Hematopoietic stem cell transplantation is effective in achieving long-term survival for post-aplastic anemia myeloid neoplasms: the EBMT Severe Aplastic Anemia Report

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Abstract

Aplastic anemia (AA) transformation into myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML) is associated with a dismal prognosis. Hematopoietic stem cell transplant offers the sole possibility of cure, but data on long-term survival are scarce. We retrospectively analyzed 270 patients transplanted for MDS, AML, or an isolated cytogenetic abnormality after a diagnosis of AA or paroxysmal nocturnal hemoglobinuria reported to the European Society for Blood and Marrow Transplantation (EBMT). The median age at transplantation was 39 years. The 5-year overall survival rate was 64%, and was unaffected by chromosome 7 abnormalities, age at transplant, sex, interval from clonal evolution to transplant, and intensity of conditioning regimen. The 5-year non-relapse mortality rates were 34% (95% Confidence Interval [CI]: 25-42%) for MDS patients and 19% (95% CI: 7-31%) for AML patients, and were higher following a myeloablative conditioning regimen. The 5-year relapse rate was 12% (95% CI: 6-19%) for MDS and 22% (95% CI: 9-35%) for AML. Our study's survival estimates reflect a younger cohort of patients, considering the bimodal distribution of AA. Conditioning regimen intensity did not affect relapse. For MDS patients, pretreating before transplant did not improve survival nor reduce relapse. Transplantation is feasible and effective in achieving long-term survival for transplant-eligible post-AA myeloid neoplasm patients. MDS patients may benefit from upfront reduced intensity conditioning transplant, limiting toxicity without higher rates of relapse. Post-transplant maintenance therapies to reduce the relapse incidence among AML patients might be warranted.

Introduction

Clonal evolution into myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML) represents a much feared complication for patients with immune-mediated aplastic anemia (AA) or paroxysmal nocturnal hemoglobinuria (PNH), affecting approximately 10-15% of non-transplanted individuals within the first decade from diagnosis.[1,2] This

progression is often associated with a dismal prognosis due to high-risk features, including excess blasts, monosomy 7, and adverse molecular profiles.[1,3,4]

Allogeneic hematopoietic stem cell transplantation (HSCT) is currently the only curative treatment for these post-AA MDS/AML cases. One previous European Society for Blood and Marrow Transplantation (EBMT) Severe Aplastic Anemia Working Party study found a 5-year overall survival (OS) of around 45%.[5] Patients in remission or receiving upfront transplantation presented better outcomes than those with refractory disease. However, the use of standard chemotherapy or hypomethylating agents before transplant is often limited by severe hematologic toxicity[6] due to the already compromised state of the hematopoietic stem cell pool in these patients.

Today, data on long-term survival following transplant for post-AA MDS/AML are scarce because of the rarity of the disease. Therefore, the predictors of good outcomes are unknown. This study describes the most significant published cohort to date and evaluates the 5-year OS of patients transplanted for myeloid neoplasms secondary to AML.

Methods

Study design

Following the scientific committee's approval, we carried out a retrospective, multicenter cohort study among centers participating in the EBMT Severe Aplastic Anemia Working Party. EBMT centers are committed to obtaining informed consent in accordance with local regulations and Institutional Review Board approvals, and reporting pseudonymized data to the EBMT. We conducted this study in agreement with the principles of the Declaration of Helsinki. We report our results in accordance with the recommendations of the STROBE statement (STrengthening the Reporting of Observational studies in Epidemiology).

Patient selection and data collection

We included all consecutive patients reported to the EBMT who received an HSCT for clonal evolution, defined as the diagnosis of a myeloid neoplasm or the acquisition of any cytogenetic abnormality after a previous diagnosis of acquired AA or PNH. We have reclassified patients lacking a myeloid neoplasm diagnosis but bearing a World Health Organization (WHO) 2016 MDS-defining cytogenetic abnormality as MDS. Transplants were carried out between January 1st, 2001, and December 31st, 2021. We excluded patients who had presented a WHO 2016-defining cytogenetic abnormality at AA diagnosis, had developed AA following chemotherapy for other hematologic malignancies, had received HSCT before clonal evolution, had a diagnosis of inherited marrow failure syndrome, and those with missing essential data (*Online Supplementary Figure S1*).

Endpoints and definitions

All outcomes in this study are calculated from the time of the first HSCT. The primary endpoint of this study was the 5-year OS. Secondary endpoints included engraftment, acute and chronic graft-*versus*-host disease (GvHD), non-relapse mortality (NRM), and graft failure, GvHD, and relapse-free survival (GGRFS). GGRFS was defined as survival without myeloid neoplasm relapse, graft failure, and grade III-IV acute or chronic extensive GvHD. NRM was defined as death from any cause without relapse of the neoplastic disease or graft failure or any death before Day (D)+100. Myeloid and platelet engraftment and conditioning regimen intensity were defined according to the EBMT guidelines.

Statistical analysis

Overall survival and GGRFS were estimated using the Kaplan-Meier product limit estimation method, and differences in subgroups were assessed by the log-rank test. Median follow-up was determined using the reverse Kaplan-Meier method. Competing risk methods were used to estimate the cumulative incidences of grade II-IV and III-IV aGvHD, cGvHD, platelet and neutrophil engraftment, and graft failure; the competing events were death, graft failure, relapse, and second transplant. Cumulative incidences of MDS/AML relapse and NRM were similarly analyzed in the subset of patients who developed MDS or AML before HSCT. Gray's test evaluated any subgroup differences in cumulative incidences of interest.

Multivariable Cox proportional hazards regression was applied to investigate the simultaneous impact of multiple co-variates on OS. The co-variate constellation was predefined based on clinical considerations. It included the clonal evolution group (AML, isolated abnormalities, and MDS), the interval between clonal evolution and HCT (in months), patient sex (female *vs*. male), age at HCT (in years), and conditioning intensity (reduced intensity conditioning [RIC] *vs*. myeloablative conditioning [MAC]).

Continuous variables are presented in the text, summarized as median and interquartile range (IQR), and categorical variables as percentages within the group of patients with available data. Subgroup differences in baseline variables are investigated with χ^2 tests for categorical variables and the Kruskal-Wallis test for continuous variables. All estimates and hazard ratios are reported with corresponding 95% Confidence Intervals (CI) in parentheses. All *P* values were two-sided. Statistical analyses were performed in R version 3.6.0 (R Development Core Team, Vienna, Austria), using packages 'survival', 'prodlim', and 'cmprsk'.

Results

Patient and transplant characteristics

We included 270 patients from 113 different EBMT centers across 28 countries. Of these patients, 16 had already been

included in a previous EBMT study.[5] The primary diagnosis was AA for 246 patients and PNH for 24. The median age at this first diagnosis was 34.7 years (range: 20-51.4 years). At clonal evolution, 46 patients were diagnosed with AML, 155 with MDS, and 69 had acquired an isolated cytogenetic abnormality without morphological criteria for MDS. The median time from AA diagnosis to clonal evolution was 30.5 months (range: 8.7-68.4 months) for MDS and 39.8 months (range: 21.5-82.6 months) for AML; the median follow-up was 5 years (range: 4.36-5.9 years). Table 1 summarizes patient and transplant characteristics.

Aplastic anemia treatment

No patient received an HSCT for severe AA (SAA)/PNH before the clonal evolution diagnosis. Initial treatment combinations for SAA included cyclosporine in 90, anti-thymocyte globulin (ATG) in 83 (with cyclosporine in 71, with other drugs in 8 and 4 ATG monotherapy), and 13 received eltrombopag (5 with ATG and cyclosporine, and one as monotherapy). For 159 patients, primary treatment was unknown.

Cytogenetic abnormalities

We retrieved cytogenetic data at clonal evolution diagnosis for 200/270 patients (74% of data completeness). A total of 149 (74.5%) patients had at least one abnormality. *Online Supplementary Figure S2* presents the cytogenetics distribution across the three groups.

Myeloid neoplasm treatment

Data were available for 156/201 patients (77.6% of data completeness). Fifty-three (34%) patients received upfront transplantation after the myeloid neoplasm diagnosis, whereas 88 (56.4%) patients received intensive chemotherapy, 11 (7.1%) hypomethylating agents, and 4 (2.6%) both chemotherapy and hypomethylating agents.

Data were available for 126 MDS patients, of whom 48 received upfront transplantation. Five AML patients received upfront HSCT (data available for 30/46).

Overall survival

The 5-year OS for the entire cohort was 64% (95%CI: 58-70%) (Figure 1A). The primary cause of death was transplant-related, accounting for 58 (66.7%) events, followed by relapse with 19 (21.8%) events. We then performed a multivariable analysis on OS adjusting for the clonal evolution group, the interval from clonal evolution diagnosis and transplant in days (D), the patient's biological sex, age at transplant, and conditioning regimen intensity. None of these factors affected survival (Table 2).

Secondly, we studied the impact of clonal evolution category and cytogenetics at clonal evolution diagnosis on survival following HSCT. There was no difference in 5-year OS among the three clonal evolution groups: 60% (95% CI: 52-68%) for MDS, 61% (95% CI: 45-76%) for AML, and 74% (95% CI: 63-85%) for isolated cytogenetic abnormality (*P*=0.19), respec-

Table 1. Patient and transplant characteristics.

	Group	Total	MDS	AML	Isolated abnormality	*P*
N (%)	-	270 (100)	155 (57.4)	46 (17.0)	69 (25.6)	-
Sex, N (%)	Male Female	151 (55.9) 119 (44.1)	91 (58.7) 64 (41.3)	27 (58.7) 19 (41.3)	33 (47.8) 36 (52.2)	0.291
Age at this treatment, years	Median (IQR)	39.1 (22.3-56.2)	38.3 (22.3-57.6)	45.2 (29.3-57.2)	32.3 (18-49)	0.034
Cytogenetics, N (%)	Abnormal Normal Missing	181 (76.7) 55 (23.3) 34 (12.6)	97 (72.4) 37 (27.6) 21 (13.5)	20 (60.6) 13 (39.4) 13 (28.3)	64 (92.8) 5 (7.2) 0 (0.0)	<0.001
Regimen intended to be myeloablative, N (%)	No Yes Missing	132 (49.8) 133 (50.2) 5 (1.9)	67 (44.1) 85 (55.9) 3 (1.9)	25 (55.6) 20 (44.4) 1 (2.2)	40 (58.8) 28 (41.2) 1 (1.4)	0.091
Donor type, N (%)	MSD Haploidentical Unrelated Missing	86 (32.3) 20 (7.5) 160 (60.2) 4 (1.5)	39 (25.5) 12 (7.8) 102 (66.7) 2 (1.3)	15 (33.3) 3 (6.7) 27 (60.0) 1 (2.2)	32 (47.1) 5 (7.4) 31 (45.6) 1 (1.4)	0.035
Stem cell source, N (%)	PB BM CB Mixed sources Missing	147 (55.3) 98 (36.8) 16 (6.0) 5 (1.9) 4 (1.5)	90 (58.8) 51 (33.3) 10 (6.5) 2 (1.3) 2 (1.3)	34 (75.6) 7 (15.6) 4 (8.9) 0 (0.0) 1 (2.2)	23 (33.8) 40 (58.8) 2 (2.9) 3 (4.4) 1 (1.4)	<0.001

Overall patient characteristics and stratified by clonal evolution. Results are based on available data. *P* values are based on χ^2 tests for categorical variables and Kruskal-Wallis test for continuous variables. The count and percentage of missing data is indicated in the last row per variable, where applicable. AML: acute myeloid leukemia; BM: bone marrow; CB: cord blood; IQR: interquartile range; MDS: myelodysplastic syndromes; MSD: matched sibling donor; PB: peripheral blood.

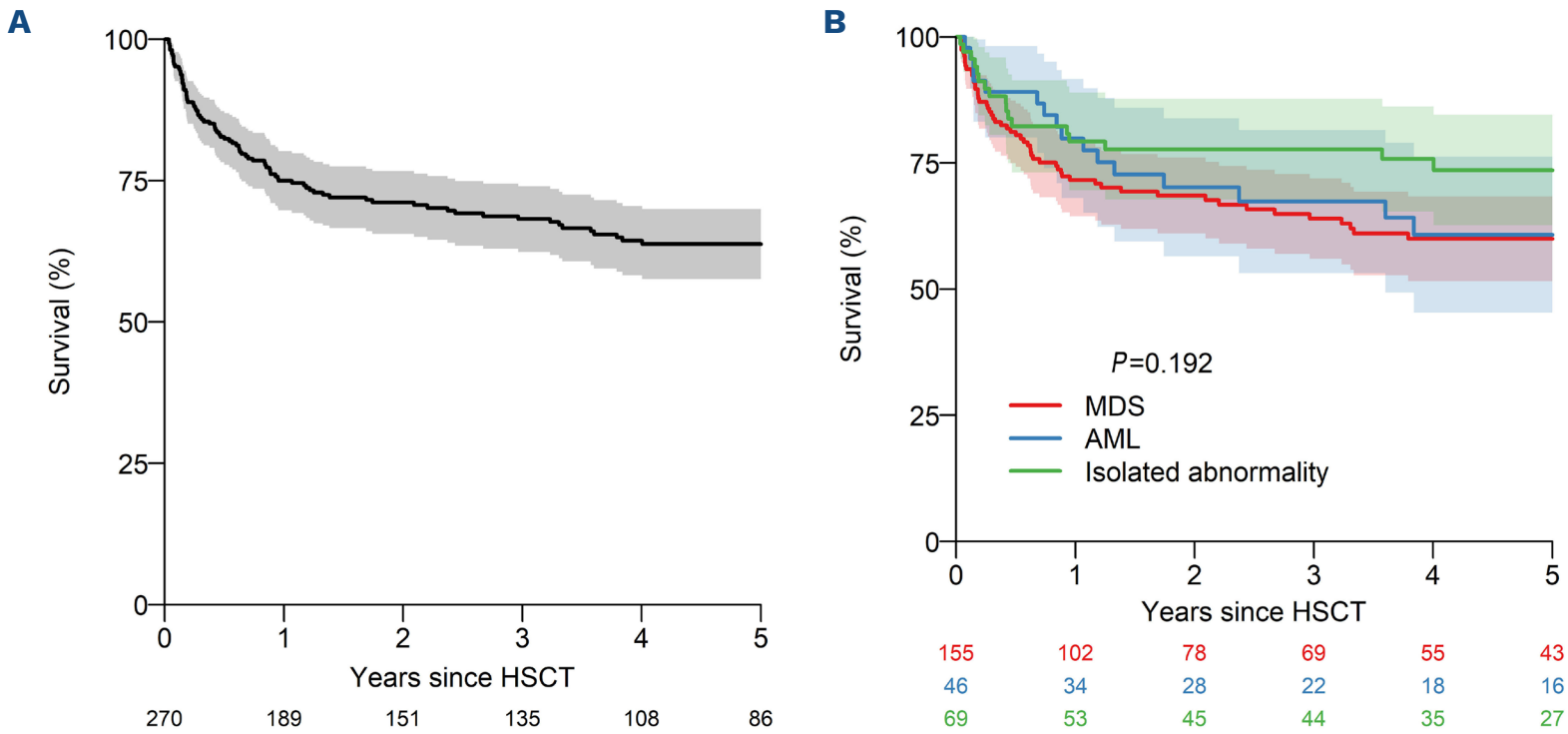

Figure 1. Kaplan Meier curves for overall survival in different patient subgroups. (A) The whole cohort, (B) stratified by clonal evolution, (C) stratified by cytogenetic abnormality and (D) stratified by pretreatment. The shaded regions indicate 95% Confidence Intervals. Numbers below the graphs show the number of patients at risk. Indicated *P* values are calculated by logrank test. OS: overall survival. AML: acute myeloid leukemia; HSCT: hematopoietic stem cell transplant; MDS: myelodysplastic syndromes.

tively (Figure 1B). There was no difference in 1- and 5-year OS among patients with normal cytogenetics (80% [95% CI: 69-91%] *vs*. 67% [95% CI: 54-81%]) chromosome 7 abnormalities (70% [95% CI: 58-82%] *vs*. 58% [95% CI: 45-72%]) and other cytogenetic abnormalities (79% [95% CI: 70-88%] *vs*. 71% [95% CI: 60-81%], respectively) (*P*=0.2) (Figure 1C). Four patients had ≥3 cytogenetic abnormalities, not including chromosome 7 (1-year OS: 75% [95% CI: 33-100%]).

Next, we studied the impact of pretreatment for MDS. There was no difference in 5-year OS between upfront transplantation and pretreated patients (71% [95% CI: 58-84%] *vs*. 56% [95% CI: 45-66%]), respectively (*P*=0.19) (Figure 1D).

Then, we studied the impact of the conditioning regimen intensity for MDS/AML patients. MAC or RIC regimens did not affect survival in the overall cohort (5-year OS 61% [95% CI: 53-70%] *vs*. 65% [95% CI: 56-74%], respectively), (*P*=0.6) (*Online Supplementary Figure S3*). In addition, the year of transplant did not affect the OS either (*Online Supplementary Figure S4*).

Engraftment

The overall cumulative incidence of neutrophil engraftment by D+28 was 85% (95% CI: 81-89%), and platelet engraftment by D+60 was 84% (95% CI: 79-89%). The median time for neutrophil and platelet engraftment was 17 (95% CI: 16-19%) and 19 (95% CI: 18-21%), respectively. Clonal evolution

category and conditioning regimen intensity did not affect neutrophil engraftment by D+28 or platelet engraftment by D+60 (*Online Supplementary Table S1*).

Graft-*versus*-host disease

The cumulative incidence of grades II-IV aGvHD by D+100 was 24% (95% CI: 19-29%). Patients with an AML diagnosis presented a higher cumulative incidence of aGvHD (35% [95% CI: 21-49%]) compared to MDS (26% [95% CI: 19-33%]) or isolated cytogenetic abnormality (12% [95% CI: 4-21%]) (*P*=0.013) (Figure 2A). Conditioning regimen intensity and year of transplant had no impact on aGvHD (*data not shown*). The cumulative incidence of chronic GvHD by five years was higher in AML than MDS or isolated cytogenetics patients (42% [95% CI: 26-57%], 32% [95% CI: 24-41%], and 22% [95% CI: 10-34%], respectively) (*P*=0.019) (Figure 2B).

Table 2. Multivariable analysis for overall survival

Risk factor	Group	N	D	HR (95% CI)	*P*
Categorized clonal evolution	MDS AML Isolated abnormality	150 44 68	56 18 19	 0.98 (0.57-1.69) 0.68 (0.40-1.16)	 0.9 0.15
Interval clonal evolution and HSCT or BMF and HSCT		262	93	1 (0.99-1.01)	0.8
Sex	Male Female	145 117	51 42	 1.11 (0.73-1.68)	 0.6
Age at HSCT, in decades		262	93	1.1 (0.97-1.24)	0.13
Conditioning	Standard Reduced	126 136	46 47	 0.86 (0.54-1.38)	 0.5

Multivariable analysis of overall survival. The number of patients at risk and that died during follow-up are indicated in the N and D columns, respectively. *P* values are based on unadjusted Wald tests. AML: acute myeloid leukemia; BMF: bone marrow failure; CI: Confidence Interval; HR: hazard ratio; HSCT: hematopoietic stem cell transplant; MDS: myelodysplastic syndromes; N: number.

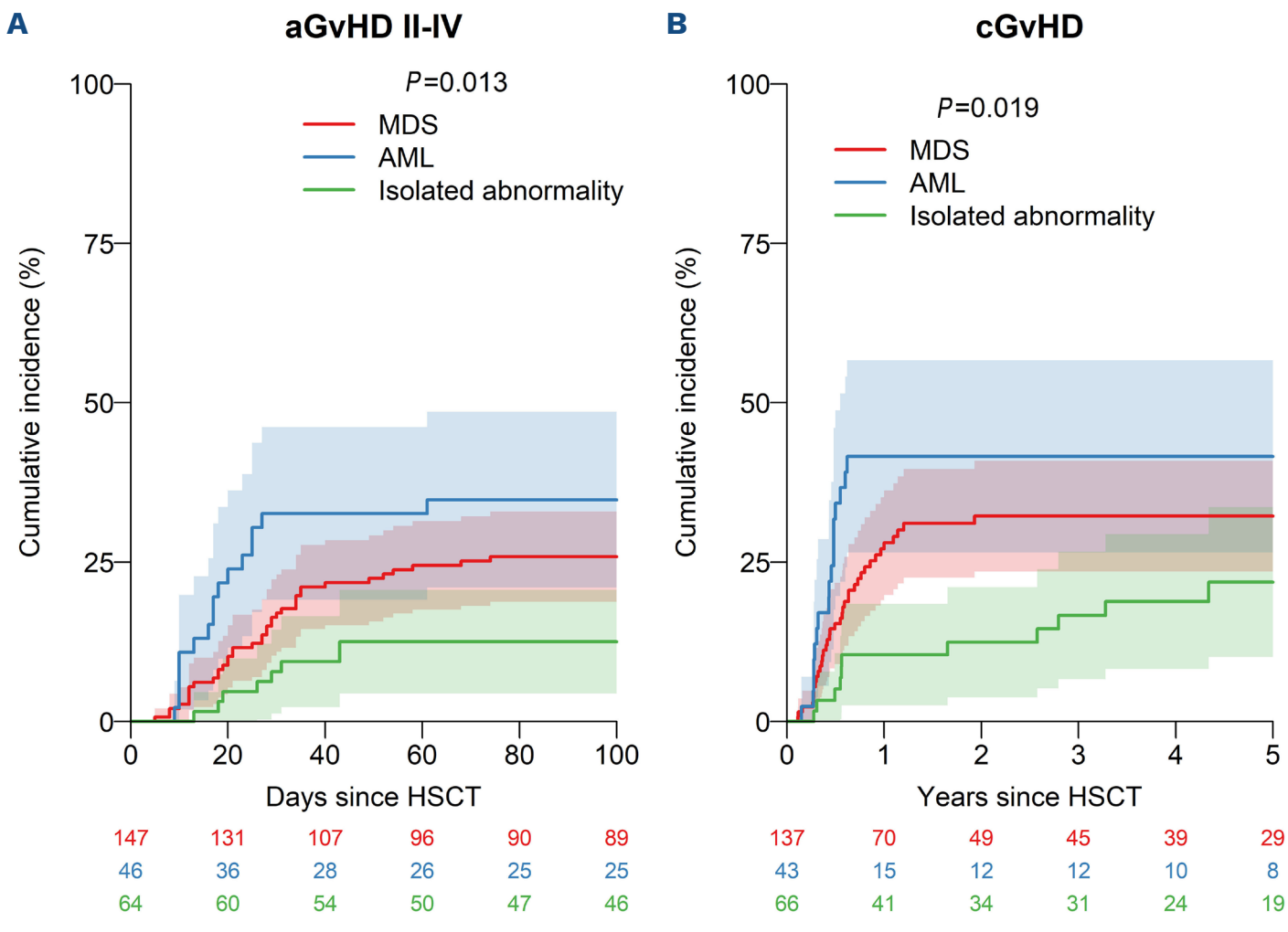

Figure 2. Cumulative incidence curves stratified by clonal evolution category. (A) Acute graft-*versus*-host disease (GvHD) grade II-IV and (B) chronic GvHD. The shaded regions indicate 95% Confidence Intervals. Numbers below the graphs show the number of patients at risk. Indicated *P* values are calculated by Gray's test. AML: acute myeloid leukemia; HSCT: hematopoietic stem cell transplant; MDS: myelodysplastic syndromes.

Relapse and non-relapse mortality

The overall 1-year cumulative incidence of relapse for MDS and AML was 7% (95% CI: 3-11%) and 15% (95% CI: 9-21%), respectively. By five years, the cumulative incidence of relapse was 12% (95% CI: 6-19%) for MDS and 22% (95% CI: 9-35%) for AML (*P*=0.09) (Figure 3A). Neither the conditioning regimen intensity (*Online Supplementary Figure S3A*) nor cytogenetics affected the relapse rate. Treatment before HSCT did not affect relapse of MDS (*Online Supplementary Figure S4A*).

The cumulative incidence of NRM by one and five years was 26% (95% CI: 20-33%) and 30% (95% CI: 23-37%), respectively. By five years, the NRM was 34% (95% CI: 25-42%) and 19% (95% CI: 7-31%) for MDS and AML patients, respectively (*P*=0.06) (Figure 3B). The use of a MAC regimen was associated with higher NRM than a RIC regimen: 1-year NRM of 34% (95% CI: 24-44%) *versus* 19% (95% CI: 10-27%), respectively (*P*=0.026) (*Online Supplementary Figure S3B*). In MDS, treatment before HSCT did not affect NRM (*Online Supplementary Figure S4B*).

Graft failure, graft-*versus*-host disease, and relapse-free survival

The overall 1- and 5-year GGRFS was 60% (54-66) and 52% (46-59). GGRFS was 51% (43-60) for MDS and 38% (23-53) for AML patients (Figure 4A). For MDS patients, upfront HSCT yielded a 67% (53-80) GGRFS by one year *versus* 54% (43-66) for pretreated patients (*P*=0.2) (Figure 4B).

Neither the year of the transplant nor the intensity of the conditioning regimen affected the GGRFS.

Online Supplementary Table S2 summarizes the univariate analyses conducted for each clinical outcome studied.

Discussion

Although post-AA MDS/AML presents high-risk characteristics, herein, we show that transplantation could potentially cure eligible patients. In this most extensive study ever performed in this setting, the 5-year OS was 64% for the entire cohort, i.e., above 60% in all three clonal evolution scenarios (cytogenetic abnormality insufficient for an MDS diagnosis, MDS, and AML), higher than the 45% previously published by the SAA WP for post-AA MDS/AML (median age: 29 years).[5] The improvement in supportive care, HLA typing, and donor choice from one study's inclusion period to another might explain the difference in survival. It is noteworthy that the median age of patients we present is 39 (22-56) years at transplantation. Therefore, survival estimates reflect a younger cohort of patients considering the bimodal distribution of AA (second peak among older patients).

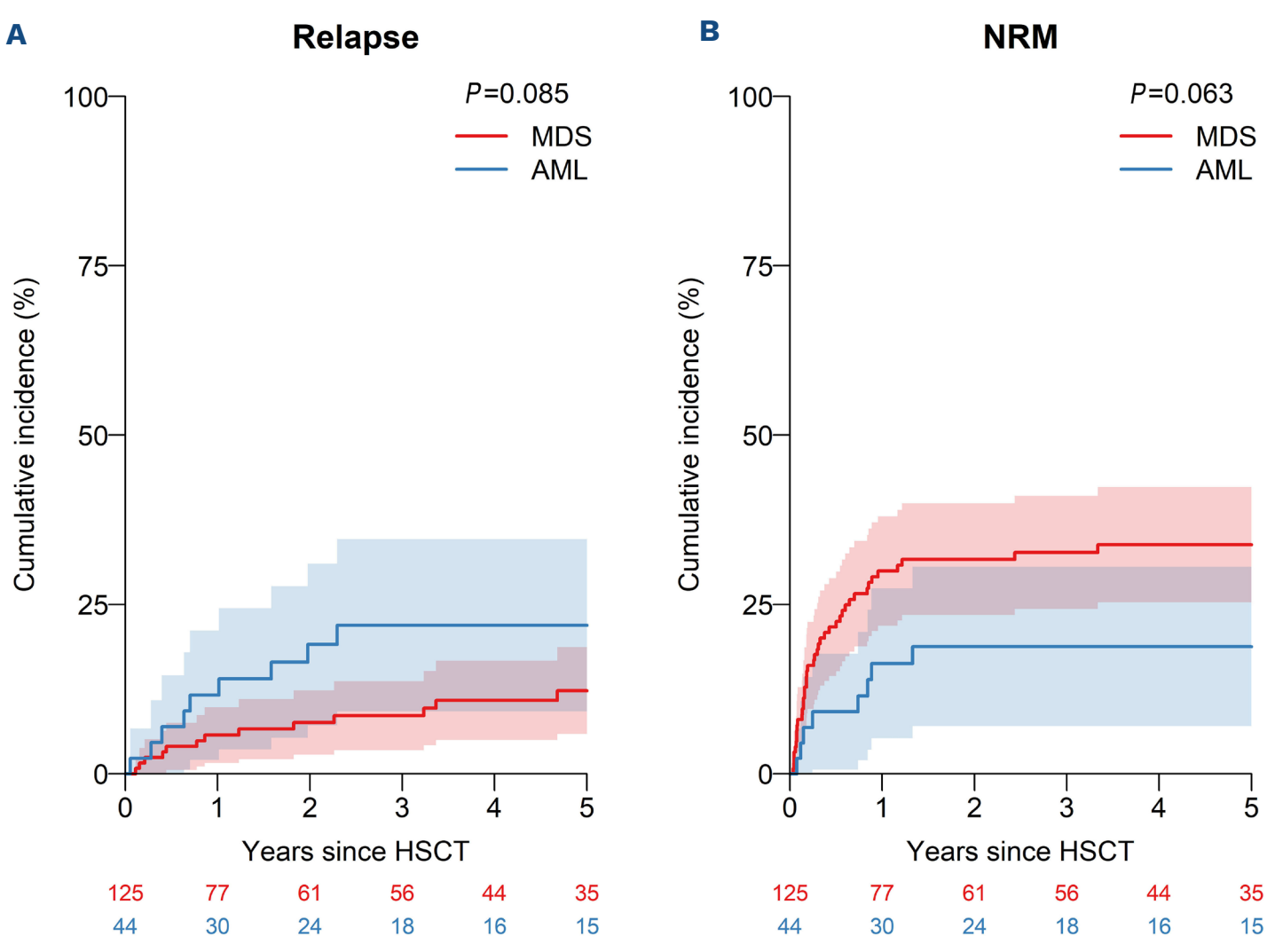

Figure 3. Cumulative incidence curves of relapse and non-relapse mortality stratified by clonal evolution category. (A) Myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML) relapse and (B) non-relapse mortality. The shaded regions indicate 95% Confidence Intervals. Numbers below the graphs show the number of patients at risk. Indicated *P* values are calculated by Gray's test. HSCT: hematopoietic stem cell transplant; NRM: non-relapse mortality.

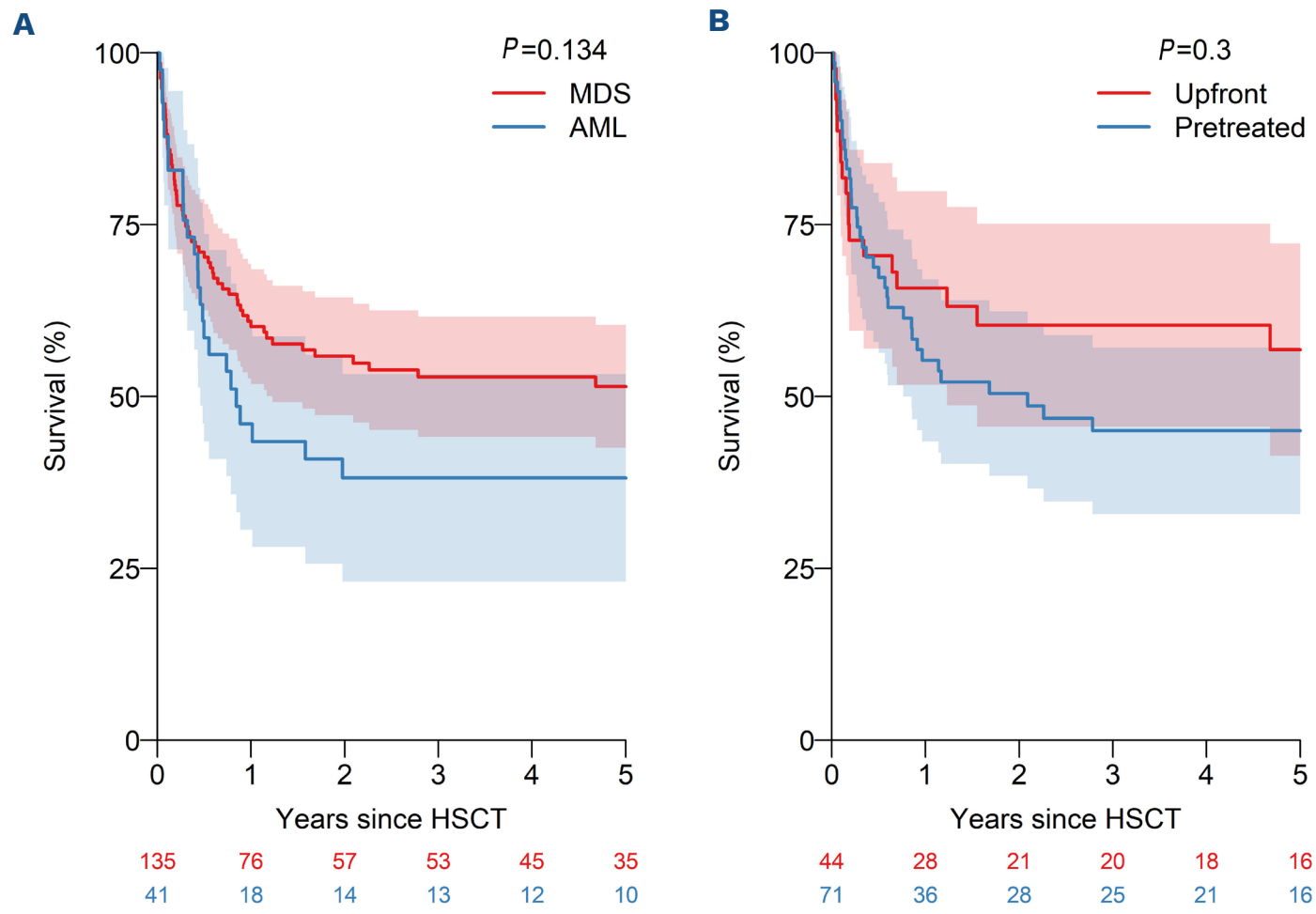

Figure 4. Kaplan Meier curves for graft failure, acute graft-*versus*-host disease III-IV, chronic graft-*versus*-host disease, and relapse-free survival. Estimates are stratified by (A) clonal evolution and (B) in the myelodysplastic syndromes cohort, stratified by pretreatment. The shaded regions indicate 95% confidence intervals. Numbers below the graphs show the number of patients at risk. Indicated *P* values are calculated by log-rank test. AML: acute myeloid leukemia; HSCT: hematopoietic stem cell transplant; MDS: myelodysplastic syndromes.

A National Institute of Health study found a 5-year OS of 57% with a median age of 19 years.[4] In the current study, the OS is comparable to studies for all coming AML[7,8] or MDS,[9,10] but patients were younger than the average MDS/AML. High disease burden has been associated with poorer survival.[1,11] Our data are inconclusive about the effect of MDS pretreatment before HSCT. Although survival estimates seem to differ, the log-rank test was not significant. While there might be a difference, the evidence is insufficient to arrive at any firm conclusions. All AML patients were pretreated; therefore, we cannot draw any conclusions for this subgroup. Patients with post-AA MDS/AML seem more prone to present severe hematopoietic toxicity even to hypomethylating agents,[6] perhaps because of a frail and reduced state of non-malignant hematopoietic stem cell pool in these patients. In agreement with previous data,[5,12] our findings suggest that post-AA MDS patients may not benefit from prior treatment before transplantation.

We have found very high NRM, particularly for MDS patients and those receiving a myeloablative conditioning regimen. Importantly, NRM was the leading cause of death in this study. NRM occurred chiefly in the first months following the transplant, which is more evident in the MDS group. RIC could be adequate for MDS patients, aiming to mitigate the very high NRM observed.

Relapse was the second most frequent cause of death. The use of MAC did not reduce the relapse incidence. Notably, half of relapses occurred after the first year post transplant, highlighting the need for post-transplant maintenance, such as targeted therapies or donor lymphocyte infusions for eligible patients. In the era of novel agents, alternative pre-transplant treatments might also be considered, such as the association of venetoclax with hypomethylating agents. Patients with chromosome 7 abnormalities did not present worse survival following transplantation than the other subgroups. This study is the first to investigate the impact of conventional cytogenetics on transplant outcomes for this specific population. Chromosome 7 abnormalities are the most frequent cytogenetic abnormality among post-AA/MDS patients and have been associated with poor OS.[3,4,13] A multicentric retrospective study conducted a multivariable analysis on 94 patients with post-AA secondary myeloid neoplasia and found that bone marrow excess blasts negatively impacted survival. In contrast, high-risk cytogenetics showed no significant effect.[1] In contrast, transplant studies on myeloid malignancies have reported higher relapse and disease progression rates among patients with unfavorable cytogenetics. However, most transplanted patients in these studies had excess blasts at diagnosis.[14-16] Notably, patients with chromosome 7 abnormalities who underwent transplantation before progressing to a higher disease stage had the best outcomes, particularly in the absence of complex

or monosomal karyotypes. In our study, complex karyotypes were rare, and data on blast counts at the time of transplantation were unavailable. The traditionally poor prognosis associated with high-risk cytogenetic abnormalities in prior transplantation studies may primarily reflect the impact of complex or monosomal cytogenetics or excess blasts rather than an isolated chromosome 7 abnormality - the most common finding in post-AA MDS patients. In other words, poor-risk cytogenetics often coincide with advanced disease, increasing susceptibility to treatment toxicity and myeloid malignancy relapse. Notably, routine hematologic surveillance in AA patients might enable early detection of chromosome 7 abnormalities, allowing for timely transplantation before the acquisition of additional high-risk features such as excess blasts or complex karyotypes.

The median time from AA to myeloid neoplasm diagnosis of around three years was similar to that of previously published studies.[1,17] Although previous data suggested post-AA MDS/AML as a long-term complication,[2,18] the median interval elapsed between AA and MDS/AML found in recent studies demonstrates that clonal evolution may be a mid-term complication.

Our data showed that most transplanted patients were between their fourth and fifth decades of life. Notably, AA is a disease with a bimodal incidence distribution that increases with age.[19] Older age is also a risk factor for clonal evolution into myeloid neoplasms.[1,17] Therefore, our results suggest that many patients presenting with post-AA MDS/AML were not eligible for transplantation. Besides its retrospective nature, other limitations of this study are the lack of disease status at transplantation and response to previous treatments, comorbidities, precise data on conditioning regimens, and blast count at transplantation. Furthermore, we were underpowered to perform some analyses, and although the difference between groups was sometimes as high as 15%, the statistical test was non-significant. The rarity of AA makes it unlikely that a more sizeable cohort could be put together or a prospective study on transplanted post-AA myeloid neoplasms be performed.

Our data showed that transplant is both feasible and effective in achieving long-term survival for transplant-eligible post-AA myeloid neoplasm patients. These real-world data provide valuable insights to help optimize HSCT strategies and long-term management in this challenging and rare patient population. Transplantation using a RIC regimen for MDS patients could help mitigate the high NRM we observed, and our data did not favor pretreating these patients before transplantation. AML patients present a higher risk of relapse and might benefit from post-transplant maintenance strategies.

Disclosures

PHP declares honoraria from Sobi and Alexion (unrelated to this work). All the other authors have no conflicts of interest to disclose.

Contributions

PHP designed the project, participated in patient recruitment, collected, analyzed, interpreted clinical data, and wrote the manuscript. DJ performed statistical analysis on clinical data. BP was the data manager for this study. AK, BD, JMLT, KV, MA, PC, TGD, AK, US, TS, JB, JC, FB, JM, ET, UP, NK, DB, SS and RS collected clinical data and provided helpful intellectual insights. AK and AR participated in patient recruitment, provided helpful intellectual insights, and edited the manuscript. RPL helped in designing the project, participated in patient recruitment, analyzed, interpreted clinical data, and edited the manuscript. All authors read and approved the final version of the manuscript and are accountable for all aspects of the work.

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Data-sharing statement

All the data have been presented in this study. Specific requests should be addressed to the corresponding author.

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