This is a repository copy of *Toxic iron species in lower-risk myelodysplastic syndrome patients: course of disease and effects on outcome*.

White Rose Research Online URL for this paper: 
http://eprints.whiterose.ac.uk/165856/

Version: Published Version

**Article:**
Hoeks, Marlijn, Bagguley, Tim orcid.org/0000-0002-6150-3467, van Marrewijk, Corine et al. (23 more authors) (2020) Toxic iron species in lower-risk myelodysplastic syndrome patients: course of disease and effects on outcome. Leukemia: official journal of the Leukemia Society of America, Leukemia Research Fund, U.K. ISSN 1476-5551

https://doi.org/10.1038/s41375-020-01022-2

**Reuse**
This article is distributed under the terms of the Creative Commons Attribution (CC BY) licence. This licence allows you to distribute, remix, tweak, and build upon the work, even commercially, as long as you credit the authors for the original work. More information and the full terms of the licence here: 
https://creativecommons.org/licenses/

**Takedown**
If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.
Toxic iron species in lower-risk myelodysplastic syndrome patients: course of disease and effects on outcome

Marlijn Hoeks 1,2,3 · Tim Bagguley 4 · Corine van Marrewijk 3 · Alex Smith 4 · David Bowen 5 · Dominic Culligan 6 · Seye Kolade 7 · Arghis Symeonidis 8 · Hege Garelius 9 · Michail Spanoudakis 10,11 · Saskia Langemeije 3 · Rian Roelofs 12 · Erwin Wiegerinck 12 · Aurelia Tatic 13 · Sally Killick 14 · Panagiotis Panagiotidis 15 · Oana Stanca 16 · Eva Hellström-Lindberg 17 · Jaroslav Cermak 18 · Melanie van der Klauw 19 · Hanneke Wouters 19 · Marian van Kraaij 3 · Nicole Blijlevens 3 · Dorine W. Swinkels 12 · Theo de Witte 20 · on behalf of the EUMDS Registry Participants

Received: 30 April 2020 / Revised: 3 August 2020 / Accepted: 6 August 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.
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.**

|                          | N (%) |
|--------------------------|-------|
| 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) |
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) \((r = 0.15, p < 0.001, \text{Fig. S1})\). 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 \((r = -0.34, p = 0.007, \text{Fig. S2})\).

Serum ferritin levels were elevated in all subgroups with a mean value of 858 µg/L at visit 5. The highest serum ferritin levels were observed in the RS-TD group (mean value at visit 5: 2092 µg/L, Table S1). Serum ferritin increased significantly per visit in the RS-TD group (beta 454.46 µg/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 µmol/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-

| Table 1 (continued) | N (%) |
|---------------------|-------|
| **ESA**             |       |
| No                  | 159 (62.1) |
| Yes                 | 97 (37.9)  |
| **Iron chelation**  |       |
| No                  | 241 (94.1) |
| Yes                 | 15 (5.9)   |
| Desferoxamine       | 5 (2.0)    |
| Deferasiro/preroxiox | 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 erythroid stimulating agents.
In line with the effect of LPI on OS progression-free survival (Table S5), elevated TSAT did in the transfusion-independent group 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 ≥ 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 non-RS 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 reticuloendothelial 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 erythroferrone, 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 Pinten-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. Stauder1, A. Walder2, M. Pfeilstöcker3, A. Schoenmetzler-Makrai1, S. Burgstaller1, J. Thaler1, I. Mandac Rogulj2, M. Krejci3, J. Voglova3, S. Rohon3, A. Jonasova2, J. Cermak2, D. Mikulenková3, I. Hochova3, P. D. Jensen3, A. Jona-Ades3, V. Siguret3, P. Fenaux4, L. Legros4, B. de Renzis4, L. Kjeldsen4, I. H. Dufva3, P. Rohon3, B. Slama5, P. Fenaux4, B. Chou4, S. Cheze4, D. Klempné2, B. Salles4, B. de Renzis5, L. Willems4, D. De Prost4, J. Gutnecht4, A. Courby5, V. Siguret4, G. Tertian4, L. Pascal5, M. Chaury4, E. Wattel8, A. Guerci5, L. Legros4, P. Fenaux4, R. Itzykson5, L. Advé5, F. Isnard5, L. Sanhe5, R. Benramdane5, A. Stamatoula5, M. Hoeks et al.

Springer Nature
S. Ame, O. Beyne-Raupz, E. Gyan, U. Platzerbecker, C. Badrakhan, M. Lübben, R. Schlenk, Kotsianidou, C. Tsatala, V. Pappe, A. Galanopoulos, E. Michi, P. Panagiotidis, N. Viniou, A. Katsigianis, P. Roussou, E. Terpos, A. Kostourou, Z. Kartasis, A. Poulis, K. Pall, V. Briassoulis, E. Hatzimichael, G. Vassiopoulos, A. Symeonidi, A. Kouraki, P. Zikos, A. Anagnostopoulou, K. Megalakak, M. Protopapa, V. Vlachakis, P. Konstantinidou, G. Stermer, A. Nemetz, U. Gotwin, O. Cohen, M. Koren, E. Levy, V. Greenbaum, S. Gino-Moor, M. Price, O. Yifrash, A. Winder, N. Goldshmidt, S. Elias, R. Sabag, I. Hellmann, M. Ellis, A. Braester, H. Rosenbaum, S. Berdichevsky, G. Izhako, O. Wolf, S. Yeganesh, O. Katz, K. Filanovsky, N. Dali, M. Mittelman, L. Malcovati, L. Fianchi, A. vd Loosdrecht, V. Matthijssen, A. Herbers, H. Fujii, N. Aboosi, F. de Vries, G. Vassilopoulos, J. Jacob, S. Langemeijer, M. MacKenzie, C. Lensen, P. Kuippe, K. Madry, M. Camara, A. Almeida, G. Vulkani, S. Stanca Ciocan, A. Tatic, A. Savic, C. Pedro, B. Xicos, P. Leiva, J. Munoz, V. Betes, B. Benavente, L. Mozano, M. Martinez, P. Iniesta, T. Bernal, M. Diez Campeo, D. Torno, R. Andreu Lapiedra, G. Sanz, E. Hesse Sundin, H. Garelus, C. Karlsson, P. Antonuv, A. Jönsson, L. Brandefors, L. Nilsson, P. Kozlowski, E. Hellstrom-Lindberg, M. Grövall, K. Larsson, J. Wallvik, F. Lorenz, E. Ceballos, D. Culligan, C. Credack, S. Kolade, P. Cahan, S. Killick, S. Ackroyd, C. Wong, A. Warren, D. Drummond, H. Hall, K. Rothwell, S. Green, S. Ali, D. Bowen, M. Karakanta, M. Dennis, G. Jone, J. Parker, A. Bowen, R. Radia, E. Das-Gupta, P. Vyai, E. Nga, D. Creagh, J. Ashcroft, J. Mills, B. Bond.

2Medical University of Innsbruck, Innsbruck, Austria; 2Bezirkshrankenhaus, Lienz, Austria; 21Hanusch Krankenhaus, Vienna, Austria; 2Klinikum Kreuzschwestern, Wels, Austria; 2Clinical Hospital Merkur, Zagreb, Croatia; 2The University Hospital Brno, Brno, Czech Republic; 2Charles University Faculty of Medicine, Hradec Králové, Czech Republic; 2University Hospital, Olomouc, Czech Republic; 2General University Hospital, 1st Clinic of Internal Medicine, Prague, Czech Republic; 2General University Hospital, Institute of Hematology and Blood Transfusion, Prague, Czech Republic; 2University Hospital Motol, Prague, Czech Republic; 2University Hospital Aalborg, Denmark; 2University Hospital, Aarhus, Denmark; 2University Hospital Rigshospitalet, Copenhagen, Denmark; 2Herlev Hospital, Herlev Ringvej, Herlev, Denmark; 2Odense University Hospital, Odense, Denmark; 2Hospital Center D´antibes Juan-Les-Pins, Antibes, France; 2Centre Hospital Avignon, France; 2Hospital Avicenne, Bobigny, France; 2Centre Hospital Boulogne-sur-Mer, Boulogne-sur-Mer, France; 2Centre Hospitalier Universitaire de Clermont-Ferrand, Clermont-Ferrand, France; 2Hotel Dieu Cochin, France; 2Louis-Mourier Hospital, Colombes, France; 2CHU Frejus Saint Raphael, Frejus, France; 2CHU Albert Michallon, Grenoble, France; 2Hospital Charles-Foix Ap-Hp, Ivry-sur-Seine, France; 2Hospital Bicetre, Le Kremlin-Bicetre, France; 2Hospital St Vincent de Paul, Lille, France; 2CHU Limoges Hospital Dupuytren, Limoges, France; 2Hospital Edouard Herriot, Lyon, France; 2CHU Nancy, Hospital Brabois (Vandouvre Les Nancy), Nancy, France; 2CHU de Nice, Hospital l’Arche, Nice, France; 2Hospital St Louis, Paris, France; 2Hospital Saint-Antoine, Paris, France; 2Centre Hospitalier Paris, 41 Centre Hospitalier Paris, France; 2CHU de Rouen, Hospital Charles-Nicolle, Rouen, France; 2CHU Hospital Haute-pierrre de Strasbourg, Strasbourg, France; 2CHU Toulouse, Hospital Purpan, Toulouse, Toulouse, France; 2CHR du Tours, Tours, France; 2University Hospital Carl Gustav Carus, Dresden, Germany; 2HELIOS: St. Johannes Hospital in Hamborn, Duisburg, Germany; 2Heinrich-Heine University Hospital, Dusseldorf, Germany; 2University Hospital Freiburg, Freiburg, Germany; 2University Hospital Ulm, Ulm, Germany; 2Democritus University of Thrace, Alexandroupolis, Greece; 2General Hospital Attikon, University of Athens Medical School, Athens, Greece; 2General Hospital G. Gennimatas, Athens, Greece; 2General Hospital Laikon, University of Athens Medical School, Athens, Greece; 2General Hospital Sotiria, University of Athens Medical School, Athens, Greece; 2Hellenic 251 Air Force General Hospital, Athens, Greece; 2Pammakaristos Hospital, Athens, Greece; 2Patisson Prefectural General Hospital: Halkida, Athens, Greece; 2St. Savvas Oncology Hospital of Athens, Athens, Greece; 2General Hospital of Chania, Chania, Greece; 2University Hospital of Ioannina, Ioannina, Greece; 2University Hospital of Larissa, Larissa, Greece; 2General University Hospital of Patras, Patras, Greece; 2St. Andreas General Hospital, Patras, Greece; 2General Hospital of Thessaloniki George Papanikolaou, Pilea Chortisias, Greece; 2Metaxa Hospital, Piraeus, Greece; 2General Hospital of Serres, Serres, Greece; 2Hippokration—General Hospital of Thessaloniki, Thessaloniki, Greece; 2Theageneio General Hospital, Thessaloniki, Greece; 2HaEmek Medical Center, Afula, Israel; 2Barzilai Medical Center, Ashkelon, Israel; 2Asaf-Harofe Medical Center, Be’er Ya’akov, Israel; 2Soroka Medical Center, Beersheba, Israel; 2Bnai Zion Medical Center, Haifa, Israel; 2Carmel Medical Center, Haifa, Israel; 2Rambam Medical Center, Haifa, Israel; 2Wolfson Medical Center, Holon, Israel; 2Hadassah Medical Center, Jerusalem, Israel; 2Meir Medical Center, Kfar Saba, Israel; 2The Western Galilee Hospital, Nahariya, Israel; 2Nazereth Towers Medical Center, Nazareth, Israel; 2Laniado Hospital, Netanya, Israel; 2Rabin Medical Center, Petah Tikva, Israel; 2Baruch Paduch Medical Center Portya, Tiberias, Israel; 2Kaplan Medical Center, Rehovot, Israel; 2Ziv Medical Center, Safed, Israel; 2Tel Aviv Sourasky Medical Centre, Tel Aviv, Israel; 2IRCCS San Matteo Hospital Foundation, Pavia, Italy; 2University Catolica del Sacro Cuore, Policlinico Gemelli, Rome, Italy; 2University Medical Center, Amsterdam, The Netherlands; 2Rijnstate Hospital, Arnhem, The Netherlands; 2Jeroen Bosch Hospital, Den Bosch, The Netherlands; 2Slingeland Hospital, Doetinchem, The Netherlands; 2Gelderse Vallei Hospital, Ede, The Netherlands; 2Elkerliek Hospital, Helmond, The Netherlands; 2Radboudumc, Nijmegen, The Netherlands; 2Barnhorn Hospital, Uden, The Netherlands; 2Maxima Medical Center, Veldhoven, The Netherlands; 2Warsawski Uniwersytet Medycyny, Warsaw, Poland; 2Centro Hospitalar de Lisboa, Lisbon, Portugal; 2District Hospital Brasov, Romania; 2Coltea Clinical Hospital, Bucharest, Romania; 2Pundeni Clinical Institute, Bucharest, Romania; 2Clinical Center of Vojvodina, Novi Sad, Serbia; 2Hospital del Mar, Barcelona, Spain; 2Hospital Universitari Germans Trias i Pujol, Barcelona, Spain; 2Hospital Del Sas, Jerez De La Frontera, Cadiz, Spain; 2Hospital Universitario Puerta del Mar, Cadiz, Spain; 2Institute of Investigacion Biomédica, Lleida, Spain; 2Hospital Clinico Universitario San Carlos, Madrid, Spain; 2Hospital Universitario Meseguer, Murcia, Spain; 2Hospital Universitario Central de Asturias, Oviedo, Spain; 2Hospital Universitario de Salamanca, Salamanca, Spain; 2Hospital Clinico Universitario de Valencia, Valencia, Spain; 2Hospital Dr. Peset, Valencia, Spain; 2Hospital Universitario La Fe, Valencia, Spain; 2Malarjukhuset, Eskilstuna, Sweden; 2Sahlgrenska University Hospital, Göteborg, Sweden; 2Teaching Hospital of Halmstad, Halmstad, Sweden; 2University Hospital Linköping, Linköping, Sweden; 2Sunderby Hospital, Lulea, Sweden; 2Lund University Hospital, Lund, Sweden; 2Orebro University Hospital, Orebro, Sweden; 2Karolinska University Hospital, Stockholm, Sweden; 2Södersjukhuset, Stockholm, Sweden; 2Sundsvalls sjukhus, Sundsvall, Sweden; 2Umea Regional Hospital, Umea, Sweden; 2Uppsala University, Uppsala, Sweden; 2Aberdeen Royal
Infirmary, Aberdeen, UK; 148Queen Elizabeth Hospital, Birmingham, UK; 149Blackpool Victoria Hospital, Blackpool, UK; 150Royal Bournemouth Hospital, Bournemouth, UK; 151Bradford Royal Infirmary, Bradford, UK; 152Addenbrooke’s Hospital, Cambridge, UK; 153Western Infirmary, Glasgow, UK; 154Harrogate District Hospital, Harrogate, UK; 155Huddersfield Royal Infirmary, Huddersfield, UK; 156Hull and East Yorkshire Hospitals NHS Trust, Hull, UK; 157Leeds Teaching Hospitals, Leeds, UK; 158Christie Hospital, Manchester, UK; 159Royal Victoria Infirmary, 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 Myelo-Dysplastic 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, 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 EUUMDS. 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, Travaglini 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, Vallumsetta 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. Hepcidin and iron homeostasis. Biochim Biophys Acta. 2012;1823:1433–43.
8. Kautz L, Jung G, Valore EV, Rivella S, Nemeth E, Ganz T. Identiﬁcation of erythropherrone as an erythroid regulator of iron metabolism. Nat Genet. 2014;46:878–84.
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, Suttnar J, 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. 2016;69:396–9.
13. Santini V, Girelli D, Sanna A, Martinelli N, Duca L, Campostrini N, et al. Hepcidin levels and their determinants in different types of myelodysplastic syndromes. PLoS ONE. 2011;6:e23109.
14. Ambaglio I, Malcovati L, Papaemmanuil E, Laurents KM, 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.