American Journal of Hematology

WILEY

RESEARCH ARTICLE

Allogeneic Hematopoietic Cell Transplantation in Patients With Acute Myeloid Leukemia With Myelodysplasia-Related Genetic Features: Relevance of the Genetic Underlying Category. A Retrospective Analysis on Behalf of the Acute Leukemia Working Party of the EBMT

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Received: 24 November 2024 | **Revised:** 31 January 2025 | **Accepted:** 20 February 2025

Funding: The authors received no specific funding for this work.

Keywords: acute myeloid leukemia | allogeneic hematopoietic cell transplantation | mutated TP53 | myelodysplasia-related cytogenetic abnormality | myelodysplasia-related gene mutation

ABSTRACT

Patients (pts) with myelodysplasia-related AML (MR-AML) are now genetically recategorized, with three different groups in the International Consensus Classification: AML with mutated TP53 (TP53-AML), with myelodysplasia-related gene mutations (MR-GM AML), and with myelodysplasia-related cytogenetic abnormalities (MR-CG AML). Moreover, TP53-AML is determined by the presence of an additional complex karyotype (TP53-mut CK and non-CK AML, respectively). Nonetheless, the relevance of this classification to transplantation outcomes is largely unknown. We analyzed the outcomes of pts. with MR-AML undergoing allogeneic

Jordi Esteve and Arnon Nagler both authors contributed equally.

Data presented in part at the Tandem Meetings: Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR, February 21–24, 2024, San Antonio, Texas, US (published in *Transplantation and Cellular Therapy* 2024;30, supplement: S6 and S7).

hematopoietic cell transplantation in first complete remission between 2010 and 2022 according to these genetic categories. Overall, 1152 patients were identified: 379 (33%), 328 (28%), 246 (21%), and 199 (17%) with MR-GM, TP53-mut CK, MR-CG, and TP53-mut non-CK AML, respectively. Median age was 60 years; median year of transplant was 2020. Unrelated donors and reduced-intensity conditioning were used in 65% and 61% of cases, respectively. Outcomes differed markedly among genetic categories, with an increasing relapse incidence (20.2%, 29.2%, 44.6%, and 57.6% at 2 years), and decreasing LFS (60%, 55.3%, 40.6%, and 20.2% at 2 years), overall survival (65.7%, 60.1%, 47.1%, and 24.5% at 2 years), and graft-versus-host disease-free, relapse-free survival (46.9%, 39.5%, 31.9%, and 13.2% at 2 years) in MR-GM, MR-CG, TP53-mut non-CK, and TP53-mut CK AML, respectively. These differences were confirmed in the multivariate analysis (hazard ratio for LFS: 0.21, 0.33 and 0.61 in MR-GM, MR-CG, and TP53-mut non-CK, with respect to reference TP53-mut CK AML group). This study confirms the strong impact of genetic grouping of MR-AML on transplant outcomes.

1 | Introduction

One of the main modifications proposed by the newer acute myeloid leukemia (AML) classification launched in 2022 corresponds to the distinction of myelodysplasia-related AML (MR-AML) subtypes according to their AML-subtype defining genetic background [1, 2]. These AML subtypes were mostly included in the former category of AML with myelodysplasia-related changes (AML-MRC), which, on the one hand, did not consider myelodysplasia-related recurrent gene mutations as a diagnostic criterion of this AML category and, on the other hand, took into consideration the presence of dysplastic features in hematopoietic precursors [3, 4]. Thus, MR-AML cases are now split into three different genetic categories in the International Consensus Classification (ICC), which establishes a hierarchical, stepwise diagnostic procedure based first on the presence of a TP53 mutation (TP53-AML), second, on the identification of any of the nine myelodysplasia-related defining gene mutations (MR-GM AML) and, finally, on the presence of any of the pre-defined myelodysplasia-related cytogenetic abnormalities (MR-CG AML) [2]. The World Health Organization (WHO) 2022 classification does not include TP53-AML patients as a separate category, and most of these patients, usually harboring a complex karyotype with recurrent loss of characteristic chromosomal regions such as 5q and 7q, are included in the group of MR-CG AML [1]. Moreover, the MR-AML category represents approximately one third of overall AML patients, and this proportion increases with age [5–7].

The vast majority of MR-AML are considered high-risk AML patients according to the 2022 European LeukemiaNet (ELN) risk stratification and therefore, allogeneic hematopoietic cell transplantation (alloHCT) is the recommended post-remission strategy in first complete response (CR1) in transplant-eligible patients [8]. Nonetheless, the prognosis of these different MR-AML subtypes seems diverse, and this intra-category heterogeneity is mainly driven by the type of genetic MR-AML defining event. Thus, patients harboring TP53 mutation show a distinctive, very poor outcome, with a fraction of long survivors of less than 25% [8–10]. On the contrary, non-TP53-AML patients within the ELN adverse risk category, with a high prevalence of MR-GM AML, show a better outcome, overlapping with that of intermediate genetic risk as defined by ELN 2022 [6, 11–13].

Accordingly, previous studies have shown a strikingly different outcome and relapse risk among diverse adverse genetic categories after alloHCT. Thus, the prognosis of patients with *TP53* mutation and additional cytogenetic abnormalities, *MECOM*-rearranged AML, or AML associated with deletion 5q/monosomy 5 or deletion/monosomy 7q with additional cytogenetic abnormalities is markedly poor, mainly due to a high risk of relapse incidence (RI) after transplant, surpassing 50% at 2 years even when the transplant is performed in CR1 [11–20]. On the contrary, the outcome of patients with other ELN 2022-defined high-risk genetic subtypes such as AML with *RUNX1* mutation is markedly better, with a 2-year relapse risk of 20% and leukemia-free survival (LFS) of 61% [21].

In this setting, we aimed to analyze the impact of the underlying myelodysplasia-related defining genetic event on the outcome of patients diagnosed with MR-AML who underwent alloHCT in CR1 and, subsequently, validate the genetically based classification proposed by the ICC and the WHO 2022.

2 | Patients and Methods

2.1 | Study Population

The aim of the study was to analyze the outcome of adult patients diagnosed with any type of MR-AML undergoing alloHCT, focusing on the impact of underlying genetics. For this purpose, a retrospective cohort study of patients reported to the European Society for Blood and Marrow Transplantation (EBMT) database was performed. The patient population comprised adult patients (i.e., ≥ 18 years) diagnosed with any of the three large genetic categories related to myelodysplastic neoplasms as classified in the recent ICC classification, that is, TP53-AML, MR-GM AML, and MR-CG AML. Other inclusion criteria were receipt of alloHCT in CR1 of their disease, from a family or unrelated donor (with a 9 or 10/10 human leukocyte antigen [HLA] match based on HLA-A, B, C, DRB1 and DQB1 loci), with an ex vivo non-T cell depleted graft during the period 2010–2022. Transplants from cord blood were excluded. Allocation to these three MR-AML genetic categories was performed in a hierarchical manner as established by the ICC classification, with *TP53* mutation as the first grouping criterion (TP53-AML), presence of any of the nine MR-related gene mutations (*ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1 or ZRSR2*) as a second hierarchical grouping criterion, and patients harboring any of the ICC MR-defining cytogenetic abnormalities (i.e., a complex karyotype defined by ≥ 3 abnormalities, del(5q)/−5, del(7q)/−7, +8, del(12p), del(13q)/−13, del(17p)/−17, del(20q), idic(X)(q13)) without any of the previous grouping criteria were allocated to the MR-CG AML group. Given the prognostic impact of additional cytogenetic abnormalities in *TP53*-mutated AML, the TP53-AML category was subdivided into two groups according

to the presence or absence of an additional complex cytogenetic karyotype (TP53-mut CK AML and TP53-mut non-CK AML, respectively). These four genetic MR-AML categories are detailed in Table S1.

Data were extracted from the EBMT registry, which comprises more than 600 transplant centers providing reports and annual follow-up on all consecutive stem cell transplantations. Audits are routinely performed to determine the accuracy of the data. Since 1990, patients have provided informed consent, authorizing the use of their personal information for research purposes. The study was approved by the general assembly and review board of the Acute Leukemia Working Party (ALWP) and complied with country-specific regulatory requirements.

2.2 | Study Endpoints

Main study endpoints were overall survival (OS), LFS, RI after alloHCT, as well as non-relapse mortality (NRM), acute graft-versus-host disease (aGVHD) at 180 days, and chronic GVHD (cGVHD) at 2 years, and GVHD-free, relapse-free survival (GRFS). OS was defined as the interval between the date of alloHCT and the date of death or last follow-up, LFS as the interval between alloSCT and the date of leukemia persistence, relapse, progression, or death. NRM was defined as death from any cause without relapse or progression. GRFS was defined as survival without aGVHD grades III-IV, cGVHD requiring systemic treatment, relapse, or death [22].

2.3 | Conditioning Intensity Definition

Definitions of conditioning regimen intensity and distinction between reduced intensity (RIC) and myeloablative conditioning (MAC) followed the definition described in Bacigalupo et al. [23]. In addition to this dichotomic RIC/MAC distinction, conditioning intensity prognostic value was further explored using the Transplant Conditioning Intensity (TCI) score, which provides a 3-category stratification resulting from the sum of the assigned intensity weight scores of the most frequently used components used in the conditioning regimen [24, 25].

2.4 | Statistical Methods

Descriptive statistics were presented using median, range (minimum to maximum) and interquartile range (IQR) for continuous data, and frequency and percentages for categorical data. Comparison of numerical variables was performed using the Mann–Whitney *U* test, whereas the Chi-square or Fisher's exact tests, when indicated, were used for comparison of categorical variables. The probability of OS, LFS, and GRFS were calculated using the Kaplan–Meier (KM) estimate. Survivors were censored at last contact. Cumulative incidence was used for estimation of RI and NRM considering death and relapse as competitive events, respectively, whereas relapse and death were considered competing events for acute and cGVHD. The median follow-up was estimated using the reverse KM method. A multivariate analysis (MVA) adjusting for potential confounding factors was performed using a Cox's proportional-hazards regression model for main outcomes. Results were expressed as a hazard ratio (HR) with a 95% confidence interval. All outcomes were censored at 2 years according to the median follow-up of the most recent period. To test for a center effect, we introduced a random effect or 'frailty' for each center into the model. All tests were 2-sided. The type I error rate was fixed at 0.05 for factors associated with time-to-event outcomes. Analyses were performed using R (version 4.3.2 R Foundation for Statistical Computing, Vienna, Austria).

3 | Results

3.1 | Characteristics of Patients

A total of 1152 MR-AML patients undergoing alloHCT in the study period were identified. They were distributed in the prespecified genetic groups (Table S1A) in the following manner: 379 patients with MR-GM AML (33%), 328 (28%) with TP53-mut CK AML, 246 (21%) with MR-CG AML, and the remaining 199 (17%) with TP53-mut non-CK AML. The main characteristics of patients are described in Table 1. The median age was 60 years, and 41% were female. Most patients presented with *de novo* AML (84%), and only 13% harbored an *FLT3*-ITD mutation. Among MR-CG AML patients, a complex karyotype was the most prevalent cytogenetic abnormality, present in 123 (50%) patients (Table S1B).

Median interval from diagnosis to alloHCT was 4.5 months, and median year of transplant was 2020. Unrelated donor was the most frequent donor type, used in 744 (65%) procedures, with a 10/10 or 9/10 HLA donor-recipient match in 464 and 123 of these procedures, respectively (148 cases with unknown HLA match), whereas an HLA-identical sibling was selected in 21% of cases and a haploidentical donor for the remaining 164 patients (14%). A reduced-intensity conditioning was used in 696 (60%) procedures (full details of regimes used are in Table S2), with in vivo T-cell depletion and use of post-transplant cyclophosphamide (PTCy) as GVHD prophylaxis in 652 (57%) and 346 (30%) transplants, respectively. Differences among the four genetic subgroups were observed in age, recipient sex, presence of *FLT3*-ITD, Karnofsky score at the time of alloHCT, conditioning intensity, and use of PTCy as GVHD prophylaxis (Table 1).

3.2 | Outcome After alloHCT According to Genetic Category

After a median follow-up of 23.6 months (IQR: 21.2–24.1), the 2-year (95% CI) RI, NRM, OS, and LFS were 37% (33.7–40.2), 18.7% (16.2–21.3), 49.4% (45.8–52.8), and 44.4% (40.9–47.8), respectively. Acute GVHD was observed in 584 (53.5%) patients, of grade II-IV and III-IV in 292 (27%) and 114 (10.6%) patients (with available information), respectively. The two-year (95% CI) cGVHD was 32.9 (29.7–36.2), with an extensive cGVHD incidence of 15.2 (12.8 –17.9). GRFS of the overall series at 2 years was 33.3% (95% CI:30–36.6).

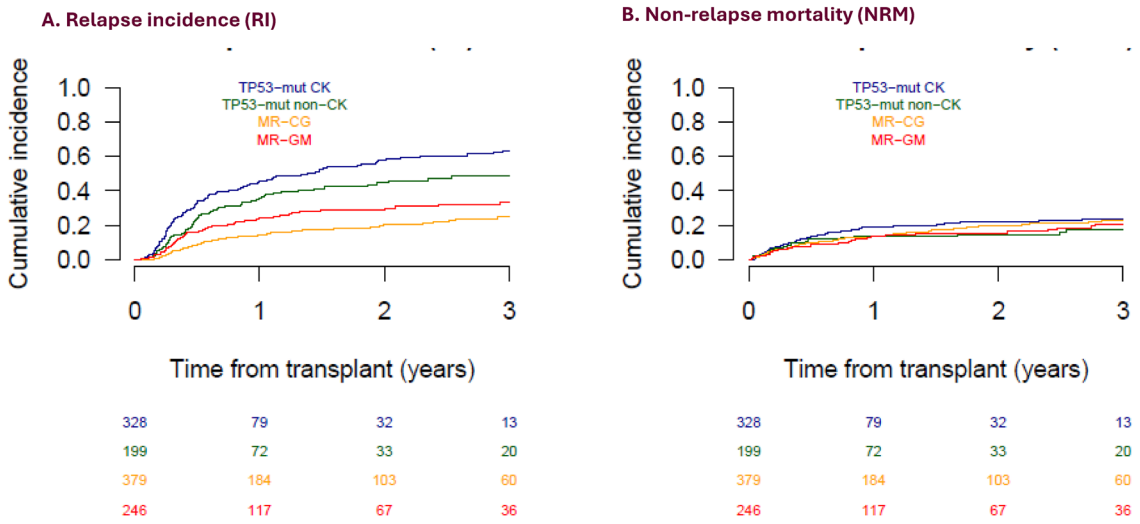
Marked differences in outcome were observed among these four genetic categories, with a progressively increasing RI in MR-GM, MR-CG, TP53-mut non-CK, and TP53-mut CK AML

TABLE 1 | Characteristics of patients and alloHCT[1].

	Overall population $n^1 = 1152$	TP53-AML[1] + complex karyotype $n = 328$	TP53-AML[1] w/o[1] complex karyotype = 199	MR-GM AML[1] $n = 379$	MR-CG AML[1] $N = 246$	p
Age						
Median (IQR[1] 25–75)	60.3 (51.4–66)	61.7 (54.6–65.9)	59.9 (50.5–64.9)	61.1 (52–67.1)	54.7 (43.5–63.6)	**< 0.001**
Sex (Female)						
n (%)	472 (41)	153 (46.8)	77 (38.7)	133 (35.2%)	109 (44.3%)	**0.01**
AML presentation						
(de novo/ secondary) *n (%)*	964 (84) /188 (16)	260 (79%) /68 (21)	167 (84%) /32 (16%)	322 (85%) /57 (15%)	215 (88%) /31 (13%)	0.054
FLT3-ITD						
n (%)	103 (12.6%)	6 (3.9%)	12 (13.5%)	62 (17.1%)	23 (10.7%)	**< 0.001**
Year of transplant						
Median (IQR 25–75)	2020 (2018–2021)	2020 (2018–2021)	2020 (2018–2021)	2020 (2018–2021)	2019 (2018–2021)	**0.017**
Interval diagnosis-alloHCT mos.						
Median (IQR 25–75)	4.5 (3.6–5.6)	4.6 (3.8–5.6)	4.7 (3.8–5.7)	4.5 (3.6–5.7)	4.3 (3.5–5.4)	0.059
Karnofsky score (< 90%)						
n (%)	315 (28.4%)	110 (34.6%)	55 (28.8%)	84 (23.2%)	66 (27.7%)	**0.012**
Donor *n* (%)						
Matched-sibling	244 (21.2%)	60 (18.3%)	35 (17.6%)	93 (24.5%)	56 (22.8%)	0.12
Unrelated	744 (64.6%)	225 (68.6%)	126 (63.3%)	235 (62%)	158 (64.2%)	
Haploidentical	164 (14.2%)	43 (13.1%)	38 (19.1%)	51 (13.5%)	32 (13%)	
Donor-recipient gender						
(Female–Male) *n (%)*	201 (17.5%)	46 (14.1%)	34 (17.3%)	76 (20.1%)	45 (18.3%)	0.21
Conditioning intensity[1] *n* (%)						
Myeloablative	453 (39.4%)	111 (33.8%)	88 (44.4%)	140 (37%)	114 (46.5%)	**0.06**
Reduced-intensity	696 (60.6%)	217 (66.2%)	110 (55.6%)	238 (63%)	131 (53.5%)	
Graft source (PB/BM) *n (%)*	1078 (94)/74 (6)	302 (92.1)/26 (7.9)	184 (92.5)/15 (7.5)	362 (95.5)/17 (4.5)	230 (93.5)/16 (6.5)	0.26
In vivo T-cell depletion *n* (%)	652 (56.7%)	207 (63.3%)	115 (57.8%)	194 (51.5%)	136 (55.3%)	0.016
PTCy	346 (30.3%)	76 (23.3%)	53 (26.9%)	146 (38.8%)	71 (29.1%)	**< 0.001**

Note: Bold values indicate statistical significance $p < 0.05$.
Abbreviations: alloHCT, allogeneic hematopoietic-cell transplantation; n, number; TP53-AML, AML with *TP53* mutation; w/o, without; MR-GM AML, AML with myelodysplasia-related gene mutations; MR.-CG ANL, AML with myelodysplasia-related cytogenetic abnormalities; IQR, interquartile range; mos, months; PB/BM, peripheral blood/bone marrow; PTCy, post-transplant cyclophosphamide.
[1]Non-available information in 3 pts. (conditioning intensity).

subgroups, of 20.2%, 29.2%, 44.6%, and 57.6% at 2 years, respectively ($p = 0.001$). This difference in relapse risk translated into a corresponding significant difference in these four genetic groups (MR-GM>MR-CG>TP53-mut non-CK>TP53-mut CK AML) in terms of LFS (60%, 55.3%, 40.6%, and 20.2% at 2 years, respectively; $p = 0.001$), OS (65.7%, 60.1%, 47.1%, and



Genetic subgroup	**RI** (% at 2 years)	**NRM** (% at 2 years)
Myelodysplasia-related gene mutation (MR-GM) AML	20.2 (15.5-25.3)	19.8% (15.2-24.8)
Myelodysplasia-related cytogenetic abnormality (MR-CG) AML	29.2 (22.9-35.8)	15.5% (10.9-20.8)
TP53-mutated, non-complex karyotype (TP53-mut non-CK) AML	44.6 (36.1-52.7)	14.8% (9.8-20.8)
TP53-mutated, complex karyotype (TP53-mut CK AML)	57.6 (50.9-63.8)	22.2% (17.2-27.5)
p value	*0.01*	***0.46***

FIGURE 1 | Difference in outcome among four genetic subgroups in terms of relapse incidence (A), LFS (C), OS (D) and GRFS (E), with a similar NRM observed in all subgroups (B). [Color figure can be viewed at wileyonlinelibrary.com]

24.5% at 2 years, respectively; $p = 0.001$), and GRFS (46.9%, 39.5%, 31.9%, and 13.2% at 2 years, respectively; $p = 0.001$) (Figure 1). On the contrary, NRM was similar in all four subgroups. The MVA confirmed these differences according to genetic subgroup, with a lower relapse risk in MR-GM, MR-CG, TP53-mut non-CK (HR: 0.21, 33, and 0.61, respectively) and longer LFS (HR: 0.32, 0.44, and 0.65, respectively), OS (HR: 0.32, 0.42, and 0.65, respectively) and GRFS (HR: 0.4, 0.54, and 0.65, respectively) compared to the reference TP53-mut CK AML category (Table 2). Patients with MR-GM AML also experienced a lower NRM (HR = 0.65, 95% CI 0.44–0.94; $p = 0.024$) and grade II-IV aGVHD incidence (HR = 0.71, 95% CI 0.51–0.97; $p = 0.033$), compared to the remaining MR-AML genetic subgroups in the MVA. Moreover, no difference in terms of cGVHD incidence was observed among these genetic subgroups (Table 2).

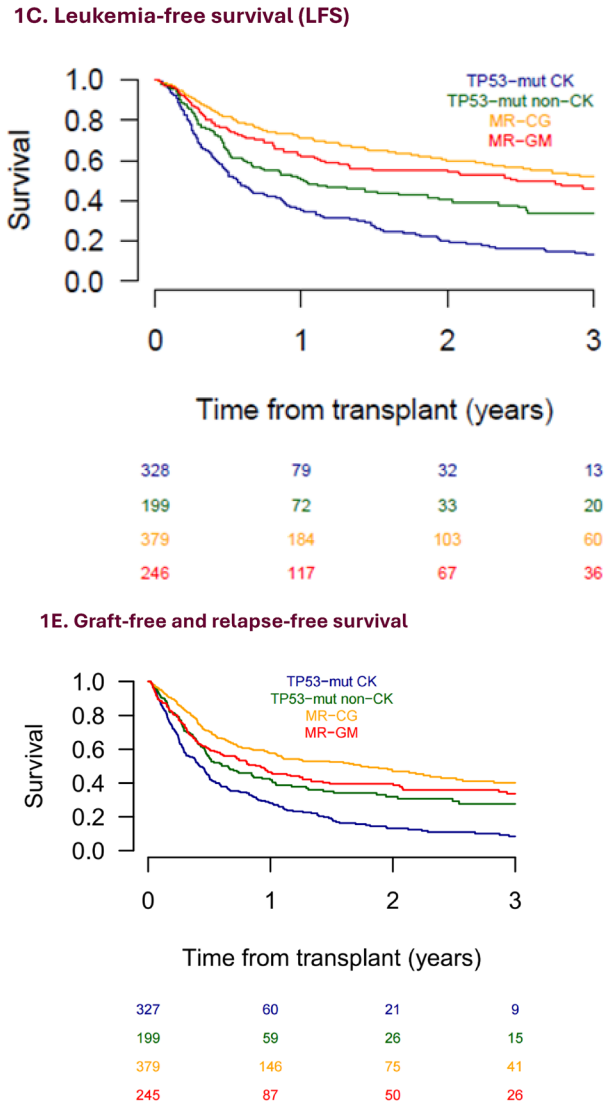
Disease progression was the main cause of death in most patients (overall, 289 of deaths, 60%) in all genetic subgroups, representing 45%, 54%, 63%, and 69% of deaths among MR-GM, MR-CG, TP53-mut non-CK, and TP53-mut CK AML subgroups, respectively. The complete list of causes of death is detailed in Table S3.

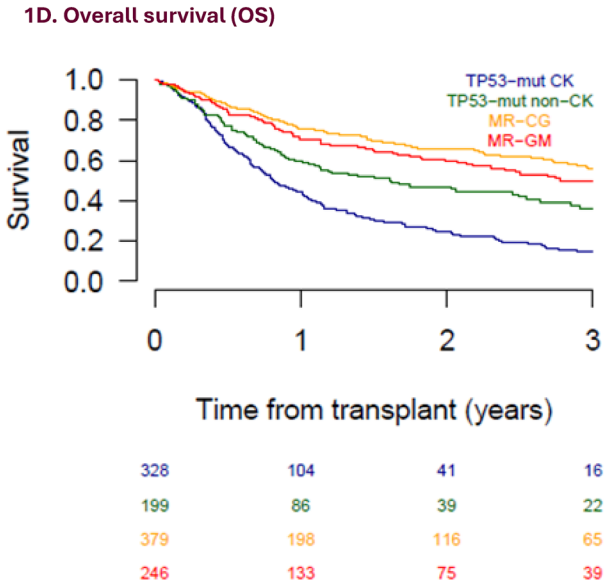
3.3 | Other Prognostic Factors

Other significant independent prognostic variables were identified in the MVA (Tables S4). An unrelated donor exerted a favorable impact on relapse (HR = 0.67, 95% CI: 0.51–0.89; $p = 0.006$), LFS (HR = 0.77, 95% CI: 0.61–0.97; $p = 0.028$), and GRFS (HR = 0.76, 95% CI: 0.62–0.94, $p = 0.011$) compared with the reference group of matched related donors. Recipient age was associated with the risk of NRM (HR per 10-year interval: 1.53, 95% CI: 1.28–1.82; $p < 0.0001$), LFS (HR per 10-year interval: 1.19, 95% CI: 1.09–1.31; $p = 0.0002$), OS (HR per 10-year interval: 1.20, 95% CI: 1.09–1.32; $p = 0.002$), and GRFS (HR per 10-year interval: 1.09, 95% CI: 1–1.18; $p = 0.041$). Finally, patient cytomegalovirus seropositivity was associated with NRM (HR = 1.46, 95% CI: 1.02–2.09; $p = 0.04$), whereas a more recent year of transplant (HR = 0.91, 95% CI: 0.84–0.97; $p = 0.008$) and the use of PTCy as GVHD prophylaxis (HR = 0.70, 95% CI: 0.49–0.98; $p = 0.037$) were associated with a lower risk of cGVHD. Conditioning intensity, as segregated between RIC/MAC standard definition, did not show independent prognostic value. Nonetheless, when using the TCI score, patients with a high TCI index experienced a higher NRM risk (HR = 2.290.70, 95% CI: 1.31–3.99; $p = 0.003$; Table S4B).

3.4 | Impact of Type and Number of Myelodysplasia-Related Mutations

Within the category of MR-GM AML, *RUNX1* and *ASXL1* were the most frequently observed gene mutations, in 55.7% and 39.8% of patients, respectively, whereas the remaining seven MR gene mutations were observed in < 10% of patients (Table S5A). The majority of patients included in this category (74%) were reported to harbor only one MR-GM, whereas 24% harbored two MR-GM, and only 2% of patients presented with > 2 mutations (Table S5B). In particular, the presence of individual *RUNX1* and *ASXL1* mutations in patients of this genetic category did not show any prognostic impact, with similar RI, LFS, and OS. Moreover, the number of MR gene mutations did not influence any outcome (Table S5C).





Genetic subgroup	**LFS** (% at 2 years)	**OS** (% at 2 years)	**GRFS** (% at 2 years)
Myelodysplasia-related gene mutation (MR-GM) AML	60 (53.7-65.8)	65.7 (59.5-71.1)	46.9 (40.6-52.9)
Myelodysplasia-related cytogenetic abnormality (MR-CG) AML	55.3 (48-62.1)	60.1 (52.5-66.9)	39.5 (32.6-46.4)
TP53-mutated, non-complex karyotype (TP53-mut non-CK) AML	40.6 (32.3-48.7)	47.1 (38.5-55.2)	31.9 (24.2-39.8)
TP53-mutated, complex karyotype (TP53-mut CK AML)	20.2 (15-26)	24.5 (19-30.4)	13.2 (8.9-18.3)
p value	***0.001***	***0.001***	***0.001***

FIGURE 1 | (Continued)

4 | Discussion

This comprehensive study demonstrates the strong impact of underlying genetics on the outcome of patients diagnosed with a MR-AML who undergo alloHCT as consolidation therapy after CR1, which is the recommended post-remission strategy for this large, but genetically heterogeneous high-risk AML category [8]. Thus, differences in outcome ranged widely, from a 2-year LFS of 60% in patients with MR-GML to only 20% in those with a TP53-mut CK subtype, and these differences in LFS mirrored differences in relapse risk among these diverse genetic categories, ranging from 20% to 58%, respectively. This study, moreover, reinforces the current distinction between MR-GM and MR-CG AML categories proposed by both the WHO 2022 and ICC AML classification models, significantly refined when a third subgroup of patients harboring *TP53* mutation is considered separately, as proposed by the ICC [1, 2].

This study confirms that the prognosis of TP53-AML is highly determined by the presence of concomitant additional cytogenetic abnormalities also in the context of alloHCT, as previously observed in a previous report by the ALWP and several other studies [9, 10, 14, 15]. The prognostic relevance of additional cytogenetic lesions probably reflects the multi-hit nature of the underlying *TP53* mutation and the lack of functional wild-type TP53 in patients harboring a concomitant complex karyotype, as proposed by Elsa Bernard in MDS patients with mutated *TP53* [26]. The dismal 2-year LFS observed in patients with TP53-mut CK AML (20%) has raised concerns

TABLE 2 | Impact of genetic subgroup on main endpoints in the multivariate analysis.

Genetic subgroup	RI		LFS		OS		GRFS		NRM	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
TP53-mut CK	1		1		1		1		1	
TP53-mut non-CK	0.61 (0.45–0.82)	**0.001**	0.65 (0.51–0.84)	**0.0008**	0.65 (0.5–0.84)	**0.001**	0.65 (0.51–0.82)	**0.003**	0.74 (0.47–1.18)	0.2
MR-CG	0.33 (0.24–0.46)	**<0.0001**	0.44 (0.34–0.57)	**<0.0001**	0.42 (0.33–0.55)	**<0.0001**	0.54 (0.43–0.68)	**<0.0001**	0.76 (0.5–1.16)	0.21
MR-GM	0.21 (0.15–0.28)	**<0.0001**	0.32 (0.25–0.41)	**<0.0001**	0.32 (0.25–0.4)	**<0.0001**	0.4 (0.32–0.49)	**<0.0001**	0.65 (0.44–0.94)	**0.024**

Genetic subgroup	Acute GVHD II-IV		Chronic GVHD	
	HR (95% CI)	*p*	HR (95% CI)	*p*
TP53-mut CK	1		1	
TP53-mut non-CK	0.86 (0.6–1.23)	0.39	0.87 (0.56–1.33)	0.51
MR-CG	0.95 (0.68–1.33)	0.79	1.12 (0.77–1.61)	0.55
MR-GM	0.71 (0.51–0.97)	**0.033**	0.89 (0.63–1.25)	0.5

Note: Bold values indicate statistical significance $p < 0.05$.

Abbreviations: RI, relapse incidence; LFS, leukemia-free survival; OS, overall survival; GRFS, graft-and-relapse-free survival; NRM, non-relapse mortality; GVHD, graft-versus-host disease; HR, hazard ratio; CI, confidence interval; TP53-mut CK, AML with *TP53* mutation and associated complex karyotype; TP53-mut non-CK, AML with *TP53* mutation without associated complex karyotype; MR-CG, AML with myelodysplasia-related cytogenetic abnormalities; MR-GM AML, AML with myelodysplasia-related gene mutations.

about the futility of this complex procedure for this subset of patients and highlights the need to specifically address novel pre- and post-transplant strategies to prevent relapse [14, 27]. Unfortunately, the failed development of agents that had previously raised hope in TP53-AML, such as the TP53-function restoring agent eprenetapopt [28] or the anti-CD47 monoclonal antibody magrolimab, a promoter of anti-tumor macrophage phagocytosis, has prompted the search for alternative strategies [29]. Moreover, the distinction between TP53-mut CK and TP53-mut non-CK AML, according to concomitant additional cytogenetics, is also warranted in patients who are candidates for alloHCT, given the significantly better outcome obtained in those without additional cytogenetic abnormalities. Thus, the TP53-mut non-CK subgroup, representing approximately one-third of TP53-AML patients in the present study, showed a significantly better outcome, in terms of RI, LFS, OS, and GRFS, compared to patients with TP53-mut CK AML, confirming a previous finding by our group [15].

The relatively favorable outcome observed among patients with MR-GM AML undergoing alloHCT in CR1 in this study is also an important observation, given the allocation of this large AML subgroup among other high-risk genetic subgroups in the ELN 2022 classification. Thus, the outcome of patients from this category, with a relatively low RI (20%), is comparable to that of patients with other intermediate-risk genetic categories and markedly different from other well-defined poor-risk genetic subtypes such as TP53-AML or MECOM-rearranged AML. This finding was also observed in recent studies aimed at validating the ELN genetic risk classification [6, 11–13], suggesting the possible existence of a beneficial graft-versus-leukemia effect in this setting. Moreover, these results also support the need for refinement of this prognostic category stratification by acknowledgment of these diverse adverse-risk subsets. Moreover, within the MR-GM subtype, some studies have identified a different outcome according to the number of MR-GM, with a worse outcome among those harboring more than one MR-GM [30], or to the type of MR-GM involved, with a worse prognosis among patients harboring *RUNX1* and/or *ASXL1* mutation [7]. However, these differences in outcome within MR-GM AML were not observed in our study, although the lack of comprehensive mutational information on the 9 MR-defining AML mutations in all patients included in this study limits the robustness of this finding.

Among the limitations of the study, we should mention the lack of measurable residual disease (MRD) data in a multicenter, registry-based clinical setting. On the other hand, MRD measurement in MR-AML is mainly based on multiparameter flow cytometry, with a limited sensitivity threshold established at 0.1%, and a lack of validated harmonization among reference labs of centers contributing to the study [31]. Emerging molecular techniques based on the surveillance of patient-specific mutations by means of next-generation sequencing MRD (NGS-MRD) or droplet digital polymerase chain reaction (ddPCR) might offer improved sensitivity and specificity in this context [32]. Pre-transplant MRD measurement might provide valuable prognostic information on post-transplant outcomes and refined information on pre-transplant AML load in all genetic subgroups contained in the vast MR-AML category.

In conclusion, the outcome after alloHCT in patients with MR-AML is mainly determined by the underlying genetic category. Thus, MR-GM AML patients showed the best post-transplant outcome, comparable to that of intermediate-risk AML genetic categories. On the contrary, TP53-AML showed the worst outcome, especially among patients with additional cytogenetic abnormalities in a complex karyotype, confirming the status of the unmet medical need of this genetic AML subset and the urgency for focused research. Altogether, these findings warrant the redefinition of the adverse risk ELN category, splitting the whole MR-AML group into different prognostic categories according to the patient genetic background.

Author Contributions

J.E. and A.N. wrote the manuscript, designed the study, interpreted the data, and edited the manuscript. M.L., F.C., and M.M. designed the study, performed the statistical analyses, interpreted the data, and edited the manuscript. J.V., J.S., T.G.D., D.B., M.R., H.L.W., P.V.D.B., G.V.G., N.C., A.N.14, E.M.W.D., and N.K. reviewed the manuscript and provided clinical data. All authors approved the final version of the manuscript.

Acknowledgments

We thank all the EBMT centers and national registries for contributing patients to this study (listed in the Supporting Information). We also thank the data managers from these centers for their excellent work.

Ethics Statement

The study was approved by the general assembly and scientific review board of the Acute Leukemia Working Party (ALWP) of the EBMT and complied with country-specific regulatory requirements.

Consent

Since 1990, patients have provided informed consent, authorizing the use of their personal information for research purposes.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

J.E., A.N., and M.L. had full access to all study data, which are available upon data-specific request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.