaard, H.; Re, D.; Slama, B.; Fenaux, P.; Choufi, B.; Cheze, S.; Klepping, D.; Salles, B.; de Renzis, B.; Willems, L.; De Prost, D.; Gutnecht, J.; Courby, S.; Siguret, V.; Tertian, G.; Pascal, L.; Chaury, M.; Wattel, E.; Guerci, A.; Legros, L.; Itzykson, R.; Ades, L.; Isnard, F.; Sanhes, L.; Benramdane, R.; Stamatoullas, A.; Amé, S.; Beyne-Rauzy, O.; Gyan, E.; Platzbecker, U.; Badrakan, C.; Germing, U.; Lübbert, M.; Schlenk, R.; Kotsianidis, I.; Tsatalas, C.; Pappa, V.; Galanopoulos, A.; Michali, E.; Panagiotidis, P.; Viniou, N.; Katsigiannis, A.; Roussou, P.; Terpos, E.; Kostourou, A.; Kartasis, Z.; Pouli, A.; Palla, K.; Briasoulis, V.; Hatzimichael, E.; Vassilopoulos, G.; Symeonidis, A.; Kourakli, A.; Zikos, P.; Anagnostopoulos, A.; Kotsopoulou, M.; Megalakaki, K.; Protopapa, M.; Vlachaki, E.; Konstantinidou, P.; Stemer, G.; Nemetz, A.; Gotwin, U.; Cohen, O.; Koren, M.; Levy, E.; Greenbaum, U.; Gino-Moor, S.; Price, M.; Ofran, Y.; Winder, A.; Goldshmidt, N.; Elias, S.; Sabag, R.; Hellman, I.; Ellis, M.; Braester, A.; Rosenbaum, H.; Berdichevsky, S.; Itzhaki, G.; Wolaj, O.; Yeganeh, S.; Katz, O.; Filanovsky, K.; Dali, N.; Mittelman, M.; Malcovati, L.; Fianchi, L.; vd Loosdrecht, A.; Matthijssen, V.; Herbers, A.; Pruijt, H.; Aboosy, N.; de Vries, F.; Velders, G.; Jacobs, E.; Langemeijer, S.; MacKenzie, M.; Lensen, C.; Kuijper, P.; Madry, K.; Camara, M.; Almeida, A.; Vulkan, G.; Stanca Ciocan, O.; Tatic, A.; Savic, A.; Pedro, C.; Xicoy, B.; Leiva, P.; Munoz, J.; Betes, V.; Benavente, C.; Lozano, M.; Martinez, M.; Iniesta, P.; Bernal, T.; Diez Campelo, M.; Tormo, D.; Andreu Lapiedra, R.; Sanz, G.; Hesse Sundin, E.; Garelius, H.; Karlsson, C.; Antunovic, P.; Jönsson, A.; Brandefors, L.; Nilsson, L.; Kozłowski, P.; Hellstrom-Lindberg, E.; Grövdal, M.; Larsson, K.; Wallvik, J.; Lorenz, F.; Ejerblad, E.; Culligan, D.; Craddock, C.; Kolade, S.; Cahalin, P.; Killick, S.; Ackroyd, S.; Wong, C.; Warren, A.; Drummond, M.; Hall, C.; Rothwell, K.; Green, S.; Ali, S.; Karakantza, M.; Dennis, M.; Jones, G.; Parker, J.; Bowen, A.; Radia, R.; Das-Gupta, E.; Vyas, P.; Nga, E.; Creagh, D.; Ashcroft, J.; Mills, J.; Bond, L.; the EUMDS Registry Participants

Published in:
Leukemia

DOI (link to publication from Publisher):
[10.1038/s41375-020-01022-2](https://doi.org/10.1038/s41375-020-01022-2)

Creative Commons License
CC BY 4.0

Publication date:
2021

Document Version
Publisher's PDF, also known as Version of record



Myelodysplastic syndrome

Toxic iron species in lower-risk myelodysplastic syndrome patients: course of disease and effects on outcome

Marlijn Hoeks^{1,2,3} · Tim Bagguley⁴ · Corine van Marrewijk³ · Alex Smith⁴ · David Bowen⁵ · Dominic Culligan⁶ · Seye Kolade⁷ · Argiris Symeonidis⁸ · Hege Garelus⁹ · Michail Spanoudakis^{10,11} · Saskia Langemeijer³ · Rian Roelofs¹² · Erwin Wiegerinck¹² · Aurelia Tatic¹³ · Sally Killick¹⁴ · Panagiotis Panagiotidis¹⁵ · Oana Stanca¹⁶ · Eva Hellström-Lindberg¹⁷ · Jaroslav Cermak¹⁸ · Melanie van der Klauw¹⁹ · Hanneke Wouters¹⁹ · Marian van Kraaij³ · Nicole Blijlevens³ · Dorine W. Swinkels¹² · Theo de Witte²⁰ · on behalf of the EUMDS Registry Participants

Received: 30 April 2020 / Revised: 3 August 2020 / Accepted: 6 August 2020 / Published online: 18 September 2020
© The Author(s) 2020. This article is published with open access

Introduction

Red blood cell transfusions (RBCT) remain the cornerstone of supportive care in lower-risk myelodysplastic syndrome (LRMDS) [1]. Transfusion dependency in LRMDS patients

is associated with inferior outcomes, mainly attributed to severe bone marrow failure [2]. However, iron toxicity, due to frequent RBCT or ineffective erythropoiesis, may be an additional negative prognostic factor [3–6]. Recently, much progress has been made in unraveling the iron metabolism. The peptide hormone hepcidin is the key regulator by inhibiting iron uptake through degradation of ferroportin, a cellular iron exporter [7]. Erythroferrone and GDF15, produced by erythroblasts, inhibit hepcidin production, which leads to increased uptake and cellular release of iron for the purpose of erythropoiesis [8].

Members of the EUMDS Registry Participants are listed below
Acknowledgements.

Supplementary information The online version of this article (<https://doi.org/10.1038/s41375-020-01022-2>) contains supplementary material, which is available to authorized users.

✉ Marlijn Hoeks
marlijn.hoeks@radboudumc.nl

- 1 Centre for Clinical Transfusion Research, Sanquin Research, Leiden, The Netherlands
- 2 Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands
- 3 Department of Hematology, Radboud University Medical Center, Nijmegen, The Netherlands
- 4 Epidemiology and Cancer Statistics Group, University of York, York, UK
- 5 St. James's Institute of Oncology, Leeds Teaching Hospitals, Leeds, UK
- 6 Department of Hematology, Aberdeen Royal Infirmary, Aberdeen, UK
- 7 Department of Hematology, Blackpool Victoria Hospital, Blackpool, Lancashire, UK
- 8 Department of Medicine, Division of Hematology, University of Patras Medical School, Patras, Greece
- 9 Department of Medicine, Sect. of Hematology and Coagulation, Sahlgrenska University Hospital, Göteborg, Sweden
- 10 Department of Hematology, Airedale NHS Trust, Airedale, UK
- 11 Department of Haematology, Warrington and Halton Teaching

- Hospitals NHS foundation Trust, Cheshire, UK
- 12 Department of Laboratory Medicine, Hepcidinanalysis.com, and Radboudumc Expertise Center for Iron Disorders, Radboud University Medical Center, Nijmegen, The Netherlands
 - 13 Center of Hematology and Bone Marrow Transplantation, Fundeni Clinical Institute, Bucharest, Romania
 - 14 Department of Hematology, Royal Bournemouth Hospital, Bournemouth, UK
 - 15 Department of Haematology, 1st Department of Propedeutic Internal Medicine, National and Kapodistrian University of Athens, Medical School, Laikon General Hospital, Athens, Greece
 - 16 Department of Hematology, Coltea Clinical Hospital, Bucharest, Romania
 - 17 Department of Medicine, Division of Hematology, Karolinska Institutet, Stockholm, Sweden
 - 18 Department of Clinical Hematology, Institute of Hematology and Blood Transfusion, Praha, Czech Republic
 - 19 Department of Endocrinology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
 - 20 Nijmegen Center for Molecular Life Sciences, Department of Tumor Immunology, Radboud University Medical Center, Nijmegen, The Netherlands

The pathophysiology of iron metabolism in MDS is still not completely understood. Exceedingly high reactive oxygen species (ROS) levels are associated with iron toxicity, disease development, and progression in MDS patients [9–12]. Malondialdehyde (MDA), resulting from lipid peroxidation of polyunsaturated fatty acids, is a biomarker of oxidative stress [10, 12]. Currently, little is known about the prognostic impact of ROS in MDS patients.

The aim of this study is twofold: (1) describe iron and oxidative stress parameters over time in LRMDS patients and (2) to assess their effect on overall and progression-free survival.

Materials and methods

The EUMDS registry prospectively collects observational data on newly diagnosed LRMDS patients from 148 centers in 16 countries in Europe and Israel as of January 2008. All patients provided informed consent. Clinical data were collected at baseline and at each six-monthly follow-up visit. Serum samples were collected prospectively at each visit from 256 patients included in six participating countries. Conventional iron parameters were measured with routine assays. We additionally analyzed hepcidin, growth differentiation factor 15 (GDF15), soluble transferrin receptor (sTfR), non-transferrin bound iron (NTBI), labile plasma iron (LPI), and MDA. Subjects were prospectively followed until death, loss to follow-up, or withdrawal of consent.

All iron parameters were measured centrally at the department of Laboratory Medicine of the Radboudumc, Nijmegen, The Netherlands. Serum samples were collected just prior to transfusion in transfusion-dependent patients and stored at -80°C . Details on the assays and reference ranges of hepcidin, GDF15, sTfR, NTBI, LPI, and MDA are provided in the supplement.

The Spearman rank test was used to evaluate correlations between iron parameters. We stratified the results by transfusion dependency per visit and the presence of ring sideroblasts. When evaluating temporal changes in iron parameters, with linear quantile mixed models, we excluded patients from the timepoint they received iron chelation therapy. Overall survival (OS) was defined as the time from MDS diagnosis to death or, in case of progression-free survival, to date of progression or death; patients still alive at the end of follow-up were censored. Time-dependent Kaplan–Meier curves and cox proportional hazards models were used.

Results

In total, 256 consecutive patients, were included in this study. Over five six-monthly visits, 1040 samples were

Table 1 Baseline characteristics.

	<i>N</i> (%)
Total	256 (100.0)
Sex	
Males	169 (66.0)
Females	87 (34.0)
Age	
35–44	2 (0.8)
45–54	7 (2.7)
55–64	51 (19.9)
65–74	78 (30.5)
75+	118 (46.1)
Mean (sd)	72.1 (9.5)
Median (min–max)	74.0 (37.0–95.0)
MDS diagnosis	
RCMD	114 (44.5)
RARS	56 (21.9)
RA	45 (17.6)
RAEB-1	16 (6.3)
RCMD-RS	10 (3.9)
5q-syndrome	10 (3.9)
MDS-U	5 (2.0)
Group	
NonRS-TI	143 (55.9)
NonRS-TD	47 (18.4)
RS-TI	48 (18.8)
RS-TD	18 (7.0)
IPSS-R category	
Very low/low	195 (76.2)
Intermediate	23 (9.0)
High/very high	4 (1.6)
Not known	34 (13.3)
IPSS category	
Low risk	144 (56.3)
Intermed-1	75 (29.3)
Intermed-2	1 (0.4)
Not known	36 (14.1)
Karnofsky performance status	
Able to work and normal activity	193 (75.4)
Unable to work	48 (18.8)
Unable to care for self	1 (0.4)
Not known	14 (5.5)
Comorbidity index	
Low risk	158 (61.7)
Intermediate risk	79 (30.9)
High risk	19 (7.4)
EQ5D index score	
Mean (sd)	0.77 (0.24)
Median (p10–p90)	0.80 (0.52–1.00)

Table 1 (continued)

	<i>N</i> (%)
ESA	
No	159 (62.1)
Yes	97 (37.9)
Iron chelation	
No	241 (94.1)
Yes	15 (5.9)
Desferoxamine	5 (2.0)
Deferiprone/deferiasirox	11 (4.3)
Hypomethylating agents	
No	245 (95.7)
Yes	11 (4.3)
Overall survival	
Median (95% CI)	4.8 (3.9—not reached)
Cause of death	
MDS unrelated	15 (34.1)
MDS related	24 (54.5)
Unknown	5 (11.4)
Follow-up time (censored last EUMDS visit)	
Median (95% CI)	6.6 (5.9–7.0)

sd standard deviation, *MDS* myelodysplastic syndrome, *RCMD* refractory cytopenia with multilineage dysplasia, *RARS* refractory anemia with ring sideroblasts, *RA* refractory anemia, *RAEB* refractory anemia with excess blasts, *RCMD-RS* refractory cytopenia with multilineage dysplasia with ring sideroblasts, *MDS-U* myelodysplastic syndrome unspecified, *RS* ring sideroblasts, *TI* transfusion-independent, *TD* transfusion-dependent, *IPSS(-R)* (revised) international prognostic scoring system, *EQ5D* EuroQoL five dimension scale, *ESA* erythropoietin stimulating agents.

collected. Table 1 describes the patient characteristics. Most patients without ring sideroblasts were transfusion-independent at diagnosis (nonRS-TI; 55.9%), 18.8% with ring sideroblasts were transfusion-independent (RS-TI), 18.4% without ring sideroblasts were transfusion-dependent (nonRS-TD), and 7% with ring sideroblasts were transfusion-dependent patients (RS-TD). The median follow-up time was 6.6 years (95% CI 5.9–7.0).

LPI was positively correlated with transferrin saturation (TSAT) ($r = 0.15$, $p < 0.001$, Fig. S1). LPI values increased exponentially at TSAT values above 80%. This effect was most pronounced in the transfusion-dependent groups, but also observed in the RS-TI group. MDA was weakly correlated with NTBI ($r = 0.09$, $p = 0.069$) and negatively correlated with hemoglobin level ($r = -0.1$, $p = 0.033$). GDF15 and hepcidin were negatively correlated in the RS-TI and nonRS-TD group and significantly negatively correlated in the RS-TD group ($r = -0.34$, $p = 0.007$, Fig. S2).

Serum ferritin levels were elevated in all subgroups with a mean value of 858 $\mu\text{g/L}$ at visit 5. The highest serum ferritin levels were observed in the RS-TD group (mean

value at visit 5: 2092 $\mu\text{g/L}$, Table S1). Serum ferritin increased significantly per visit in the RS-TD group (beta 454.46 $\mu\text{g/L}$; 95% CI 334.65–574.27), but not in the other groups (Table S2).

All subgroups, except for the nonRS-TI, had elevated TSAT levels. TSAT levels were most markedly increased in the RS-TD group with a mean TSAT of 88% at visit 5 (Table S1). In both transfusion-dependent groups the median increase per visit was significant (Table S2).

LPI was elevated in the RS-TD group exclusively with a mean value of 0.59 $\mu\text{mol/L}$ at visit 5 (Table S1). NTBI was elevated in all subgroups, with the highest values in the RS-TD group (Table S1). The increase in median NTBI level was significant in both transfusion-dependent groups (Table S2).

Hepcidin levels were markedly elevated in the nonRS-TD group. Interestingly, hepcidin levels were lower in the RS-TD group, probably reflecting ineffective erythropoiesis, likewise supported by lower hepcidin/ferritin ratios in RS groups (Table S1). Median hepcidin levels increased over time in the transfusion-dependent subgroups only (Table S2).

GDF15 levels, analyzed in the light of its potential role in hepcidin suppression, were increased in all subgroups (Table S1). The RS subgroups had higher GDF15 levels compared to the nonRS groups, reflecting increased erythropoiesis.

Mean sTfR levels were within the reference range in all subgroups except for the RS-TI group, which showed elevated levels, reflecting increased erythropoiesis (Table S1).

MDA levels were within the reference range in the nonRS-TI group and above the upper limit of the reference range in all other subgroups with the highest levels in the RS-TD group (Table S1). MDA levels at diagnosis were markedly higher in the RCMD-RS group compared to other subtypes (Table S3.1). As expected, in the group with elevated MDA levels, the transfusion density was markedly higher as compared with patients with low MDA levels (Table S3.2). Overall MDA levels increased over time ($p < 0.0001$). The steepest increase was observed in transfusion-dependent patients, with the highest median levels over time in the RS-TD group (Table S3.3).

Overall survival (OS)

Figure 1 shows a Kaplan–Meier curve for OS, stratified by LPI above or below the lower limit of detection (LLOD) and transfusion status as time-varying variables. Transfusion-dependent patients with elevated LPI levels have inferior OS compared to other subgroups. The Cox model shows an adjusted hazard ratio (HR) for OS, corrected for age at diagnosis and IPSS-R, of 2.7 (95% CI 1.5–5.0, $p = 0.001$) for LPI > LLOD. With the transfusion-

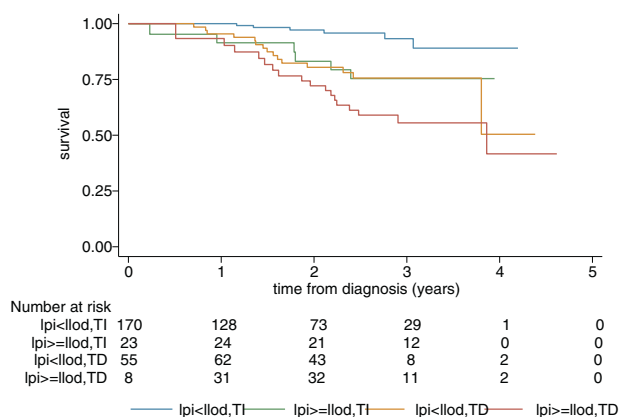


Fig. 1 Kaplan–Meier curve overall survival stratified by labile plasma iron above or below the lower limit of detection and transfusion status as time-dependent variables. LPI labile plasma iron, LLOD lower limit of detection, TI transfusion-independent, TD transfusion-dependent.

independent group with LPI values <LLOD as a reference, the HR for OS in the transfusion-independent group with LPI > LLOD was 4.5 (95% CI 1.4–13.9, $p = 0.01$), for the transfusion-dependent group with LPI < LLOD: 3.9 (95% CI 1.5–10.4, $p = 0.006$), and for the transfusion-dependent group with LPI > LLOD: 6.7 (95% CI 2.5–17.6, $p < 0.001$, Table S4).

The adjusted HR for OS for elevated NTBI was 1.6 (95% CI 0.8–3.1, $p = 0.17$). Transfusion-independent patients with normal NTBI levels have superior OS when compared with the other subgroups, who have significantly increased HRs for OS (Table S5).

Elevated TSAT (>80%) alone did not influence OS. However, when we repeated the analysis in the whole EUMDS registry as a dichotomous and continuous variable ($n = 1076$, 2853 visits), elevated TSAT did influence OS with an adjusted HR of 2.1 (95% CI 1.6–2.7, $p < 0.001$) and 1.009 (95% CI 1.004–1.014, $p < 0.001$), respectively. Transfusion-dependent patients with a TSAT $\geq 80\%$ had the worst OS with an adjusted HR of 4.2 (95% CI 2.9–5.9, $p < 0.001$).

Progression-free survival

In line with the effect of LPI on OS progression-free survival is significantly inferior in transfusion-dependent patients with LPI levels >LLOD (HR 9.2, 95% CI 3.8–22.5, $p < 0.001$).

Discussion

The results of this study suggest that LRMDs patients who are transfusion-dependent and have a MDS subtype with

ring sideroblasts have the highest levels for markers that reflect iron toxicity. Likewise, the highest hepcidin levels were observed in the transfusion-dependent nonRS group, but importantly, hepcidin levels and hepcidin/ferritin ratios were markedly lower in the transfusion-dependent patients with ring sideroblasts. Despite the excess of iron due to RBCT, hepcidin levels were lower than expected, thereby increasing the iron uptake from the gut and release of iron from the reticulo-endothelial system. Transfusion dependency is a known risk factor for iron toxicity. However, ineffective erythropoiesis in RS subgroups evidently leads to additional iron toxicity and potentially to increased morbidity and mortality [13–15]. Therefore, transfusion-dependent LRMDs patients with ring sideroblasts should be closely monitored for signs of iron toxicity and treated accordingly.

Our data suggest that LPI levels above the LLOD are associated with inferior overall and progression-free survival, irrespective of transfusion status. This highlights the importance of rational RBCT strategies in LRMDs patients. Novel hepcidin regulators as erythropherrone, hepcidin agonists, and early start of iron chelation are subjects for future research.

Overall MDA levels, as a marker of oxidative stress, increased significantly over time in our patient group. Oxidative stress due to iron toxicity could lead to organ damage as well as mutagenesis and clonal instability contributing to a higher progression risk [9–12]. Nevertheless, MDA is not an exclusive marker for oxidative stress, future research should focus on both oxidant and antioxidant factors thereby unraveling the exact relation between iron toxicity and oxidative stress.

In conclusion, iron toxicity is associated with inferior survival in LRMDs patients. More restrictive RBCT strategies and pre-emptive iron reducing interventions may prevent or reverse these unwanted effects.

Acknowledgements The authors would like to thank the other EUMDS Steering Committee members, local investigators and their teams (Table S4), and patients for their contribution to the EUMDS Registry; Jan Verhagen for his contribution in the measurement of the iron parameters; Margot Rekers, Karin van der Linden, and Siem Klaver for sample handling; Elise van Pinxten-van Orsouw and Linda van der Landen for data entry of all iron parameters; and Louise de Swart for her contribution to the analyses on the iron parameters.

EUMDS Registry Participants R. Stauder²¹, A. Walder²², M. Pfeilstöcker²³, A. Schoenmetzler-Makrai²³, S. Burgstaller²⁴, J. Thaler²⁴, I. Mandac Rogulj²⁵, M. Krejci²⁶, J. Voglova²⁷, P. Rohon²⁸, A. Jonsova²⁹, J. Cermak³⁰, D. Mikulenkova³⁰, I. Hochova³¹, P. D. Jensen³², M. S. Holm³³, L. Kjeldsen³⁴, I. H. Dufva³⁵, H. Vestergaard³⁶, D. Re³⁷, B. Slama³⁸, P. Fenaux³⁹, B. Choufi⁴⁰, S. Cheze⁴¹, D. Klepping⁴², B. Salles⁴², B. de Renzis⁴³, L. Willems⁴⁴, D. De Prost⁴⁵, J. Gutnecht⁴⁶, S. Courby⁴⁷, V. Siguret⁴⁸, G. Tertian⁴⁹, L. Pascal⁵⁰, M. Chaury⁵¹, E. Wattel⁵², A. Guerci⁵³, L. Legros⁵⁴, P. Fenaux⁵⁵, R. Itzykson⁵⁵, L. Ades⁵⁵, F. Isnard⁵⁶, L. Sanhes⁵⁷, R. Benramdane⁵⁸, A. Stamatoullas⁵⁹,

S. Amé⁶⁰, O. Beyne-Rauzy⁶¹, E. Gyan⁶², U. Platzbecker⁶³, C. Badrakan⁶⁴, U. Germing⁶⁵, M. Lübbert⁶⁶, R. Schlenk⁶⁷, I. Kotsianidis⁶⁸, C. Tsatalas⁶⁸, V. Pappa⁶⁹, A. Galanopoulos⁷⁰, E. Michali⁷⁰, P. Panagiotidis⁷¹, N. Viniou⁷¹, A. Katsigiannis⁷², P. Roussou⁷², E. Terpos⁷³, A. Kostourou⁷⁴, Z. Kartasis⁷⁵, A. Pouli⁷⁶, K. Palla⁷⁷, V. Briasoulis⁷⁸, E. Hatzimichael⁷⁸, G. Vassilopoulos⁷⁹, A. Symeonidis⁸⁰, A. Kourakli⁸⁰, P. Zikos⁸¹, A. Anagnostopoulos⁸², M. Kotsopoulou⁸³, K. Megalaki⁸³, M. Protopapa⁸⁴, E. Vlachaki⁸⁵, P. Konstantinidou⁸⁶, G. Stermer⁸⁷, A. Nemetz⁸⁸, U. Gotwin⁸⁹, O. Cohen⁸⁹, M. Koren⁸⁹, E. Levy⁹⁰, U. Greenbaum⁹⁰, S. Gino-Moor⁹¹, M. Price⁹², Y. Ofran⁹³, A. Winder⁹⁴, N. Goldshmidt⁹⁵, S. Elias, R. Sabag⁹⁵, I. Hellman⁹⁶, M. Ellis⁹⁶, A. Braester⁹⁷, H. Rosenbaum⁹⁸, S. Berdichevsky⁹⁹, G. Itzhaki¹⁰⁰, O. Wolaj¹⁰⁰, S. Yeganeh¹⁰¹, O. Katz¹⁰¹, K. Filanovsky¹⁰², N. Dali¹⁰³, M. Mittelman¹⁰⁴, L. Malcovati¹⁰⁵, L. Fianchi¹⁰⁶, A. vd Loosdrecht¹⁰⁷, V. Matthijssen¹⁰⁸, A. Herbers¹⁰⁹, H. Pruijt¹⁰⁹, N. Aboosy¹¹⁰, F. de Vries¹¹⁰, G. Velders¹¹¹, E. Jacobs¹¹², S. Langemeijer¹¹³, M. MacKenzie¹¹³, C. Lensen¹¹⁴, P. Kuijper¹¹⁵, K. Madry¹¹⁶, M. Camara¹¹⁷, A. Almeida¹¹⁷, G. Vulkan¹¹⁸, O. Stanca Ciocan¹¹⁹, A. Tatic¹²⁰, A. Savic¹²¹, C. Pedro¹²², B. Xicoy¹²³, P. Leiva¹²⁴, J. Munoz¹²⁵, V. Betés¹²⁶, C. Benavente¹²⁷, M. Lozano¹²⁸, M. Martinez¹²⁸, P. Iniesta¹²⁹, T. Bernal¹³⁰, M. Diez Campelo¹³¹, D. Tormo¹³², R. Andreu Lapiedra¹³³, G. Sanz¹³⁴, E. Hesse Sundin¹³⁵, H. Garelius¹³⁶, C. Karlsson¹³⁷, P. Antunovic¹³⁸, A. Jönsson¹³⁸, L. Brandefors¹³⁹, L. Nilsson¹⁴⁰, P. Kozlowski¹⁴¹, E. Hellstrom-Lindberg¹⁴², M. Grövdal¹⁴³, K. Larsson¹⁴⁴, J. Wallvik¹⁴⁴, F. Lorenz¹⁴⁵, E. Ejerblad¹⁴⁶, D. Culligan¹⁴⁷, C. Craddock¹⁴⁸, S. Kolade¹⁴⁹, P. Cahalin¹⁴⁹, S. Killick¹⁵⁰, S. Ackroyd¹⁵¹, C. Wong¹⁵², A. Warren¹⁵², M. Drummond¹⁵³, C. Hall¹⁵⁴, K. Rothwell¹⁵⁵, S. Green¹⁵⁶, S. Ali¹⁵⁶, D. Bowen¹⁵⁷, M. Karakantza¹⁵⁷, M. Dennis¹⁵⁸, G. Jones¹⁵⁹, J. Parker¹⁶⁰, A. Bowen¹⁶⁰, R. Radia¹⁶¹, E. Das-Gupta¹⁶¹, P. Vyas¹⁶², E. Nga¹⁶³, D. Creagh¹⁶⁴, J. Ashcroft¹⁶⁵, J. Mills¹⁶⁶, L. Bond¹⁶⁷

²¹Medical University of Innsbruck, Innsbruck, Austria; ²²Bezirkskrankenhaus, Lienz, Austria; ²³Hanusch Krankenhaus, Vienna, Austria; ²⁴Klinikum Kreuzschwestern, Wels, Austria; ²⁵Clinical Hospital Merkur, Zagreb, Croatia; ²⁶The University Hospital Brno, Brno, Czech Republic; ²⁷Charles University Faculty of Medicine, Hradec Kralove, Czech Republic; ²⁸University Hospital, Olomouc, Czech Republic; ²⁹General University Hospital, 1st Clinic of Internal Medicine, Prague, Czech Republic; ³⁰General University Hospital, Institute of Hematology and Blood Transfusion, Prague, Czech Republic; ³¹University Hospital Motol, Prague, Czech Republic; ³²University Hospital, Aalborg, Denmark; ³³University Hospital, Aarhus, Denmark; ³⁴University Hospital: Rigshospitalet, Copenhagen, Denmark; ³⁵Herlev Hospital, Herlev Ringvej, Herlev, Denmark; ³⁶Odense University Hospital, Odense, Denmark; ³⁷Hospital Center D'antibes Juan-Les-Pins, Antibes, France; ³⁸Centre Hospital, Avignon, France; ³⁹Hospital Avicenne, Bobigny, France; ⁴⁰Centre Hospital Boulogne-sur-Mer, Boulogne-sur-Mer, France; ⁴¹Centre Hospital Universitaire Clemenceau, Caen, France; ⁴²Centre Hospital William Morey, Chalon-sur-Saone, France; ⁴³Centre Hospital Universitaire, Clermont-Ferrand, France; ⁴⁴Hospital Hotel Dieu, Cochin, France; ⁴⁵Louis-Mourier Hospital, Colombes, France; ⁴⁶CHI Frejus Saint Raphael, Frejus, France; ⁴⁷CHU Albert Michallon, Grenoble, France; ⁴⁸Hopital Charles-Foix Ap-Hp, Ivry-sur-Seine, France; ⁴⁹Hospital Bicetre, Le Kremlin-Bicetre, France; ⁵⁰Hospital St Vincent de Paul, Lille, France; ⁵¹CHU Limoges Hospital Dupuytren, Limoges, France; ⁵²Hospital Edouard Herriot, Lyon, France; ⁵³CHU Nancy: Hospital Brabois (Vandoeuvre Les Nancy), Nancy, France; ⁵⁴CHU de Nice: Hospital l'Archet, Nice, France; ⁵⁵Hopital St Louis, Paris, France; ⁵⁶Hospital Saint-Antoine, Paris, France; ⁵⁷Centre Hospital Marechal Joffre, Perpignan, France; ⁵⁸Centre Hospital de Pontoise, Pontoise, France; ⁵⁹CHU de Rouen: Hospital Charles-Nicolle, Rouen, France; ⁶⁰CHU Hospital Haute-pierre de Strasbourg, Strasbourg, France; ⁶¹CHU Toulouse: Hospital Purpan, Toulouse, Toulouse, France; ⁶²CHRU de Tours, Tours, France; ⁶³University

Hospital Carl Gustav Carus, Dresden, Germany; ⁶⁴HELIOS: St. Johannes Hospital in Hamborn, Duisburg, Germany; ⁶⁵Heinrich-Heine University Hospital, Dusseldorf, Germany; ⁶⁶University Hospital Freiburg, Freiburg, Germany; ⁶⁷University Hospital Ulm, Ulm, Germany; ⁶⁸Democritus University of Thrace, Alexandroupolis, Greece; ⁶⁹General Hospital Attikon, University of Athens Medical School, Athens, Greece; ⁷⁰General Hospital G. Gennimatas, Athens, Greece; ⁷¹General Hospital Laikon, University of Athens Medical School, Athens, Greece; ⁷²General Hospital Sotiria, University of Athens Medical School, Athens, Greece; ⁷³Hellenic 251 Air Force General Hospital, Athens, Greece; ⁷⁴Pammakaristos Hospital, Athens, Greece; ⁷⁵Patission Prefectural General Hospital: Halkida, Athens, Greece; ⁷⁶St. Savvas Oncology Hospital of Athens, Athens, Greece; ⁷⁷General Hospital of Chania, Chania, Greece; ⁷⁸University Hospital of Ioannina, Ioannina, Greece; ⁷⁹University Hospital of Larissa, Larissa, Greece; ⁸⁰General University Hospital of Patras, Patras, Greece; ⁸¹St. Andreas General Hospital, Patras, Greece; ⁸²General Hospital of Thessaloniki George Papanikolaou, Pilea Chortiatis, Greece; ⁸³Metaxa Hospital, Piraeus, Greece; ⁸⁴General Hospital of Serres, Serres, Greece; ⁸⁵Hippokraton—General Hospital of Thessaloniki, Thessaloniki, Greece; ⁸⁶Theageio General Hospital, Thessaloniki, Greece; ⁸⁷HaEmek Medical Center, Afula, Israel; ⁸⁸Barzilai Medical Center, Ashkelon, Israel; ⁸⁹Asaf-Harofe Medical Center, Be'er Ya'akov, Israel; ⁹⁰Soroka Medical Center, Beersheba, Israel; ⁹¹Bnai Zion Medical Center, Haifa, Israel; ⁹²Carmel Medical Center, Haifa, Israel; ⁹³Rambam Medical Center, Haifa, Israel; ⁹⁴Wolfson Medical Center, Holon, Israel; ⁹⁵Hadassah Medical Center, Jerusalem, Israel; ⁹⁶Meir Medical Center, Kfar Saba, Israel; ⁹⁷The Western Galilee Hospital, Nahariya, Israel; ⁹⁸Nazareth Towers Medical Center, Nazareth, Israel; ⁹⁹Laniado Hospital, Netanya, Israel; ¹⁰⁰Rabin Medical Center, Petah Tikva, Israel; ¹⁰¹Baruch Padeh Medical Center Poriya, Tiberias, Israel; ¹⁰²Kaplan Medical Center, Rehovot, Israel; ¹⁰³Ziv Medical Center, Safed, Israel; ¹⁰⁴Tel Aviv Sourasky Medical Centre, Tel Aviv, Israel; ¹⁰⁵IRCCS San Matteo Hospital Foundation, Pavia, Italy; ¹⁰⁶University Cattolica del Sacro Cuore, Policlinico Gemelli, Rome, Italy; ¹⁰⁷VU University Medical Center, Amsterdam, The Netherlands; ¹⁰⁸Rijnstate Hospital, Arnhem, The Netherlands; ¹⁰⁹Jeroen Bosch Hospital, Den Bosch, The Netherlands; ¹¹⁰Slingeland Hospital, Doetinchem, The Netherlands; ¹¹¹Gelderse Vallei Hospital, Ede, The Netherlands; ¹¹²Elkerliek Hospital, Helmond, The Netherlands; ¹¹³Radboudumc, Nijmegen, The Netherlands; ¹¹⁴Bernhoven Hospital, Uden, The Netherlands; ¹¹⁵Maxima Medical Center, Veldhoven, The Netherlands; ¹¹⁶Warszawski Uniwersytet Medyczny, Warsaw, Poland; ¹¹⁷Centro Hospitalar de Lisboa, Lisbon, Portugal; ¹¹⁸Districtal Hospital, Brasov, Romania; ¹¹⁹Coltea Clinical Hospital, Bucharest, Romania; ¹²⁰Fundeni Clinical Institute, Bucharest, Romania; ¹²¹Clinical Center of Vojvodina, Novi Sad, Serbia; ¹²²Hospital del Mar, Barcelona, Spain; ¹²³Hospital Universitari Germans Trias i Pujol, Barcelona, Spain; ¹²⁴Hospital Del Sas, Jerez De La Frontera, Cadiz, Spain; ¹²⁵Hospital Universitario Puerta del Mar, Cadiz, Spain; ¹²⁶Institute de Investigacion Biomedica, Lleida, Spain; ¹²⁷Hospital Clinico Universitario San Carlos, Madrid, Spain; ¹²⁸Hospital Universitario Meseguer, Murcia, Spain; ¹²⁹Hospital Universitario Virgen de la Arrixaca, Murcia, Spain; ¹³⁰Hospital Universitario Central de Asturias, Oviedo, Spain; ¹³¹Hospital Universitario de Salamanca, Salamanca, Spain; ¹³²Hospital Clinico Universitario de Valencia, Valencia, Spain; ¹³³Hospital Dr. Peset, Valencia, Spain; ¹³⁴Hospital Universitario La Fe, Valencia, Spain; ¹³⁵Malarsjukhuset, Eskilstuna, Sweden; ¹³⁶Sahlgrenska University Hospital, Göteborg, Sweden; ¹³⁷Teaching Hospital of Halmstad, Halmstad, Sweden; ¹³⁸University Hospital Linköping, Linköping, Sweden; ¹³⁹Sunderby Hospital, Lulea, Sweden; ¹⁴⁰Lund University Hospital, Lund, Sweden; ¹⁴¹Orebro University Hospital, Orebro, Sweden; ¹⁴²Karolinska University Hospital, Stockholm, Sweden; ¹⁴³Södersjukhuset, Stockholm, Sweden; ¹⁴⁴Sundsvalls sjukhus, Sundsvall, Sweden; ¹⁴⁵Umea Regional Hospital, Umea, Sweden; ¹⁴⁶Uppsala University, Uppsala, Sweden; ¹⁴⁷Aberdeen Royal

Infirmiry, Aberdeen, UK; ¹⁴⁸Queen Elizabeth Hospital, Birmingham, UK; ¹⁴⁹Blackpool Victoria Hospital, Blackpool, UK; ¹⁵⁰Royal Bournemouth Hospital, Bournemouth, UK; ¹⁵¹Bradford Royal Infirmiry, Bradford, UK; ¹⁵²Addenbrooke's Hospital, Cambridge, UK; ¹⁵³Western Infirmiry, Glasgow, UK; ¹⁵⁴Harrogate District Hospital, Harrogate, UK; ¹⁵⁵Huddersfield Royal Infirmiry, Huddersfield, UK; ¹⁵⁶Hull and East Yorkshire Hospitals NHS Trust, Hull, UK; ¹⁵⁷Leeds Teaching Hospitals, Leeds, UK; ¹⁵⁸Christie Hospital, Manchester, UK; ¹⁵⁹Royal Victoria Infirmiry, Newcastle upon Tyne, UK; ¹⁶⁰Northampton General Hospital, Northampton, UK; ¹⁶¹City Hospital, Nottingham, UK; ¹⁶²John Radcliffe Hospitals NHS Trust, Oxford, UK; ¹⁶³Airedale NHS Trust, Steeton, UK; ¹⁶⁴Royal Cornwall Hospital, Truro, UK; ¹⁶⁵Mid Yorkshire Hospitals, Wakefield, UK; ¹⁶⁶Worcestershire Acute Hospitals NHS Trust, Worcester, UK; ¹⁶⁷York Hospital, York, UK

Funding The EUMDS Registry is supported by an educational grant from Novartis Pharmacy B.V. Oncology Europe, and Amgen Limited. This work is part of the MDS-RIGHT activities, which has received funding from the European Union's Horizon 2020 Research and Innovation Programme under Grant Agreement No. 634789 MDS-RIGHT—"Providing the right care to the right patient with Myelodysplastic Syndrome at the right time." The Lifelines Biobank initiative has been made possible by subsidy from the Dutch Ministry of Health, Welfare and Sport, the Dutch Ministry of Economic Affairs, the University Medical Center Groningen (UMCG the Netherlands), University Groningen, and the Northern Provinces of the Netherlands. The authors wish to acknowledge the services of the Lifelines Cohort Study, the contributing research centers delivering data to Lifelines, and all the study participants.

Author contributions Design: MH, TB, CvM, ASm, SL, TdW; provision of patients, assembly of data: DB, DC, SK, ASy, HG, MS, SL, AT, SK, PP, OS, EH-L, JC, MvK, HW, RR, EW, DWS; statistical analysis and interpretation: MH, TB, CvM, ASm, TdW; manuscript writing: all authors; final approval: all authors.

Compliance with ethical standards

Conflict of interest CvM: project manager of the EUMDS Registry, is funded by the EUMDS and MDS-RIGHT project budget; ASm: research funding from Novartis, Cilag-Janssen, and Boehringer Ingelheim; ASy: honoraria and consulting fees from Amgen, Celgene/GenesisPharma, Genzyme/Sanofi, Gilead, Janssen-Cilag, Pfizer, MSD, and Novartis; HG: honoraria from Celgene, Novartis, and Alexion; SK: honoraria from Novartis, Jazz, and Celgene; EH-L: research funding from Celgene; NB: research funding from Novartis, Bristol Meyer Squibb, Pfizer, Ariad, MSD, Astellas, Xenikos, and Celgene, educational grant from Novartis, Celgene, and Janssen-Cilag; DWS: paid employee of RadboudUMC, which offers hepcidin measurements via Hepcidinanalysis.com at a fee for service basis; TdW: research funding from Amgen, Celgene, and Novartis, as project coordinator EUMDS. The other authors declare that they have no conflict of interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if

changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>.

References

1. Cazzola M, Della Porta MG, Malcovati L. Clinical relevance of anemia and transfusion iron overload in myelodysplastic syndromes. *Hematology Am Soc Hematol Educ Program*. 2008;1:166–75.
2. Malcovati L, Porta MG, Pascutto C, Invernizzi R, Boni M, Travaglino E, et al. Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. *J Clin Oncol*. 2005;23:7594–603.
3. Leitch HA, Fibach E, Rachmilewitz E. Toxicity of iron overload and iron overload reduction in the setting of hematopoietic stem cell transplantation for hematologic malignancies. *Crit Rev Oncol Hematol*. 2017;113:156–70.
4. Shenoy N, Vallumsetla N, Rachmilewitz E, Verma A, Ginzburg Y. Impact of iron overload and potential benefit from iron chelation in low-risk myelodysplastic syndrome. *Blood*. 2014;124:873–81.
5. de Swart L, Reiniers C, Bagguley T, van Marrewijk C, Bowen D, Hellström-Lindberg E, et al. Labile plasma iron levels predict survival in patients with lower-risk myelodysplastic syndromes. *Haematologica*. 2018;103:69–79.
6. Porter JB, de Witte T, Cappellini MD, Gattermann N. New insights into transfusion-related iron toxicity: Implications for the oncologist. *Crit Rev Oncol Hematol*. 2016;99:261–71.
7. Ganz T, Nemeth E. Heparidin and iron homeostasis. *Biochim Biophys Acta*. 2012;1823:1434–43.
8. Kautz L, Jung G, Valore EV, Rivella S, Nemeth E, Ganz T. Identification of erythroferrone as an erythroid regulator of iron metabolism. *Nat Genet*. 2014;46:678–84.
9. Ye ZW, Zhang J, Townsend DM, Tew KD. Oxidative stress, redox regulation and diseases of cellular differentiation. *Biochim Biophys Acta*. 2015;1850:1607–21.
10. Pimková K, Chrastinová L, Suttar J, Štikarová J, Kotlín R, Čermák J, et al. Plasma levels of aminothiols, nitrite, nitrate, and malondialdehyde in myelodysplastic syndromes in the context of clinical outcomes and as a consequence of iron overload. *Oxid Med Cell Longev*. 2014;2014:416028.
11. Pilo F, Angelucci E. A storm in the niche: Iron, oxidative stress and haemopoiesis. *Blood Rev*. 2018;32:29–35.
12. de Souza GF, Barbosa MC, Santos TE, Carvalho TM, de Freitas RM, Martins MR, et al. Increased parameters of oxidative stress and its relation to transfusion iron overload in patients with myelodysplastic syndromes. *J Clin Pathol*. 2013;66:996–8.
13. Santini V, Girelli D, Sanna A, Martinelli N, Duca L, Campostrini N, et al. Heparidin levels and their determinants in different types of myelodysplastic syndromes. *PLoS ONE*. 2011;6:e23109.
14. Ambaglio I, Malcovati L, Papaemmanuil E, Laarakkers CM, Della Porta MG, Galli A, et al. Inappropriately low hepcidin levels in patients with myelodysplastic syndrome carrying a somatic mutation of SF3B1. *Haematologica*. 2013;98:420–3.
15. Zipperer E, Post JG, Herkert M, Kündgen A, Fox F, Haas R, et al. Serum hepcidin measured with an improved ELISA correlates with parameters of iron metabolism in patients with myelodysplastic syndrome. *Ann Hematol*. 2013;92:1617–23.