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Savic, Aleksandar, TAYLOR, ADELE, Fenaux, Pierre et al. (2026) Clinical outcomes of patients with lower risk myelodysplastic syndrome from EUMDS registry eligible for transplantation: Implications for transplantation strategies. British Journal of Haematology. ISSN: 0007-1048

https://doi.org/10.1111/bjh.70384

Clinical outcomes of patients with lower-risk myelodysplastic syndrome from EUMDS registry eligible for transplantation: implications for transplantation strategies

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Word count: 3282

Abstract word count: 199 words

Figures: 3

Tables: 4

Supplementary Figures: 1

Supplementary Tables: 4

Running title: Patients with lower-risk MDS eligible for transplant

Keywords: myelodysplastic syndrome; allogeneic hematopoietic stem cell transplantation; survival; comorbidity; performance status

Acknowledgements: The authors and members of the steering committee of the EUMDS registry would like to thank all local investigators (list is in Table S4), operational team members, data managers, research nurses and patients for their contribution to the EUMDS Registry. We would like to thank Editage for English language editing.

Conflict of interest disclosure

AS reports a consulting or advisory role at Pfizer, Amicus Therapeutics, Roche; speakers' bureau from Takeda, Abbvie, Roche, AstraZeneca, and Sandoz; and travel accommodations and expenses from Amicus Therapeutics, Takeda, Astra Zeneca, and Roche.

ASy reports honoraria from Abbvie, Astra-Zeneca, BMS, Glaxo, Janssen, Novartis, Pfizer, Sanofi; and participation in advisory/DSM board for Abbvie, Astra-Zeneca, BMS, Glaxo, Janssen, Novartis, Sanofi, and Sobi.

CC reports honoraria from Novartis and Astellas and travel support from Novartis

MM reports consulting fees from BioCenvergence, TALENT Group and Dr. Reddy's; honoraria for lectures from Dr. Reddy's and FibroGen; and meeting/travel support from FibroGen.

VP reports research funding from BMS; receipt of honoraria from BMS, GSK, Novartis, Johnson & Johnson, AOP-Health, and Takeda; and travel support/conference attendance from Johnson & Johnson, Pfizer, Gilead, GSK, and AOP-Health.

GS reports research funding from Novartis, BMS/Celgene, Janssen, Takeda, Amgen, Menarini, Bayer, and Pfizer; honoraria from Chugai Pharma, AstraZeneca, and GlaxoSmithKline; consulting/advisory fees from Novartis, and ExCellThera; speakers' bureau from BMS/Celgene; and travel support from BeiGene.

MDA reports consulting fees from BMS; and meeting/travel support from Sanofi.

DC reports honoraria for speaking at educational events from Celgene/BMS; support for attending haematology conferences from Celgene/BMS; and participation in advisory board for Roche and Celgene/BMS.

IK reports research funding from BMS; and lecture honoraria, meeting/travel support, and participation in advisory/DSM board for BMS and Janssen.

CvM, project manager of the EUMDS Registry, is funded by the EUMDS (educational grants from Novartis Pharmacy B.V. Oncology Europe, BMS/Celgene International, Amgen Limited, Janssen Pharmaceutica, Takeda Pharmaceuticals International, Lumanity RWE Limited and Gilead Sciences Inc).

TdW reports research funding (educational grants for EUMDS Registry) from Novartis Pharmacy B.V. Oncology Europe, Amgen Limited, BMS/Celgene International, Janssen Pharmaceutica, and Takeda Pharmaceuticals International, and EC (H2020).

AT, PF, JC, SL, EH-L, TC, PP, ASm, SC, and LM report no conflict of interest.

Data availability statement

This article is based on data from the European MDS Registry (www.EUMDS.org). The data are not publicly available due to privacy or ethical restrictions. Access to data that support the findings of this study can be obtained from the EUMDS project management office upon reasonable request. A fee might be required.

Author contributions: Aleksandar Savic, Adele Taylor, Alex Smith, Simon Crouch, Corine van Marrewijk, Theo de Witte, and Luca Malcovati conceptualized and designed the study. Aleksandar Savic, Pierre Fenaux, Argiris Symeonidis, Catherine Cargo, Moshe Mittelman, Verena Petzer, Guillermo Sanz, Jaroslav Čermák, Saskia Langemeijer, Eva Hellström-Lindberg, Comont Thibault, Maud D'Aveni, Dominic Culligan, Ioannis Kotsianidis, Panagiotis Panagiotidis, Theo de Witte, and Luca Malcovati gathered the patients and collected the data.

Aleksandar Savic, Adele Taylor, Alex Smith, Simon Crouch, Corine van Marrewijk, and Luca Malcovati analysed and interpreted the results. Aleksandar Savic, Adele Taylor, Alex Smith, Corine van Marrewijk, and Luca Malcovati drafted the manuscript. All authors reviewed the results and approved the final version of the manuscript.

Funding information

The EUMDS Registry is supported by an educational grant from Novartis Pharmacy B.V. Oncology Europe, Bristol-Myers Squibb/Celgene International, Amgen Limited, Janssen Pharmaceutica, Takeda Pharmaceuticals International, Lumanity RWE Limited and Gilead Sciences Inc. This work is part of the MDS-RIGHT activities, which has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement no. 634789 ‘Providing the right care to the right patient with MyeloDysplastic Syndrome at the right time’.

Ethics approval statement

The EUMDS Registry was approved by each institution’s Ethics Committee in accordance with national legislation.

Patient consent statement

Written informed consent was obtained from each patient.

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Not applicable.

Clinical trial registration

The EUMDS Registry (ClinicalTrials.gov: Identifier NCT00600860).

Abstract

Selecting eligible allogeneic hematopoietic stem-cell transplantation (allo-HSCT) candidates with low-risk and intermediate-risk myelodysplastic syndrome (MDS) remains controversial. The International Working Group (IWG) for MDS prognosis identified a revised international prognostic scoring system (IPSS-R) score > 3.5 for benefits from early transplantation; the MDS-RIGHT group uses a broader set of poor-risk features. We analysed 1145 lower-risk MDS (lower-risk and intermediate-risk IPSS-R) patients aged <75 years, using real-world European Myelodysplastic Syndromes registry data and identifying those meeting IWG or MDS-RIGHT criteria for allo-HSCT at baseline and 6-month follow-up. Fit patients were characterised by Karnofsky score ≥ 70 and hematopoietic cell transplantation-specific comorbidity index < 3. We evaluated clinical outcomes of transplant candidates, including survival, disease-progression risk, new-comorbidity risk, and performance-status decline. The IWG criterion, and not MDS-RIGHT criteria, identified patients with lower-risk and intermediate-risk MDS with poorer baseline survival. Fit lower-risk patients showed 2-year cumulative risks of incident comorbidity and performance-status deterioration of 20% and 5%, respectively. In summary, IWG and MDS-RIGHT features identify patients with lower- or intermediate-risk MDS as candidates for early transplantation. Lower-risk patients fit for transplantation have a cumulative incidence of adverse outcomes possibly jeopardising transplantation eligibility and should be carefully selected when planning delayed transplantation strategies.

Keywords: myelodysplastic syndrome; allogeneic hematopoietic stem cell transplantation; survival; comorbidity; performance status

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only curative treatment for patients with myelodysplastic syndrome (MDS).[1,2] However, advanced age,[3] comorbidities, performance status, and frailty are important patient-related factors that significantly affect patient selection and the outcome of allo-HSCT,

substantially increasing transplant-related mortality and toxicity.[1,2] There is a consensus that allo-HSCT is indicated for high-risk patients[1,4-6] soon after diagnosis, whereas the selection of eligible lower- and intermediate-risk patients for transplantation and timing of this intervention remain controversial.

The International Working Group (IWG) for MDS prognosis defines intermediate-risk patients as having a revised international prognostic scoring system (IPSS-R) score >3.5,[7] and this threshold is accepted as an indication for transplantation in the European Society for Medical Oncology[8] and National Comprehensive Cancer Network MDS guidelines[5] and a recent review paper[9] (hereafter referred to as the IWG criteria).

An international expert panel, including members of the European Society for Blood and Marrow Transplantation, European LeukemiaNet, the Blood and Marrow Transplant Clinical Trial Group, and the International Myelodysplastic Syndromes Foundation, recommended allo-HSCT in good-performance status (fit) patients with lower and intermediate IPSS-R risk with poor risk features (i.e., poor or very poor risk cytogenetic/molecular characteristics, persistent blast increase (>50% increase from baseline or with >15% bone marrow blasts), life-threatening cytopenia (neutrophil count $< 0.3 \times 10^9$/L; platelet count $<30 \times 10^9$/L), and high transfusion intensity (≥2 units/month for 6 months).[1] The MDS-RIGHT research group established guidelines to provide the right care to the right patient with MDS at the right time; the same recommendations were adopted, and a poor-risk feature defined by a drop in platelets >25% within 6 months after diagnosis was added (hereafter referred to as the MDS-RIGHT criteria).[10-12]

Additional critical factors for transplant decisions include performance status and non-haematological comorbidities, which significantly limit transplant eligibility. The MDS-RIGHT research group defined patients fit for transplant based on Karnofsky scores ≥ 70 and hematopoietic cell transplantation-specific comorbidity index (HCT-CI) scores < 3.[10,13] Although there are robust data on performance status and comorbidities at discrete time points, including the time of diagnosis and transplantation, the information retrieved from transplant registries suffers from severe selection bias and robust data on temporal dynamics are lacking. This is relevant when planning delayed transplantation strategies in lower-risk patients with MDS as the decline in performance status and occurrence of relevant non-haematological comorbidities might translate into a loss of eligibility for transplantation.

The primary aim of this study was to analyse relevant clinical outcomes of lower-risk MDS (very low-, low-, and intermediate-risk IPSS-R) candidates for transplantation in patients aged <75 years. These included survival, risk of disease progression, risk of time-dependent co-morbidities, and deterioration in performance status using unbiased prospective real-world registry data as a basis for transplantation decision making.

Methods

Patients

The European Myelodysplastic Syndromes (EUMDS) registry is a prospective longitudinal registry of newly diagnosed adult patients with MDS who are registered within 3 months of diagnosis from centres in 17 countries across Europe and Israel.[3,14] Data were collected at baseline and 6-month follow-up visits. Patients were followed until death, loss to follow-up, or withdrawal of informed consent.

The EUMDS Registry (ClinicalTrials.gov: Identifier NCT00600860) was approved by each Institutional Review Board and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient.

Patients in the EUMDS registry with very low-, low-, and intermediate-risk IPSS-R scores were included. The following parameters were analysed: demographics, body mass index, laboratory parameters, diagnoses according to the 2016 WHO classification,[15] IPSS-R risk group,[16] high-intensity transfusion dependency (≥2/months),[1] Karnofsky performance score, HCT-CI,[13] MDS treatment, progression to high-risk MDS (defined as a progression to high and very high IPSS-R risk groups), and progression to acute myeloid leukaemia (AML). The transplant candidates were divided into two groups. The first group included patients with intermediate IPSS-R risk score >3.5 according to the IWG recommendations.[7] The second group included patients with poor-risk features according to the MDS-RIGHT group recommendations[10]: life-threatening cytopenia (neutrophil count $<0.3 \times 10^9$/L; platelet count $<30 \times 10^9$/L); persistent blast increase (>50% increase from baseline or with >15% bone marrow blasts); poor or very-poor risk cytogenetics; high transfusion intensity ≥ 2 units/month for 6 months; decrease in platelets > 25% for 6 months; and progression to a higher-risk IPSS-R group. Patients with IPSS-R <3.5 and those without very-poor risk features according to the MDS-RIGHT criteria were deemed non-

candidates for allo-HSCT. Patients fit for transplantation were defined according to the MDS-RIGHT group criteria, Karnofsky score ≥ 70, and HCT-CI score < 3.[10] Patients were identified as eligible for transplantation based on data collected in the first year of registration from information recorded at the baseline line visit, visit 2 (6 months) and visit 3 (12 months).

We collected transplant status for 265 patients who met either transplant criteria at baseline, along with data already collected in the registry (12 transplanted patients); in total, 57 patients underwent transplantation (37 men and 20 women; 11 in the 65–74 years age group). Twenty-six patients with low risk MDS underwent transplantation; 28 patients underwent transplantation post-progression to high-risk MDS/AML (risk status for five patients was unknown).

Statistical analysis

Standard descriptive methods were used to describe patient characteristics at baseline and 6-months follow-up with frequencies for categorical variables and means and standard deviations for continuous variables. Overall survival (OS), progression-free survival (PFS), and AML-free survival (AMLFS) were estimated from the first visit at which the patient met the transplantation criteria and patients were censored at the date of transplantation, withdrawal from the study, loss to follow-up, or last visit. For the OS analysis of the transplant cohort, patients were censored at the withdrawal from the study, loss to follow-up, or last visit. Survival was analysed using the Kaplan–Meier method and groups were compared using the log-rank test. Cumulative incidences were estimated using the Aalen-Johansen method for the occurrence of new comorbidities with progression to AML and death treated as competing risks. The cumulative incidence of progression to AML directly from lower-risk and intermediate-risk IPSS-R patients was estimated using progression to higher-risk MDS and death as competing risks, and the cumulative incidence of a decline in Karnofsky performance status score below 70 was estimated using death as a competing risk. We also used a Fine-Gray model to estimate the cumulative incidence of a new comorbidity or decline in Karnofsky performance status score below 70 using death as a competing risk, red blood cell transfusion status as a time-varying covariate, and all other covariates fixed at baseline. All analyses were performed using Stata 18.0 (StataCorp, College Station, TX, USA).

Results

Clinical and prognostic characteristics of the population

In total, 2402 patients were registered from April 2008 to April 2022, and 2284 patients (1145 aged <75 years) for whom IPPS-R could be calculated were classified as lower-risk or intermediate-risk. Baseline clinical and prognostic characteristics of patients aged <75 years are shown in Table 1. In total, at baseline 208 patients (18.2%) were candidates for transplantation using either transplant criteria (IPSS-R >3.5: 149 [13.0%]; MDS-RIGHT: 96 [8.4%]); 37 (17.7%) of the 208 patients were recommended for transplantation using both strategies. The age and sex distribution were comparable for all patients; the mean age of the transplant candidates was 65.0 years, and the male-to-female ratio was 2:1. As expected, transplant candidates were more likely to have higher risk disease (WHO diagnosis and poorer risk factors as the components of the IPSS-R score) but had similar Karnofsky performance status (Table 1). Candidates for transplantation were treated at baseline as follows: erythropoiesis-stimulating agents, 20%; hypomethylating agents, 4%; corticosteroids, 6%; immunosuppressive agents, 1%; granulocyte colony-stimulating factor, 2%; and hydroxyurea, 1%.

When the MDS-RIGHT criteria to define fitness for transplant were applied, 124 (10.8%) patients were candidates for transplant at baseline, 88 (7.7%) of these were candidates for transplant according to the IPSS-R > 3.5 criterion, 60 (5.2%) were candidates according to the MDS-RIGHT criteria, and 24 (19%) were selected for transplantation using both strategies.

The characteristics of the candidate patients for transplantation who first met the criteria at the 6-month and 12-month follow-up are presented in Table S1 and Figure S1. At the 6-month follow-up, 47 (5%) of the 986 patients were candidates for transplantation according to the IPSS-R > 3.5 criterion and 211 (21%) were candidates according to the MDS-RIGHT criteria. At the 12-month follow-up, 39 (5%) patients were new candidates for transplant based on the IPSS-R > 3.5 criterion and 72 (9%) of 817 patients were candidates for transplant based on MDS-RIGHT criteria (first meeting the criteria). The total number of candidates for transplant that reached

the criteria at any point during follow-up according to the IWG criteria was 174 (15.2%) and that according to the MDS-RIGHT criteria was 343 (29.9%) of 1145 patients.

Survival and risk of disease progression in the study population

The median follow-up time was 5.6 years (95% confidence interval [CI]: 5.2–6.1); the median survival of all 1145 very low-, low-, and intermediate-IPSS-R-risk patients in the EUMDS registry was 6.1 years (95%CI: 5.4–6.6). Median OS, PFS, and AMLFS rates in transplant candidates at baseline according to the IWG criterion differed significantly compared to noncandidate patients but not in transplant candidates at baseline according to MDS-RIGHT criteria (Table 2, Figure 1). However, the MDS-RIGHT criteria were significant at baseline in OS, PFS, and AMLFS analyses of 2284 patients from the EUMDS registry, regardless of age or transplant eligibility ($p<0.01$, Table S2). MDS-RIGHT candidates with IPSS-R > 3.5 (25% of the IWG group) had unfavourable median OS, PFS, and AMLFS rates compared with MDS-RIGHT candidates with IPSS-R ≤ 3.5 ($p <0.05$, Table 2, Figure 2A). Most MDS-RIGHT patients with IPSS-R ≤ 3.5 fulfilled only one MDS-RIGHT criterion for transplant at baseline, with the severe cytopenia criteria dominating: 45% and 55% of patients had ANC $< 0.3 \times 10^9$/L and platelet count $< 30 \times 10^9$/L, respectively. There were no significant differences in OS, PFS, or AMLFS on comparing patients with single severe cytopenia with the remaining MDS-RIGHT patients with IPSS-R ≤ 3.5, which included patients with poor cytogenetics and patients who fulfilled more than one criterion (Table S3).

Median OS was better in fit patients than in nonfit patients; the median survival of the 660 fit patients was 6.4 (95%CI: 5.5–7.4) years, whereas that of 485 unfit patients was 5.7 (95%CI: 4.5–6.5) years ($p < 0.001$). Outcomes (OS, PFS, and AMLFS) differed significantly between candidate and non-candidate patients who first met the criteria at 6-months according to either the IWG or MDS-RIGHT criteria (Table 2).

Median OS (from date-reaching criteria) of the candidate patients selected at any time point during follow-up (visits 1–3) was poorer in the IWG group than in the MDS-RIGHT group: OS: 2.5 (95%CI: 2.1–2.8) years and 3.6 (95%CI: 3.0–4.3) years, respectively. Similar observations were noted for median PFS (IWG, 1.8 [95%CI: 1.3–2.2]; MDS-RIGHT, 2.9 [95%CI: 2.3–3.4]), and AMFS (IWG, 2.4 [95%CI 2.0–2.9]; MDS Right, 3.7 [95%CI: 3.1–4.4]).

Median OS of the 581 non-transplanted transplant eligible patients was 3.5 years (95%CI; 2.9–4.0); median OS of 25 patients transplanted while in low-risk MDS was 3.0 years (95%CI: 1.1–) and that of 26 patients transplanted after progression was 8.2 years (95%CI: 1.7–) (Figure 2b; p=0.36).

Competing risk incidence analysis of clinical events compromising eligibility to transplantation

We analysed the cumulative risk of developing clinical events compromising eligibility to transplantation in candidate patients fit for transplantation, i.e. new comorbidities, decline in performance status, sudden AML transformation, or death. The cumulative incidence of new comorbidities affecting the fitness for transplant was 20% at 2 years, and 31% at 5 years in candidates fit for transplant according to both guidelines (estimated with progression to AML and death as competing risks) (Table 3, Figure 3A,B).

The cumulative incidence of AML transformation directly from lower- and intermediate-IPSS-R-risk MDS was 21% at 2 years, and 28% at 5 years in candidates fit for transplant according to both guidelines (estimated with progression to higher-risk MDS and death as competing risks) (Table 3, Figure 3C,D).

The cumulative incidence of a decline in Karnofsky performance status to below 70 was 5% at 2 years, and 9% at 5 years in candidates fit for transplant according to both guidelines (estimated with death as a competing risk) (Table 3, Figure 3E,F).

The cumulative incidence of a new comorbidity, a decline in performance status to below 70, transformation to AML, or death, whichever happened first, was 35% at 1 year, 52% at 2 years, and 80% at 5 years, respectively, in candidates fit for transplant according to both guidelines.

Multivariable analysis of fit transplant candidates showed that red blood cell transfusion status (as a time-varying covariate) and baseline HCT-CI were significantly associated with the cumulative incidence of new comorbidities or decline in performance status below 70, accounting for death as a competing risk (Table 4). However, in the analysis of fit transplant candidates aged <75 years, there were no significant associations.

Discussion

The only curative treatment for MDS, allo-HSCT, is recommended upfront for patients with high-risk MDS.[1,4,17,18] Different approaches have been used for lower- and intermediate-risk patients. Our study of 1145 patients aged <75 years with very low-, low-, and intermediate-IPSS-R-risk MDS from the EUMDS registry compared the survival outcomes of candidates for transplantation with the outcomes of non-candidate patients, according to IWG and MDS-RIGHT criteria.[1,7,10] The IWG approach is based on the definition of higher-risk MDS as an IPSS-R score above 3.5 points.[7] The MDS-RIGHT recommendations include a set of variables recognised as relevant to clinical decision making based on a consensus among experts.[1] This approach reflects the clinical practice of recommending transplantation in patients with poor-risk features, including excess blasts, life-threatening cytopenia, and poor-risk cytogenetic or genetic characteristics. These recommendations also include high transfusion intensity and platelet decline at 6 months of follow-up as established unfavourable prognostic factors.[1,12] In our study, patients aged <75 years who were transplant candidates by the IWG criterion had worse survival outcomes than non-candidate patients, at baseline and the 6-month follow-up; MDS-RIGHT criteria shown significance at 6 months when the worsening of cytopenia was measurable. Therefore, the MDS-RIGHT criteria seem to be more useful as a dynamic transplant selection approach during follow-up; this supposition requires further validation in independent, prospective cohorts.

According to our results, a combination of the assessed criteria seems to support the most effective selection of patients candidate to transplant. In fact, we have shown that patients who fulfil the MDS-RIGHT criteria and have IPSS-R scores above 3.5 have a particularly unfavourable prognosis. Almost all MDS-RIGHT transplant candidate patients with IPSS-R scores ≤3.5 at the baseline visit satisfied only one of the MDS-RIGHT criteria, which were most commonly severe neutropenia or thrombocytopenia. Severe neutropenia or thrombocytopenia without additional poor risk factors in the context of lower-risk IPSS-R categories does not represent a clear poor risk marker for justifying upfront transplantation. We suggest that the MDS-RIGHT criteria should be used for decision-making for upfront transplantation in the context of patients with intermediate IPSS-R scores, particularly when IPSS-R scores are greater than 3.5. A recent study provided evidence that early transfusion

patterns improve the Molecular International Prognostic Scoring System (IPSS-M) prediction in MDS, suggesting that MDS-RIGHT criteria complement a decision-making strategy integrating molecular profiles.[6,19]

Although allo-HSCT is the only curative treatment option for patients with MDS, it is still associated with substantial morbidity and mortality.[1] Age, associated comorbidities, decline in performance status, and frailty are critical factors that significantly affect accessibility to transplantation and transplant outcomes in eligible patients.[1] Using the relatively strict MDS-RIGHT definition of transplant fitness (Karnofsky score ≥ 70 and HCT-CI score < 3), we identified 11% of patients aged <75 years with lower-risk MDS at baseline, according to the IWG and MDS-RIGHT criteria, as candidates for allo-HSCT. The international panel on behalf of the European Society for Blood and Marrow Transplantation (EBMT) has recently recommended even more stringent Karnofsky performance criteria of ≥80 for defining transplant fitness.[20]

Several prospective observational clinical studies based on donor availability have been performed in patients with higher-risk MDS, with the common conclusion that allo-HSCT improves survival compared with non-transplant approaches.[21,22] However, few prospective observational studies have investigated transplantation based on donor availability in patients with lower-risk MDS.[23–26] One small, randomised study compared the outcome of transplanted and non-transplanted patients with low- and intermediate-risk MDS and demonstrated that the former group experiences survival benefits after transplantation.[27]

A few studies have compared transplanted and non-transplanted patients using Markov models, suggesting that a delayed transplantation strategy until disease progression maximises life expectancy in lower-risk patients.[2,28-31] According to the International Bone Marrow Transplantation Registry, transplantation should be delayed in low- and intermediate-IPSS-risk patients.[2] Another decision analysis study[28] used IPSS-R scores and concluded that upfront transplantation should be recommended for intermediate- and high-risk patients. More recently,[31] a novel IPSS-M prognostic model was investigated, showing that patients with low- and moderate-low-risk IPSS-M scores benefit from delayed transplantation, whereas in patients belonging to the moderately high-, high-, and very high-risk groups, upfront transplantation results in prolonged life expectancy. However, the EBMT study by Brand et al.,[32] which compared allo-HSCT and non-transplant approaches in elderly patients with advanced MDS, questioned the reliability of such observational comparison studies based on the problems of left and right

truncation, proper matching of transplant and non-transplant cohorts, and different timing of transplantation. In our study, we could compare the outcome of LR-MDS patients under three different strategies, i.e. no transplant, transplant while in low-risk MDS, and transplant after progression, in a prospective, unselected cohort. Although the sample size of transplanted patients is limited, reflecting current real-life attitude, we did not find significant difference in survival under these three different strategies.

A critical factor in delayed transplantation strategies, which was not appropriately accounted for in the abovementioned decision analysis, is the risk of events or complications that may preclude eligibility for transplantation or significantly worsen transplant outcomes. Thus far, no studies have reported the dynamics of comorbidities and performance status decline in patients with MDS. We took advantage of unbiased prospective data from the EUMDS registry and showed that patients with lower-risk MDS are at substantial risk of developing incident comorbidities and that their Karnofsky performance status decreases in the first years after diagnosis, jeopardising or even precluding the potential benefit of transplantation. In the case of AML transformation, there is a consistent risk of treatment failure and mortality due to infectious complications and other factors.

Our analysis in transplant-eligible patients indicated that transfusion dependency is associated with a higher incidence of new comorbidities and decreases in performance status among patients with lower and intermediate-risk MDS. In the subgroup analysis of transplant eligible patients aged <75 years, we were unable to confirm this finding, because of the smaller number of patients. Nonetheless, we should aim to prevent transfusion dependency through various treatment strategies,[19] and once transfusion dependency occurs, eligible patients should be referred for transplantation.

This study had certain limitations. In particular, the absence of molecular genetic data influenced the analysis of the MDS-RIGHT criteria for selecting transplant candidates and the evaluation of IPSS-M in the same context.

In conclusion, the IWG and MDS-RIGHT transplant criteria identify low-risk and intermediate-risk IPSS-R patients who have unfavourable survival and increased risk of disease progression; the usefulness of the MDS-RIGHT criteria at baseline is limited in the intermediate IPSS-R risk group. These patients might benefit from early transplantation strategies. Transplant eligible patients with lower-risk MDS tended to accumulate new comorbidities, suffer a decline in performance status, and have an increased risk of AML transformation during

the first years after diagnosis, which may result in the loss of eligibility for transplantation. These findings should be carefully taken into account when considering delaying allo-HSCT in patients who are potentially eligible for transplantation.

Acknowledgements: The authors and members of the steering committee of the EUMDS registry would like to thank all local investigators (list is in Table S4), operational team members, data managers, research nurses and patients for their contribution to the EUMDS Registry. We would like to thank Editage for English language editing.

Author contributions: Aleksandar Savic, Adele Taylor, Alex Smith, Simon Crouch, Corine van Marrewijk, Theo de Witte, and Luca Malcovati conceptualized and designed the study. Aleksandar Savic, Pierre Fenaux, Argiris Symeonidis, Catherine Cargo, Moshe Mittelman, Verena Petzer, Guillermo Sanz, Jaroslav Čermák, Saskia Langemeijer, Eva Hellström-Lindberg, Comont Thibault, Maud D'Aveni, Dominic Culligan, Ioannis Kotsianidis, Panagiotis Panagiotidis, Theo de Witte, and Luca Malcovati gathered the patients and collected the data. Aleksandar Savic, Adele Taylor, Alex Smith, Simon Crouch, Corine van Marrewijk, and Luca Malcovati analysed and interpreted the results. Aleksandar Savic, Adele Taylor, Alex Smith, Corine van Marrewijk, and Luca Malcovati drafted the manuscript. All authors reviewed the results and approved the final version of the manuscript.

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Table 1. Baseline demographic and clinical characteristics of the study cohort by eligibility criteria (International Working Group and MDS-RIGHT) for transplantation and fitness

	All Mean/N (SD/%)		Eligible for Transplantation Mean/N (SD/%)			
			Total	Criteria		Fitness for transplant [1]
				IWG	MDS-RIGHT	
Total	**1145 (100)**		**208 (100)**	**149 (100)**	**96 (100)**	**124 (100)**
Sex						
Males	711 (62.1)		139 (66.8)	96 (64.4)	66 (68.8)	82 (66.1)
Females	434 (37.9)		69 (33.2)	53 (35.6)	30 (31.2)	42 (33.9)
Age (years):						
Mean (SD)	65.2 (8.2)		65.0 (8.2)	65.6 (7.9)	64.1 (8.9)	63.9 (9.1)
<50	62 (5.4)		9 (4.3)	6 (4.0)	5 (5.2)	7 (5.6)
50–59	162 (14.1)		27 (13.0)	16 (10.7)	16 (16.7)	19 (15.3)
60–69	509 (44.5)		107 (51.4)	76 (51.0)	47 (49.0)	69 (55.6)
70–74	412 (36.0)		65 (31.2)	51 (34.2)	28 (29.2)	29 (23.4)
Diagnosis (WHO 2016):						
MDS-SLD	165 (14.4)		16 (7.7)	11 (7.4)	6 (6.2)	8 (6.5)
MDS-RS	228 (19.9)		18 (8.7)	12 (8.1)	12 (12.5)	8 (6.5)
MDS-MLD	479 (41.8)		86 (41.3)	49 (32.9)	56 (58.3)	49 (39.5)
MDS with excess blasts	144 (12.6)		65 (31.2)	61 (40.9)	11 (11.5)	45 (36.3)
MDS with isolated 5q-	77 (6.7)		11 (5.3)	8 (5.4)	4 (4.2)	8 (6.5)
MDS, unclassifiable	46 (4.0)		11 (5.3)	7 (4.7)	7 (7.3)	6 (4.8)
MDS/MPN, unclassifiable	4 (0.3)		1 (0.5)	1 (0.7)	-	-
MDS/MPN-RS-T	2 (0.2)		-	-	-	-
IPSS-R prognostic risk category						
Very low	311 (27.2)		6 (2.9)	-	6 (6.2)	5 (4.0)
Low	579 (50.6)		41 (19.7)	-	41 (42.7)	23 (18.5)
Intermediate	255 (22.3)		161 (77.4)	149 (100)	49 (51.0)	96 (77.4)
IPSS-R cytogenetics risk group						
Poor	15 (1.3)		15 (7.2)	9 (6.0)	15 (15.8)	9 (7.3)
Intermediate	146 (13.0)		59 (28.5)	50 (33.6)	18 (18.9)	33 (26.8)
Good	893 (79.3)		124 (59.9)	88 (59.1)	54 (56.8)	76 (61.8)
Very good	72 (6.4)		9 (4.3)	2 (1.3)	8 (8.4)	5 (4.1)
Haemoglobin, g/dL	10.5 (2.0)		9.8 (1.8)	9.4 (1.8)	10.2 (1.8)	9.8 (1.8)
Absolute neutrophil count, 10^9/L	2.7 (2.1)		2.2 (2.3)	2.2 (2.2)	1.8 (2.3)	1.8 (1.8)
Platelets, 10^9/L	206.5 (146.9)		151.2 (142.6)	158.2 (140.2)	120.0 (129.2)	149.9 (134.2)
Peripheral blasts (%)	0.2 (0.9)		0.3 (1.0)	0.4 (1.2)	0.4 (1.0)	0.3 (1.0)
Bone marrow blasts (%)	2.8 (2.7)		4.8 (4.0)	6.0 (4.0)	3.7 (5.1)	4.9 (3.3)
Karnofsky Performance Scale Index (0-100)	87.8 (13.3)		87.3 (12.6)	87.1 (12.9)	88.6 (11.2)	90.2 (9.3)

[1]Fit patients defined as Karnofsky score ≥70 and hematopoietic cell transplantation-specific comorbidity index (HCT-CI) <3. IWG, International Working Group for MDS prognosis; MDS, myelodysplastic syndrome; MDS-SLD, MDS with single lineage dysplasia; MDS-RS, MDS with ringed sideroblasts; MDS-MLD, MDS with multilineage dysplasia; IPSS-R, revised international prognostic scoring system; MDS/MPN, myelodysplastic/myeloproliferative neoplasms.

Table 2. Overall, progression-free, and AML-free survival by transplantation criteria at baseline (visit 1) and the 6-month follow-up (visit 2)

		N	Overall Survival Median, years (95% CI)	P-value	PFS Median, years (95% CI)	P-value	AML-free survival Median, years (95% CI)	P-value
All patients at baseline (Visit 1)	**Total**	**1145**	**6.1 (5.4–6.6)**		**5.0 (4.5–5.7)**		**6.1 (5.5–6.7)**	
IPSS-R >3.5 criterion	No	996	6.4 (5.8–6.9)	<0.0001	5.7 (4.9–6.4)	<0.0001	6.4 (5.7–7.0)	<0.0001
	Yes	149	2.9 (2.4–4.7)		2.2 (1.4–2.8)		2.8 (2.3–3.8)	
MDS-RIGHT criteria	No	1049	6.2 (5.5–6.6)	0.156	5.1 (4.6–5.7)	0.081	6.2 (5.5–6.7)	0.093
	Yes	96	5.4 (3.0–.)		3.4 (2.0–8.3)		4.8 (3.0–.)	
Patients meeting MDS-RIGHT criteria	IPSS-R ≤3.5	58	7.8 (3.4–.)	<0.05	5.4 (3.0–.)	<0.01	7.8 (3.4–.)	<0.01
	IPSS-R >3.5	38	2.5 (1.3–.)		1.4 (0.7–3.3)		1.6 (0.9–.)	
Fit patients	**Total**	**660**	**6.4 (5.5–7.4)**		**5.5 (4.8–6.4)**		**6.4 (5.5–7.4)**	
IPSS-R >3.5 criterion	No	572	6.6 (5.7–8.2)	<0.001	6.1 (5.1–6.8)	<0.0001	6.7 (5.7–8.7)	<0.0001
	Yes	88	3.2 (2.5–7.4)		2.3 (1.3–3.2)		3.5 (2.3–7.4)	
MDS-RIGHT criteria	No	600	6.4 (5.5–7.4)	0.464	5.5 (4.8–6.5)	0.132	6.5 (5.6–7.8)	0.297
	Yes	60	12.9 (2.9–.)		3.9 (1.7–.)		4.8 (2.1–.)	
All Patients (Visit 2)	**Total**	**984**	**6.0 (5.4–6.5)**		**5.1 (4.4–5.8)**		**6.0 (5.3–6.6)**	
IPSS-R >3.5 criterion	No	937	6.1 (5.6–7.0)	<0.0001	5.2 (4.7–6.1)	<0.0001	6.1 (5.6–7.0)	<0.0001
	Yes	47	2.1 (1.3–2.9)		1.3 (0.8–2.6)		2.1 (1.0–3.0)	
MDS-RIGHT criteria	No	773	6.6 (5.8–7.7)	<0.0001	5.8 (5.1–6.6)	<0.0001	6.9 (5.8–7.8)	<0.0001
	Yes	211	3.5 (2.6–4.5)		2.8 (2.1–3.4)		3.5 (2.8–4.4)	
Fit patients	**Total**	**262**	**5.8 (4.7–8.2)**		**4.0 (3.4–4.7)**		**4.7 (3.9–5.6)**	
IPSS-R >3.5 criterion	No	251	6.0 (5.2–8.3)	<0.0001	4.7 (4.1–6.1)	<0.0001	6.1 (4.9–8.3)	<0.0001
	Yes	11	1.3 (0.2–.)		0.7 (0.1–2.6)		0.8 (0.2–.)	
MDS-RIGHT criteria	No	202	8.2 (5.2–10.0)	<0.01	5.2 (4.5–8.2)	<0.0001	6.9 (5.2–10.0)	<0.01
	Yes	60	4.1 (2.7–5.8)		2.8 (1.8–3.6)		3.6 (2.7–5.8)	

IPSS-R, revised international prognostic scoring system; MDS, myelodysplastic syndrome; CI, confidence interval; PFS, progression-free survival; AML, acute myeloid leukaemia.

Table 3. Cumulative incidence of new comorbidities, decline in performance status to <70, AML transformation, or death in all patients with MDS and fit transplant candidate patients aged <75 years at baseline

	Incidence of new comorbidities	Incidence of AML transformation	Incidence of decline in Karnofsky performance status to below 70	Cumulative incidence of new comorbidity, decline in performance status to below 70, AML transformation, or death
All patients with MDS:				
1-year	17.3%	8.2%	6.2%	39.7%
2-year	23.6%	18.0%	9.4%	58.7%
5 years	33.9%	22.8%	13.6%	84.4%
Fit candidate patients:				
1-year	15.4%	8.5%	3.9%	34.8%
2-year	19.7%	21.2%	5.0%	52.0%
5 years	30.7%	28.4%	9.4%	80.0%

MDS, myelodysplastic syndrome; AML, acute myeloid leukaemia

Table 4. Multivariable analysis of the new comorbidity or performance status decline below 70 with death as a competing risk

		Hazard ratio (95% CI)	p-value
Age at diagnosis (years)		1.01 (0.98–1.04)	0.726
Sex	Male	1 (ref)	
	Female	0.93 (0.52–1.67)	0.807
Red blood cell transfusion status	No	1 (ref)	
	Yes	4.10 (2.12–7.94)	<0.0001
Baseline HCT-CI	Low	1 (ref)	
	Intermediate	2.24 (0.97–5.12)	0.060
	High	3.74 (1.70–8.22)	0.001

CI, confidence Interval; HCT-CI. hematopoietic cell transplantation-specific comorbidity index

Figure 1 Overall survival of patients according to the (A) International Working Group (IWG) for myelodysplastic syndrome (MDS) prognosis criterion at baseline and (B) according to the MDS-RIGHT criteria at baseline. Overall survival of fit patients according to the (C) IWG criterion at baseline and (D) of fit patients according to the MDS-RIGHT criteria at baseline

Figure 2 Overall survival of (A) myelodysplastic syndrome (MDS)-RIGHT candidates for transplant according to the revised international prognostic scoring system (IPSS-R) >3.5 criterion at baseline and (B) of patients according to transplant status

Figure 3 Cumulative incidence of new comorbidities in (A) all patients with myelodysplastic syndrome (MDS) at baseline and (B) transplant candidate patients at baseline. Cumulative incidence of new transformation to acute myeloid leukaemia (AML) (without previous progression to higher-risk MDS) in (C) all patients with MDS at baseline and (D) transplant candidate patients at baseline. Cumulative incidence of decline in performance status in (E) all patients with MDS at baseline and (F) transplant candidate patients at baseline.