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RESEARCH ARTICLE

Outcomes of CMML patients undergoing allo-HCT are significantly worse compared to MDS—a study of the CMWP of the EBMT

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Abstract

Although CMML since long has been separated from MDS, many studies continue to evaluate the outcomes of both diseases after hematopoietic cell transplantation (allo-HCT) together. Data evaluating outcomes of a large CMML cohort after allo-HCT compared to MDS are limited. We aim to compare outcomes of CMML to MDS patients who underwent allo-HCT between 2010 and 2018. Patients ≥18 years with CMML and MDS undergoing allo-HCT reported to the EBMT registry were analyzed. Progression to AML before allo-HCT was an exclusion criterion. Overall survival (OS), progression/relapse-free survival (PFS), relapse incidence (including progression) (REL), and non-relapse mortality (NRM) were evaluated in univariable and multivariable (MVA) Cox proportional hazard models including interaction terms between disease and confounders. In total, 10832 patients who underwent allo-HCT were included in the study, there were a total of 1466 CMML, and 9366 MDS. The median age at time of allo-HCT in CMML (median 60.5, IQR 54.3–65.2 years) was significantly higher than in the MDS cohort (median 58.8, IQR 50.2–64.5 years; $p < .001$). A significantly higher percentage of CMML patients were male (69.4%) compared to MDS (61.2%; $p < .001$). There were no clinically meaningful differences in the distribution of Karnofsky score, Sorror HCT-CI score at allo-HCT, and donor type, between the CMML and MDS patients. RIC platforms were utilized in 63.9% of CMML allo-HCT, and in 61.4% of

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MDS patients ($p = .08$). In univariable analyses, we found that OS, PFS, and REL were significantly worse in CMML when compared with MDS (all $p < .0001$), whereas no significant difference was observed in NRM ($p = .77$). In multivariable analyses, the HR comparing MDS versus CMML for OS was 0.81 (95% CI, 0.74–0.88, $p < .001$), PFS 0.76 (95% CI 0.70–0.82, $p < .001$), relapse 0.66 (95% CI 0.59–0.74, $p < .001$), and NRM 0.87 (95% CI 0.78–0.98, $p = .02$), respectively. The association between baseline variables and outcome was found to be similar in MDS and CMML (all interaction $p > .05$) except for a decreasing trend over time of the risk of relapse in CMML (HR allo-HCT per year later 0.94, 95% CI 0.90–0.98), whereas no such trend was observed in MDS (HR 1.00, 95% CI 0.98–1.02). The poor outcome observed for CMML could be related to variables not measured in this study or to factors inherent to the disease itself. This study demonstrates that outcomes of CMML patients after allo-HCT are significantly worse compared to MDS. The results of this study may contribute to future recommendations for allo-HCT in CMML patients.

1 | INTRODUCTION

Chronic myelomonocytic leukemia (CMML) is a clonal heterogenic hematopoietic stem cell disorder characterized by peripheral blood monocytosis and features of both myeloproliferative neoplasms (MPN) and myelodysplastic syndromes (MDS).[1–3] The French American British (FAB) Group originally classified CMML as a form of MDS.[4,5] In 2001, the World Health Organization (WHO) reclassified the disease as part of a newly created MDS/MPN overlap entity[6] and the same classification concept has been maintained in subsequent revisions.[7,8] Although CMML and MDS have common features such as the presence of dysplasia, cytopenia, and that both frequently affects older patients, CMML differs by its proliferative behavior, always present at least in the monocyte lineage, and by its molecular signature.[1,9–15] Making decisions on CMML patients based on data obtained from clinical studies including only MDS patients, therefore, nowadays is no longer appropriate. Despite relatively high mortality and relapse rates, allogeneic hematopoietic cell transplantation (allo-HCT) remains the only curative treatment for both CMML and MDS.[16–25]

CMML is a disease that classically occurs in older patients, with a reported median age at presentation between 70 and 75 years. Current transplant recommendations in patients with malignant diseases no longer consider chronological age as an insurmountable restriction for intensive treatments, including allo-HCT.[17,26–28] Due to increased life expectancy and a greater number of fit adult-aged patients considered for therapeutic interventions, the additional consideration of "biological age" has arisen. Biological age is defined by a set of parameters that include the state of physical and mental health alongside comorbidities as well as chronological age. Indeed, the implementation of a geriatric assessment seems to contribute to a refined selection of older patients becoming candidates for allo-HCT.[29] Consequently, during the last few decades, a clear increase in the proportion of patients over 65 years undergoing allo-HCT has been reported within the *European Society for Blood and Marrow Transplantation* (EBMT) registry. In a retrospective study of the EBMT-CMWP that included a large cohort of more than 1200 MDS patients who underwent allo-HCT between 2003 and 2014, 23.4% were between the ages of 65 and 79 at the time of transplantation.[30] In another retrospective EBMT study, data of 6434 MDS and secondary acute myeloid leukemia (AML) adult patients from 21 countries who received a first allo-HCT between 2000 and 2012 showed that the percentage of patients older than 65 years at the time of allo-HCT increased from 5% to 17%).[31] Utilization of reduced intensity conditioning (RIC) regimens has progressively increased over time, constituting approximately 38% of all the conditioning regimens reported to the EBMT in the year 2018.[32] Prognostic assessment of patients with CMML is based on hematological and clinical features, including phenotypic disease sub-classification into proliferative and dysplastic and the proportion of marrow and blood blasts.[33–35] More recently, gene mutation profiling has been shown to impact both the progression and prognosis to a certain extent.[36–38]

Likewise, the role of allo-HCT in CMML, especially in elderly patients, remains unclear. Over the years, a number of clinical research efforts have attempted to establish optimal prognostic scores for CMML patients undergoing allo-HCT[39,40]; however, the limited number of patients analyzed in the different and heterogeneous series has represented a major limitation.[41] Therefore, in this retrospective EBMT registry-based study, we aimed to identify factors associated with allo-HCT outcomes in CMML patients, particularly focusing on age, and to compare them with a population of MDS patients undergoing allo-HCT in the same period.

2 | MATERIALS/SUBJECTS AND METHODS

2.1 | Data source

The study was performed on behalf of the EBMT, a non-profit scientific society comprising more than 600 transplant centers from Europe and

beyond. Accreditation as a member center requires submission of minimal essential data on patient and donor characteristics, treatment, and follow-up on clinical outcomes from all patients undergoing blood and bone marrow transplantation to a central database. EBMT centers commit to obtain informed consent according to the local regulations applicable at the time in order to report pseudonymized data to the EBMT.

2.2 | Collection of data and patient selection

Data were extracted from the EBMT registry. We selected CMML and MDS patients who underwent first allo-HCT between January 1, 2010 and December 31, 2018 and were 18 years of age or older at time of allo-HCT and had follow-up available beyond day of transplantation. CMML and MDS patients who progressed to AML before transplantation were excluded from this study.[42]

2.3 | Outcome and definitions

The main objective of the study was to assess the outcomes of CMML patients undergoing allo-HCT and compare them with a population of MDS patients undergoing allo-HCT during the same period. Second, we aimed to identify factors associated with allo-HCT outcomes in both cohorts, particularly focusing on the importance of recipient age. Outcomes studied were overall survival (OS), progression/relapse-free survival (PFS), relapse incidence (REL), non-relapse mortality (NRM), primary graft failure, and acute and chronic graft-versus-host disease (aGvHD and cGvHD). OS was defined as the time from allo-HCT to death from any cause and PFS was defined as the time from allo-HCT to relapse or progressive disease or death from any cause, whichever came first. Event time in patients with continuous progression (without a recorded date of the event) relapse was assumed 3 weeks after allo-HCT. aGvHD was defined as grade II-IV and cGvHD as either limited or extensive.

Patients with CMML were categorized according to the WHO 2008 staging approach (CMML 1 or 2) and the FAB [proliferative (MP-CMML), with WBC count ≥13 $\times 10^9$/L and dysplastic (MD-CMML), with WBC count <13 $\times 10^9$/L], sub-classification systems.[36,43] Cytogenetic data obtained at time of allo-HCT was used when it was available; otherwise, data collected at diagnosis were used.

2.4 | Statistical analysis

Clinical, demographical, and transplantation-related characteristics at baseline were tabulated for MDS and CMML patients as median and interquartile range (IQR) for continuous variables and frequencies and proportions for categorical variables. Differences in characteristics between CMML and MDS patients were assessed using p-values obtained with the χ^2 test for categorical variables and the Wilcoxon rank sum test for continuous data. Median follow-up after baseline and 95% confidence intervals were calculated using the reverse Kaplan–Meier (KM) method.

The probability of primary graft failure was compared in CMML and MDS patients using the χ^2 test. OS and PFS probabilities were analyzed using the Kaplan–Meier method and groups were compared using the log-rank test. Competing risks NRM together with REL, aGvHD together with death before aGvHD and cGvHD together with death before cGvHD were analyzed using the crude cumulative incidence estimator in a competing risks framework and groups were compared with Gray's test. Multivariable (MVA) Cox proportional hazard models were used to obtain (cause specific) hazard ratios (HR). Variables included in the MVA, apart from disease (CMML, MDS) were as follows: age at allo-HCT (as a binary variable < and ≥ 65 years, as a continuous linear variable, and in a more flexible manner using restricted cubic splines), sex (male, female), karyotype (normal, abnormal), stage of disease at allo-HCT (CR, untreated, other), type of donor (HLA-identical siblings; unrelated donors; both matched (MUD) and mismatched (MMUD); mismatched-related donors (MMRD), including haploidentical); Karnofsky-score (KPS) (90 or 100, ≤80), HCT- comorbidity index (HCT-CI) risk score[44] (0, 1–2, ≥3), year of allo-HCT (as a continuous linear variable) and intensity of the conditioning (RIC, MAC). To evaluate whether the association between these variables and outcome after allo-HCT was different in patients with CMML or MDS we tested for interaction disease x confounder using p-values obtained with the Wald test, where a low *p*-value provides evidence that the association of MDS/CMML and the outcome is different between different values of the confounder variable. Finally, we analyzed the same outcomes separately in just the CMML patients. All MVA included complete cases only.

All statistical tests were two-sided, and significance was determined when $p \leq .05$. All analyses were performed in R version 4.2.2[45]; using "survival," "cmprsk," "prodlim", and "rms" packages. No adjustment for multiple comparisons were made.

3 | RESULTS

Patient-, disease-, and transplant characteristics of 10 832 patients are summarized in Table 1. There were a total of 1466 CMML, and 9366 MDS patients who underwent allo-HCT. The median age at time of allo-HCT in CMML (median 60.5, IQR 54.3–65.2 years) was significantly higher than in the MDS cohort (median 58.8, IQR 50.2–64.5 years; $p < .001$). The median age at allo-HCT increased over time from 57.6 year (IQR 51.4–61.7) in 2010, to 61.9 year (IQR 57.0–66.8) in 2018 for CMML and 56.2 year (IQR 47.4–62.0) to 60.4 year (IQR 52.7–66.1) for MDS.

A total of 324 (22.1%) CMML patients were aged between 65 and 70 years and 64 (4.4%) aged 70 years or more. A significantly higher percentage of CMML patients were male (69.4%) compared to MDS (61.2%; $p < .001$), while the percentage of patients with low KPS (≤80) was not significantly different between CMML (28.7%) and MDS patients (27.8%; $p = .49$). The distribution of the HCT-CI score did not significantly differ between CMML and MDS patients; 22.6% and 24.2% of the CMML and MDS cohort, respectively, had a HCT-CI ≥3, ($p = .35$). Regarding disease status at time of allo-HCT, 28.6% of

TABLE 1 Patient, disease, and transplant characteristics at baseline for CMML and MDS patients.

	CMML	MDS	
	N (%)	*N* (%)	*p*
Total number of patients	1466 (100)	9366 (100)	
Age at allo-HCT (years), median (IQR)	60.5 (54.3–65.2)	58.8 (50.2–64.5)	<.001
<65 years	1078 (73.5)	7234 (77.2)	<.001
65–70 years	324 (22.1)	1667 (17.8)	
≥70 years	64 (4.4)	465 (5.0)	
Sex			
Male	1018 (69.4)	5736 (61.2)	<.001
Female	448 (30.6)	3630 (38.8)	
Cytogenetics at allo/diagnosis (missing in 33 and 38%, respectively)			
Normal	663 (67.4)	2709 (46.7)	<.001
Abnormal	320 (32.6)	3094 (53.3)	
Molecular biology at diagnosis (missing in 61 and 73%, respectively)			<.001
No mutations	236 (41.5)	1275 (50.9)	
At least one	333 (58.5)	1231 (49.1)	
Pretreatment, (missing in 69 and 75%, respectively)*			
Hypomethylating agents	389 (28.7)	967 (41.0)	<.001
Hydroxyurea	136 (29.6)	33 (1.4)	<.001
Disease stage at allo-HCT, (missing in 4 and 5%, respectively)			
Complete remission	402 (28.6)	2322 (26.0)	<.001
Stable disease/minor response	393 (28.0)	1766 (19.8)	
Relapse/progression/refractory	331 (23.5)	1952 (21.9)	
Untreated	235 (16.7)	2654 (29.7)	
Other	45 (3.2)	229 (2.6)	
KPS at allo-HCT, (missing in 7 and 7%, respectively)			
80 or lower	389 (28.7)	2417 (27.8)	.49
90 or 100	966 (71.3)	6291 (72.2)	
Sorror HCT-CI risk group, (missing in 26 and 29%, respectively)			
Low risk (0)	548 (50.3)	3357 (50.4)	.35
Intermediate risk (1–2)	295 (27.1)	1688 (25.4)	
High risk (≥3)	246 (22.6)	1610 (24.2)	
Type of Donor, (missing in 0.2 and 0.1%, respectively)			
MRD	417 (28.5)	2783 (29.8)	.55
Unrelated (MUD or MMUD)	926 (63.3)	5848 (62.5)	
Mismatched-related donor (Haplo)	120 (8.2)	721 (7.7)	
Source of stem cell, (missing in 0.1 and 0.1%, respectively)			.23
BM	129 (8.8)	936 (10.0)	
PB stem cell	1306 (89.1)	8165 (87.3)	
CB	26 (1.8)	179 (1.9)	
BM + PBSC	3 (0.2)	40 (0.4)	
BM + CB	0 (0.0)	1 (0.0)	
PBSC+CB	1 (0.1)	23 (0.2)	
BM + PBSC+CB	0 (0.0)	13 (0.1)	
Year of allo-HCT, median (IQR)	2015 (2013–2017)	2015 (2012–2017)	<.001
2010–2014	610 (41.6)	4488 (47.9)	<.001

TABLE 1 (Continued)

	CMML	MDS	
	N (%)	*N* (%)	*p*
2015–2018	856 (58.4)	4878 (52.1)	
Conditioning regimen, (missing in 2 and 2%, respectively)			
RIC	914 (63.9)	5623 (61.4)	.08
MAC	516 (36.1)	3540 (38.6)	

Note: *p*-values were obtained using the χ^2 test for categorical variables and Wilcoxon test for continuous variables. Percentages are calculated over patients with data available.

Abbreviations: BM, bone marrow; CB, cord blood;IQR, interquartile range; KPS, Karnofsky Performance Score; MAC, myeloablative conditioning; MRD, matched related donor; MUD, matched unrelated donor; PBSC, peripheral blood stem cell; RIC, reduced intensity conditioning.

*Pretreament drugs are not mutually exclusive.

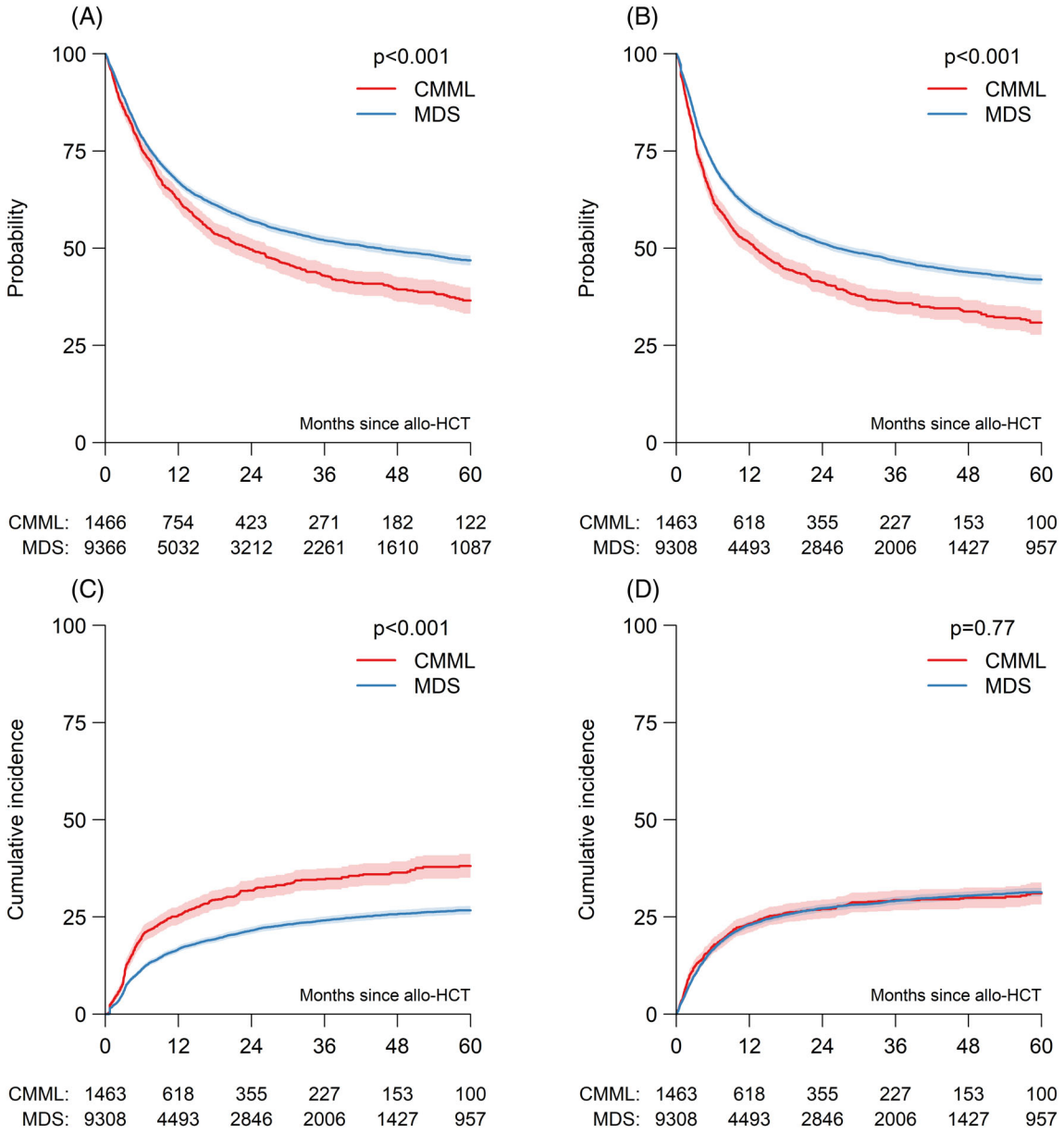

FIGURE 1 Outcome after allo-HCT in CMML and MDS patients: (A) Overall survival (OS), (B) progression-free survival (PFS), (C) cumulative incidence of relapse, and (D) cumulative incidence of non-relapse mortality (NRM). Numbers below the graph indicate the number of patients at risk. The shaded areas show the 95% confidence intervals. In three CMML and 58 MDS patients, relapse status was unknown.

the CMML and 26.0% of MDS patients were in CR at allo-HCT ($p < .001$). A total of 32.6% of CMML and 53.3% of MDS patients with data available had an abnormal cytogenetic result ($p < .001$). Cytogenetic data were missing in 37.4% of all patients. Donors were unrelated (matched or mismatched) in 63.3% of CMML patients, while 8.2% had a MMRD, including haploidentical. The distribution of donor types was similar in MDS patients ($p = .55$). RIC platforms were utilized in the vast majority (63.9%) of CMML allo-HCT, and to a somewhat smaller extent (61.4%) in MDS patients ($p = .08$).

CMML FAB subtype and disease stage at allo-HCT were missing in 68.0% and 50.5% of CMML patients, respectively. In the remaining CMML patients with available data at allo-HCT, FAB subtype was CMML-MD in 42.0% and CMML-MP in 58.0%, while stage was CMML-1 in 52.5% and CMML-2 in 47.5% of patients. In 64.2% of all MDS patients, ≥5% blasts at allo-HCT were observed.

3.1 | Primary graft failure and GvHD

The probability of primary graft failure was similar for CMML and MDS patients, at 3.8% and 3.5%, respectively ($p = .55$). No significant differences in the cumulative incidence of grade 2–4 aGvHD were observed between both disease entities (100-day cumulative incidence 28% in both diseases, Gray's test $p = .91$). A higher cumulative incidence of cGvHD was observed in MDS transplant recipients (2-year cumulative incidence 40%, 95% CI 39%–41%) as compared to those transplanted for CMML (36%, 95% CI 33–38%), Gray's test $p < .001$. In contrast, cumulative incidence of death before cGvHD was higher in CMML compared to MDS patients (38%, 95% CI 36%–41% vs. 31%, 95% CI 30%–32%, Gray's test $p < .0001$).

3.2 | Outcomes in CMML versus MDS cohort

For CMML, the median follow-up was 29.2 months (IQR 13.8 to 57.3) and for MDS this was 32.9 (IQR 13.1–60.0) months. In CMML patients, 5 year OS, PFS, and cumulative incidence of relapse and NRM was 37% (95% CI 33%–40%), 31% (95% CI 28%–34%), 38% (95% CI 35%–41%), and 31% (95% CI 28%–34%), respectively. In MDS patients, these 5-year estimates were 47% (95% 46%–48%), 42% (95% CI 41%–43%), 27% (95% CI 26%–28%), and 31% (95% CI 30%–32%), respectively. In univariable analysis, OS, PFS, and REL were significantly worse for CMML than MDS ($p < .001$, Figure 1), regardless of the blast percentage in MDS patients at allo-HCT (data not shown). No difference was apparent for NRM (Gray's test $p = .77$, Figure 1). When OS was analyzed by age categories, as expected, a significant inverse association was observed for both CMML and MDS (Figure 2); albeit OS for CMML patients was lower compared to MDS patients in each category. Male CMML patients had a (borderline) significantly poorer OS (log-rank $p = .06$), PFS (log-rank $p = .02$), and NRM ($p = .02$) than female CMML patients yet with no significant difference (Gray's test $p = .89$) in the cumulative incidence of relapse (Figure 1). Regarding CMML-MD and CMML-MP, despite the high percentage of missing data (68%), the available data were analyzed. No significant differences between CMML-MD and CMML-MP were observed in OS (log-rank $p = .90$), PFS (log-rank $p = .25$), cumulative incidence of relapse (Gray's test $p = .06$), and NRM ($p = .49$). Nor did we observe significant differences between CMML type I and type II in OS log-rank ($p = .43$), PFS ($p = .44$), cumulative incidence of relapse (Gray's test $p = .54$) and NRM ($p = .84$). (Figure 2). CPSS information was only available in 416 (28%) CMML patients. Indeed, when allo-HCT outcomes were analyzed according to the CPSS classification, we only observed small differences among groups, with no

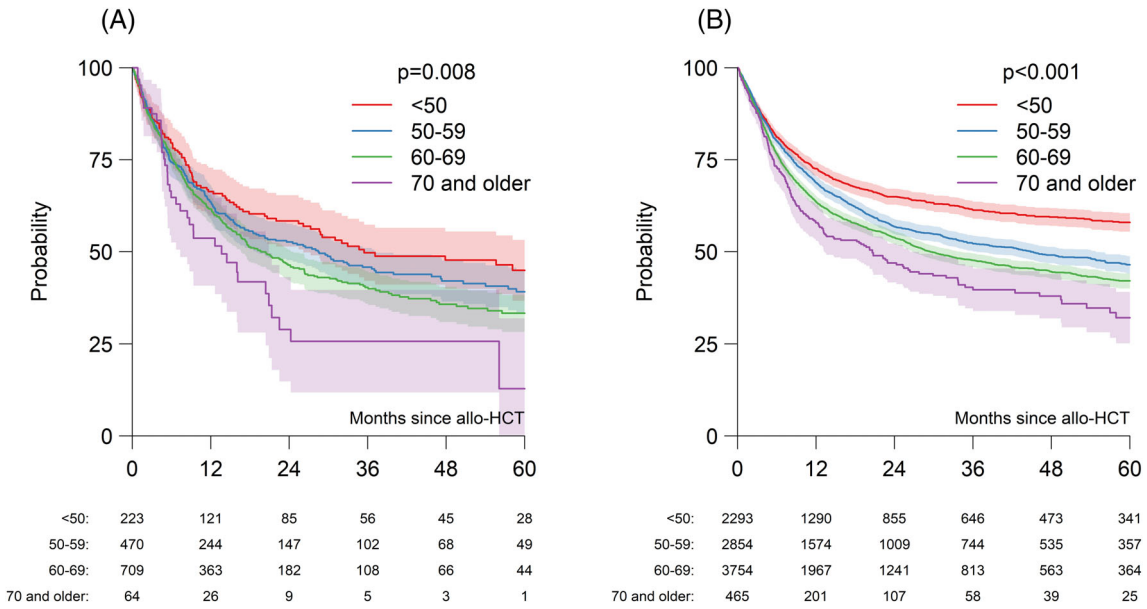

FIGURE 2 Overall survival after allo-HCT in (A) CMML and (B) MDS patients. Numbers below the graph indicate the number of patients at risk. The shaded areas show the 95% confidence intervals.

TABLE 2 (Cause specific) hazard ratio's and 95% confidence intervals (CI) of overall survival (OS), progression/relapse-free survival (PFS), relapse, and non-relapse mortality (NRM) obtained with multivariable Cox proportional hazard models in CMML and MDS patients.

		OS			PFS			Relapse			NRM		
		HR (95% CI)	(Overall) p*	Interaction p**	HR (95% CI)	(Overall) p*	Interaction p**	HR (95% CI)	(Overall) p*	Interaction p**	HR (95% CI)	(Overall) p*	Interaction p**
Disease	CMML	1.00			1.00			1.00			1.00		
	MDS	0.81 (0.74–0.88)	<.0001		0.76 (0.70–0.82)	<.0001		0.66 (0.59–0.74)	<.0001		0.87 (0.78–0.98)	.02	
Age	per 10 year increase	1.17 (1.13–1.20)	<.0001	.60	1.15 (1.11–1.18)	<.0001	.25	1.09 (1.04–1.14)	<.0001	.17	1.20 (1.15–1.25)	<.0001	.89
Sex	Male	1.00		.46	1.00		.33	1.00		.55	1.00		.33
	Female	0.92 (0.86–0.98)	.008		0.92 (0.86–0.98)	.006		0.99 (0.90–1.08)	.75		0.86 (0.79–0.94)	.0005	
Type of donor	MRD	1.00	(<.0001)	.40	1.00	(<.0001)	.45	1.00	(.007)	.55	1.00	(<.0001)	.32
	MMRD	1.50 (1.33–1.70)	<.0001		1.36 (1.21–1.52)	<.0001		0.89 (0.74–1.06)	.21		1.96 (1.68–2.28)	<.0001	
	MUD	1.08 (1.00–1.17)	.04		1.02 (0.95–1.10)	.51		0.84 (0.76–0.93)	.0006		1.26 (1.13–1.40)	<.0001	
	MMUD	1.39 (1.26–1.53)	<.0001		1.25 (1.14–1.37)	<.0001		0.82 (0.72–0.95)	.008		1.80 (1.59–2.04)	<.0001	
	Unrelated, MM unknown	1.20 (1.07–1.33)	.001		1.12 (1.02–1.24)	.04		0.85 (0.73–0.99)	.03		1.47 (1.28–1.69)	<.0001	
Year of allo HCT	per year later	0.96 (0.95–0.98)	<.001	.26	0.96 (0.95–0.98)	<.0001	.16	0.99 (0.97–1.00)	.15	.006	0.95 (0.93–0.96)	<.0001	.48
Karnofsky score	80 or lower	1.00		.80	1.00		.48	1.00		.62	1.00		.83
	100 or 90	0.72 (0.67–0.77)	<.0001		0.75 (0.71–0.80)	<.0001		0.86 (0.78–0.94)	.002		0.68 (0.62–0.73)	<.0001	
Conditioning	RIC	1.00		.67	1.00		.35	1.00		.23	1.00		.73
	MAC	1.10 (1.02–1.17)	.000		1.07 (1.00–1.14)	.04		0.92 (0.84–1.02)	.11		1.21 (1.10–1.32)	<.0001	
Stage of disease at allo HCT	CR	1.00	(<.0001)	.65	1.00	(<.0001)	.29	1.00	(<.0001)	.05	1.00	(<.0001)	.82
	Untreated	0.95 (0.88–1.02)	.30		0.92 (0.84–0.99)	.04		0.64 (0.56–0.72)	<.0001		1.23 (1.10–1.37)	.0003	
	Other	1.17 (1.08–1.26)	<.0001		1.16 (1.08–1.24)	<.0001		1.10 (0.99–1.21)	.06		1.23 (1.11–1.36)	<.0001	

Abbreviations: CI, confidence interval; CR, complete remission; HR, hazard ratio; MAC, myeloablative conditioning; MMRD, mismatched related donor; MMUD, mismatched unrelated donor; MRD, matched related donor; MUD, matched unrelated donor; RIC, reduced intensity conditioning.

*Test whether the risk/hazard of the outcome is different between categories of the variable. For donor type and stage of disease at allo-HCT, the overall p-value obtained with the Wald test is given between brackets.

**Test for interaction tests whether the association between the risk/hazard of the outcome and the variable is different in MDS and CMML patients.

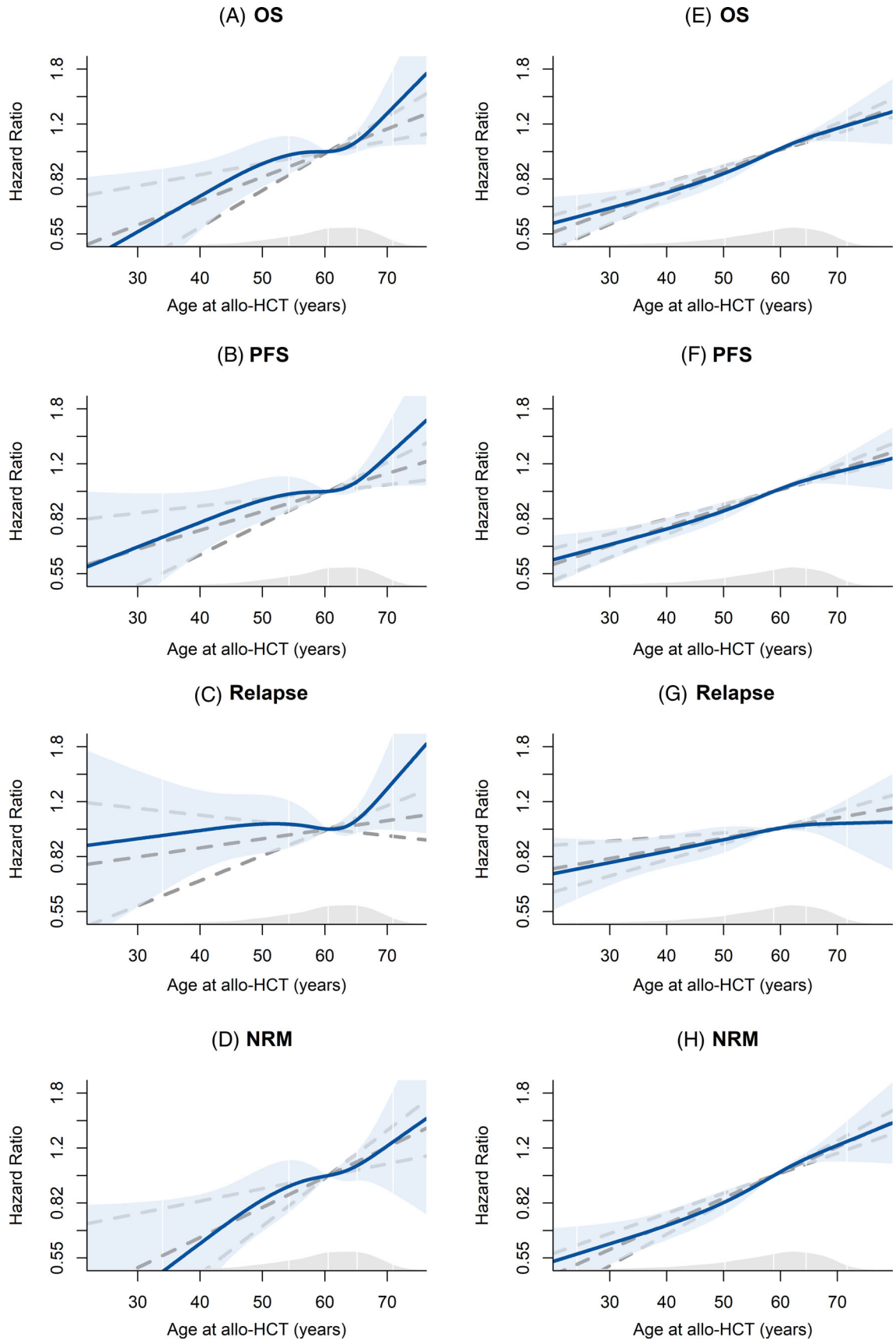

FIGURE 3 Legend on next page.

statistical significance (Table S2). IPSS and IPSS-R information was limited in our cohort with less than 25% available data. Outcome based on calculation of the available data is summarized in the supplementary data (Tables S3 and S4). As expected, the probability of survival according to IPSS and IPSS-R risk groups was consistently higher in MDS patients compared to CMML patients.

Results of MVA of OS, PFS, relapse, and NRM in both CMML and MDS are summarized in Table 2 (for CMML analyzed separately also in Table S1) and show significantly better outcomes after allo-HCT for MDS patients than CMML patients. The HR comparing MDS versus CMML for OS was 0.81 (95% CI, 0.74–0.88, $p < .001$), PFS 0.76 (95% CI 0.70–0.82, $p < .001$), relapse 0.66 (95% CI 0.59–0.74, $p < .001$), and NRM 0.87 (95% CI 0.78–0.98, $p = .02$), respectively. Older age at allo-HCT, male gender, earlier year of allo-HCT, low KPS, MAC conditioning, and being in a state of disease at time of allo-HCT other than CR or untreated were all associated with a worse OS, PFS, and NRM. The use of a donor other than a MRD also associated with worse survival and NRM outcomes, even though PFS in MUD was similar to MRD. Older age at allo-HCT and low KPS, were significantly associated with a higher risk of relapse, whereas being transplanted with a MUD or MMUD (as compared to MRD) and patients who were untreated prior to allo-HCT (as compared to patients in CR) were associated with a lower risk of relapse.

We then evaluated whether the association of each prognostic factor and the outcome was different between CMML and MDS cohorts by including interaction terms between each variable and disease (CMML/MDS). With the exception of a significant interaction between year of allo-HCT and disease on risk of relapse ($p = .006$), we found no significant interaction between disease and any variables included in the model on any outcome. There was no change in the risk of relapse in MDS patients according to the calendar year of allo-HCT (for each year later HR 1.00, 95% CI 0.98–1.02), whereas in CMML the risk decreased over time (HR 0.94, 95% CI 0.90–0.98).

Finally, we modeled age as a continuous linear variable and in a more flexible manner using restricted cubic splines for each disease separately, and including the variables listed in Table 2. In CMML patients, the hazard of death increased strongly in patients ≥65 years but as there are only few patients in this age range the confidence intervals were wide and there was no evidence that this model was significantly different from the linear model ($p = .47$), (Figure 3A). Also for PFS, relapse, and NRM, there was no evidence that the restricted cubic spline model was better than the linear age model ($p = .49$, $p = .39$, and $p = .86$, respectively). In MDS patients, the confidence intervals were narrower due to the larger number of patients. Also, when using the flexible age modeling the HR increased in a linear manner with older age for each outcome.

4 | DISCUSSION

This study evaluated relevant transplant-specific outcomes of a large CMML cohort who underwent allo-HCT and compared results to a MDS cohort transplanted over the same period. In MVA, adjusted for age and stage at allo-HCT, sex, year of allo-HCT, donor type, KPS, and conditioning intensity, there was still an increased risk of death, relapse, and NRM in CMML compared to MDS patients. Comparison of post-transplant outcomes for CMML patients to other myeloid diseases has been previously analyzed in a study that assessed the impact of the primary disease on allo-HCT outcomes for transformed secondary acute leukemia.[42] That study evaluated populations at different risk than the one evaluated here, since transformation to AML was an exclusion criterion in our study. Although there are a number of studies investigating the outcomes of CMML[40,46–49] and MDS[30,50–53] patients after allo-HCT, comparative studies of both diseases including such a large number of patients, as in our study, have not been performed to date.

In this study, we observed that rates of allo-HCT for CMML increased over time, as 59% of the evaluated patients underwent allo-HCT between 2014 and 2018, that is, the second half of the evaluated period, with a predominant use of RIC regimens (63.7%). Moreover, our data also confirm the ongoing trend of allo-HCT use in older patients[30,32] as 21.8% of the CMML analyzed population were aged between 65 and 70 years of age and 4.3% were older than 70 years. We want to emphasize that the focus of this study was to evaluate outcomes of CMML patients after allo-HCT, excluding those who transformed into AML before transplantation. It was important to analyze CMML outcomes separately from MDS patients since little information in this regard is available in the literature (CMML data are summarized in Table S1), and subsequently compare these results with MDS.

Comparing CMML versus MDS allo-HCT populations, we found that the CMML cohort comprised of older individuals, contained more males, and had a lower number of patients in CR at time of allo-HCT. KPS and Sorror HCT-CI score, as well as the type of donor did not differ in the MDS cohort. Conditioning intensity, as expected due to disease type, was predominantly RIC in both cohorts, but quantitatively there was a significantly higher percentage of patients transplanted with this modality in patients with CMML. For the MDS population, there was, as expected given the incidence of the disease, a greater number of patients. In summary, apart from the differences concerning the disease per se and their epidemiological aspects, patients' clinical characteristics, as well as the type of donors and conditioning regimens used, both populations were comparable.

FIGURE 3 Adjusted hazard ratios (HR) by age at allo-HCT (with 60 year of as reference, i.e., HR = 1) for (A) Overall-Survival (OS), (B) progression/relapse free-survival (PFS), (C) Relapse and (D) Non-Relapse Mortality (NRM) in CMML patients and (E) OS, (F) PFS, (G) relapse and (H) NRM in MDS patients. In every graph, the gray dashed lines show the HR and 95% confidence intervals (CI) obtained using a linear age model (HR and 95% CI). The blue line and shading show the HR and 95% CI obtained when age was modeled using restricted cubic splines. The gray shading at the bottom shows the age distribution among CMML and MDS patients.

In univariable analysis, OS, PFS, and REL were significantly worse in the CMML cohort when compared with MDS, whereas NRM was similar in CMML and MDS. Age at allo-HCT ≥65 years in the adjusted model conferred a negative impact on OS, PFS, and NRM in both diseases, indeed, one of the primary objectives of this study was to assess the role of age on the outcomes of patients with CMML and compared to the MDS group. There was no evidence that age "acted differently" in CMML or MDS: older age, as expected, was associated with worse outcomes in both diseases.

Other groups have previously reported a high cumulative incidence of disease recurrence post-allo-HCT for CMML patients. By way of example, in a nationwide retrospective analysis of 159 CMML patients who underwent allo-HCT in Japan, the 3-year total cumulative incidence of death after relapse was 39%.[47] Another study showed that the 3-year-CI of relapse was 33.3% in 83 CMML patients analyzed retrospectively, including 36 with CMML progressed to AML, who received an allo-HCT between April 1991 and December 2013 at MD Anderson Cancer Center.[46] In the current study, we demonstrate a significantly higher cumulative incidence of relapse in CMML patients compared to MDS. This difference remained in the MVA and can therefore not be explained by differences in the distribution of risk factors in CMML and MDS patients. There was also no evidence for interaction between disease and any clinical confounder included in the model on any outcome, meaning that the association between risk factors and outcomes is similar for both diseases. The postulated immunological protective effect of cGVHD against relapse,[54] it was not particularly observed in this cohort, even though in our study we did not specifically investigated on the association between cGvHD and relapse. This could be explained due to the lower rate of cGVHD observed in CMML patients, which could be possibly explained by the observed higher cumulative incidence of death before cGVHD in comparison to MDS patients.

The explanation for the worse outcome in CMML as compared to MDS might therefore be explained by the disease biology or unmeasured confounders. Interestingly, there was only one favorable exception for CMML, as we observed that there was a reduction over time in the probability of relapse in CMML patients, whereas no reduction was seen in MDS patients. This trend could be reflective of greater experience across transplant centers undertaking allo-HCT for CMML patients or indeed differing pre- or post-allo-HCT interventions; however, additional data confirming this trend are required before firm conclusions can be drawn. In CMML patients, there is a clear need to introduce strategies that allow better post-transplant control of the disease. In that sense, disease control models used in other myeloid diseases after allo-HCT, as, for example, MDS and AML,[55–57] could be used as a reference to define maintenance strategies specifically designed for CMML.

This retrospective study has both strengths and limitations. Given the nature of a registry-based study, one major strength is the sheer volume of collected data from both cohorts, analyzed in two quite rare diseases, which allowed us to show that the post-allo-HCT outcome in CMML compared to MDS differs, being worse in CMML. There were also several limitations, mainly related to the retrospective nature of studies based on patient registry data, commonly characterized by limited availability and underreporting of data, in particular the lack of cytogenetic and molecular annotations, a number of missing clinical relevant information (e.g., splenomegaly) and its variable quality.[58,59]

5 | CONCLUSIONS

The comparison of OS, PFS, and REL shows significantly worse post-allo-HCT outcomes in CMML compared to MDS, regardless of the percentage of blasts in MDS patients at allo-HCT, with no difference in NRM in univariate analysis. After adjustment for evaluated variables, an increased risk for all outcomes in CMML compared to MDS was still observed. There was no evidence that the association between age at allo-HCT and outcome after allo-HCT was different in CMML or MDS patients, and, as expected, advanced age was associated with more adverse outcomes in both diseases, suggesting that the underlying disease biology may be the pivotal factor. The worse survival outcomes in CMML in comparison to MDS appear to be the consequence of the significantly higher rate of post-transplant relapse. These results may contribute to future recommendations for allo-HCT indications in CMML patients. Future research should focus on both pre- and post-transplant strategies to improve disease control.

AUTHOR CONTRIBUTIONS

Alicia Rovó had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Alicia Rovó, Francisco Onida, Marie Robin, Ibrahim Yakoub-Agha. Acquisition, analysis, or interpretation of data: Alicia Rovó, Luuk Gras, Brian Piepenbroek, Francisco Onida, and Donal P. McLornan. Statistical analysis: Luuk Gras, Liesbeth C. de Wreede. Administrative, technical, or material support: Alicia Rovó, Luuk Gras, Brian Piepenbroek, Francisco Onida, and Donal P. McLornan. Supervision: Alicia Rovó, Luuk Gras, Francisco Onida, Marie Robin and Donal P. McLornan. Drafting of the manuscript: Alicia Rovó, Luuk Gras, Francisco Onida. Critical revision of the manuscript for important intellectual content: Liesbeth C. de Wreede, Donal P. McLornan, Marie Robin, Brian Piepenbroek, Nicolaus Kröger, H. Christian Reinhardt, Aleksandar Radujkovic, Didier Blaise, Guido Kobbe, Riitta Niityvuopio, Uwe Platzbecker, Katja Sockel, Mathilde Hunault-Berger, J.J. Cornelissen, Edouard Forcade, Jean Henri Bourhis, Yves Chalandon, Francesca Kinsella, Stéphanie Nguyen-Quoc, Johan Maertens, Ahmet Elmaagacli, Nicola Mordini, Patrick Hayden, Kavita Raj, Joanna Drozd-Sokolowska, Ibrahim Yakoub-Agha.

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DATA AVAILABILITY STATEMENT

EBMT Policy: Data cannot be shared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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