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Transplantation outcomes and risk stratification of pediatric acute myeloid leukemia, myelodysplasia-related: A nationwide registry study

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Article

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Abstract

Data on allogeneic hematopoietic stem cell transplantation (allo-HSCT) for pediatric acute myeloid leukemia, myelodysplasia-related (AML-MR) remain limited. We retrospectively analyzed 732 children and adolescents who underwent first allo-HSCT for AML-MR (n = 252) or AML, defined by differentiation (AML-DD; n = 480) between 2000 and 2018, using Japanese nationwide registry data. The 5-year leukemia-free survival and overall survival (OS) did not differ significantly between AML-MR and AML-DD (44.5% versus 48.2% and 52.6% versus 51.1%, respectively). Within AML-MR, outcomes were heterogeneous: monosomal karyotype (MK) without − 7/del(7q) was associated with inferior OS compared with AML-DD, whereas MK with − 7/del(7q) was not. Among patients with MK, those with − 7/del(7q) had better OS than those without (71.1% versus 31.0%, $P = 0.023$). A cytogenetics-based three-tier risk model stratified AML-MR outcomes (5-year OS: 63.6%, 51.1%, and 31.8% for low-, intermediate-, and high-risk groups, $P < 0.001$). Non-remission at HSCT and poor performance status independently predicted inferior survival. Although overall allo-HSCT outcomes in pediatric AML-MR were comparable to AML-DD, subgroup heterogeneity—particularly the adverse impact of MK without − 7/del(7q)—warrants risk-adapted strategies.

Introduction

In 2008, the World Health Organization (WHO) classification introduced acute myeloid leukemia with myelodysplasia-related changes (AML-MRC) as a distinct disease entity defined by the presence of at least one of the following criteria: multilineage dysplasia, a prior history of myelodysplastic syndrome (MDS) or MDS/myeloproliferative neoplasm (MPN), or MDS-related cytogenetic abnormalities [1]. In the 5th edition of the WHO classification, this entity has been retained with substantial revisions and renamed as AML, myelodysplasia-related (AML-MR) [2]. AML-MR is defined by the presence of MDS-related cytogenetic or molecular abnormalities and/or a history of MDS or MDS/MPN. Notably, multilineage dysplasia alone is no longer sufficient for a diagnosis, representing a major conceptual change from the previous WHO classifications. In the 5th edition of the WHO classification, AML is divided into two major lineages: AML, defined by differentiation (AML-DD), and AML with defining genetic abnormalities, including AML-MR; AML not otherwise specified (AML-NOS) is no longer applicable.

AML-MR is associated with inferior outcomes in comparison to AML-NOS [3–8]. Given its adverse-risk features, allogeneic hematopoietic stem cell transplantation (allo-HSCT) is often considered for eligible patients with AML-MR. However, data on transplantation outcomes in AML-MR remain limited [9, 10]. This evidence gap is particularly pronounced in children and adolescents, whose biological and clinical features of AML-MR may differ from those observed in adults. Consequently, the outcomes of allo-HSCT and prognostic factors that influence post-transplant survival in pediatric AML-MR remain insufficiently defined.

In the present study, we retrospectively analyzed a nationwide cohort of children and adolescents who underwent allo-HSCT for AML-MR or AML-DD using registry data from the Japanese Society for

Transplantation and Cellular Therapy (JSTCT). We aimed to clarify transplantation outcomes and identify prognostic factors in pediatric AML-MR compared with those in AML-DD.

Patients and Methods

Patients

This study was approved by the Institutional Ethics Committee of Jichi Medical University. Written informed consent was obtained from the patients or their parents in accordance with the Declaration of Helsinki. Transplant data were obtained from the JSTCT registry [11, 12]. The criteria for patient selection were as follows: (i) diagnosed with AML-MR or AML-DD; (ii) age 0–19 years at the time of transplantation; (iii) no prior allo-HSCT; and (iv) allo-HSCT performed between 2000 and 2018. All patients with AML-MR and AML-DD were diagnosed at the participating institutions, and the diagnoses were reviewed by the first author in accordance with the criteria provided by the 5th edition of the WHO [2]. Patients with therapy-related myeloid neoplasms and acute erythroid leukemia were excluded. Since our registry data did not include information on MDS-related molecular abnormalities, AML-MR in this study consisted of patients with MDS-related cytogenetic abnormalities and/or a prior history of MDS or MDS/MPN. However, MR-related molecular abnormalities that define AML-MR in adults are exceedingly rare in children, accounting for only 0.1–2.1% of pediatric AML cohorts [13]. Therefore, we considered that the lack of data on MDS-related molecular abnormalities was unlikely to substantially affect our analyses.

Results

Patient and transplantation characteristics

A total of 732 patients were eligible for this study; 252 and 480 were classified into the AML-MR and AML-DD groups, respectively. The characteristics of the patients and transplantation are presented in Table 1. The median age at HSCT was 8 years (range, 0–19). The median follow-up period for survivors was 6.0 years (range, 0.1–19.6 years). Of the 732 patients, 446 (60.9%) received allo-HSCT at CR and 286 (39.1%) at no remission (NR). Regarding donor sources, 153 (20.9%) patients received transplants from matched related donors (MRD), 127 (17.3%) from mismatched related donors (MMRD), 128 (17.5%) from matched unrelated donors (MUD), 79 (10.8%) from mismatched unrelated donors (MMUD), and 245 (33.5%) from cord blood. Most patients (85.5%) received the MAC regimen.

Table 1
Patient and transplantation characteristics

Characteristic	All	AML-MR	AML-DD	*P*
	(*n* = 732)	(*n* = 252)	(*n* = 480)	
Age at HSCT, *n* (%)				
0–9 years	403 (55.1)	143 (56.7)	260 (54.2)	0.532
10–19 years	329 (44.9)	109 (43.3)	220 (45.8)	
Patient sex, *n* (%)				
Male	369 (50.4)	118 (46.8)	251 (52.3)	0.162
Female	363 (49.6)	134 (53.2)	229 (47.7)	
PS, *n* (%)				
0–1	520 (71.0)	193 (76.6)	327 (68.1)	0.005
≥2	72 (9.9)	27 (10.7)	45 (9.4)	
Unknown	140 (19.1)	32 (12.7)	108 (22.5)	
HCT-CI, *n* (%)				
0–2	459 (62.7)	165 (65.4)	294 (61.2)	0.167
≥3	19 (2.6)	9 (3.6)	10 (2.1)	
Unknown	254 (34.7)	78 (31.0)	176 (36.7)	
Disease status at HSCT, *n* (%)				
CR	446 (60.9)	141 (56.0)	305 (63.5)	0.047
NR	286 (39.1)	111 (44.0)	175 (36.5)	
Donor source, *n* (%)				
MRD	153 (20.9)	46 (18.3)	107 (22.3)	0.091
MMRD	127 (17.3)	36 (14.3)	91 (19.0)	

Differences between categorical variables were analyzed using the χ^2 test.

AML-DD acute myeloid leukemia, defined by differentiation; *AML-MR* acute myeloid leukemia, myelodysplasia-related; *CB* cord blood; *CK* complex karyotype; *CR* complete remission; *GVHD* graft-versus-host disease; *HCT-CI* hematopoietic cell transplant-specific comorbidity index; *HSCT* hematopoietic stem cell transplantation; *MAC* myeloablative conditioning; *MDS* myelodysplastic syndrome; *MK* monosomal karyotype; *MMRD* mismatched related donor; *MMUD* mismatched unrelated donor; *MPN* myeloproliferative neoplasm; *MRD* matched related donor; *MUD* matched unrelated donor; *NR* no remission; *PS* performance status; *RIC* reduced intensity conditioning.

Characteristic	All	AML-MR	AML-DD	*P*
	(*n* = 732)	(*n* = 252)	(*n* = 480)	
MUD	128 (17.5)	47 (18.7)	81 (16.9)	
MMUD	79 (10.8)	24 (9.5)	55 (11.5)	
CB	245 (33.5)	99 (39.3)	146 (30.4)	
Conditioning, *n* (%)				
MAC	626 (85.5)	205 (81.3)	421 (87.7)	0.046
RIC	101 (13.8)	45 (17.9)	56 (11.7)	
Unknown	5 (0.7)	2 (0.8)	3 (0.6)	
GVHD prophylaxis, *n* (%)				
Cyclosporine-based	236 (32.2)	77 (30.6)	159 (33.1)	0.779
Tacrolimus-based	460 (62.9)	162 (64.3)	298 (62.1)	
Others	36 (4.9)	13 (5.1)	23 (4.8)	
HSCT year, *n* (%)				
2000–2009	378 (51.6)	119 (47.2)	259 (54.0)	0.087
2010–2018	354 (48.4)	133 (52.8)	221 (46.0)	
AML-MR classification, *n* (%)				
History of MDS or MDS/MPN		29 (11.5)		
MK with − 7/del(7q)		15 (6.0)		
MK without − 7/del(7q)		37 (14.7)		
CK		88 (34.9)		
Isolated − 5/del(5q)		13 (5.1)		
Isolated − 7/del(7q)		60 (23.8)		
Others		10 (4.0)		

Differences between categorical variables were analyzed using the χ^2 test.

AML-DD acute myeloid leukemia, defined by differentiation; *AML-MR* acute myeloid leukemia, myelodysplasia-related; *CB* cord blood; *CK* complex karyotype; *CR* complete remission; *GVHD* graft-versus-host disease; *HCT-CI* hematopoietic cell transplant-specific comorbidity index; *HSCT* hematopoietic stem cell transplantation; *MAC* myeloablative conditioning; *MDS* myelodysplastic syndrome; *MK* monosomal karyotype; *MMRD* mismatched related donor; *MMUD* mismatched unrelated donor; *MPN* myeloproliferative neoplasm; *MRD* matched related donor; *MUD* matched unrelated donor; *NR* no remission; *PS* performance status; *RIC* reduced intensity conditioning.

Regarding the classification of AML-MR, there were 29 cases (11.5%) with a history of MDS or MDS/MPN, 15 cases (6.0%) with MK with − 7/del(7q), 37 cases (14.7%) with MK without − 7/del(7q), 88 cases (34.9%) with CK, 13 cases (5.1%) with isolated − 5/del(5q), 60 cases (23.8%) with isolated − 7/del(7q), and 10 cases (4.0%) with others. Patients with AML-MR had better performance status (PS), were less likely to be in CR, and were less likely to receive MAC.

Transplantation outcomes in the total patient group

The LFS and OS rates at 5 years for all 732 patients after allo-HSCT were 46.9% (95% confidence interval [CI], 43.1–50.6) and 51.6% (95% CI, 47.7–55.4), respectively. The cumulative incidence rates of relapse and NRM at 5 years after allo-HSCT were 38.0% (95% CI, 34.4–41.6) and 15.1% (95% CI, 12.5–17.9), respectively. The cumulative incidence rates of neutrophil recovery at day 42 and platelet engraftment at 6 months were 93.0% (95% CI, 90.9–94.7) and 85.9% (95% CI, 83.0–88.3), respectively. The cumulative incidence rates of aGVHD grades II–IV and III–IV on day 100 after allo-HSCT were 39.2% (95% CI, 35.6–42.7) and 16.8% (95% CI, 14.1–19.6), respectively, while that of cGVHD at 1 year after allo-HSCT was 24.3% (95% CI, 21.2–27.5).

Prognostic factors in the total patient group

The associations between clinical characteristics and outcomes are summarized in Table 2. In the univariate analysis, transplantation outcomes did not differ significantly between patients with AML-MR and those with AML-DD (Fig. 2). In contrast, PS ≥ 2 and NR at HSCT were associated with worse LFS, inferior OS, and a higher relapse rate. Other factors associated with outcomes included hematopoietic cell transplant-specific comorbidity index, donor source, conditioning intensity, GVHD prophylaxis, HSCT year, and GVHD.

Table 2
Univariate analysis of transplantation outcomes in children and adolescents with AML-MR or AML-DD (total patients, n = 732)

Variable	LFS	*P*	OS	*P*	Relapse	*P*	NRM	*P*
	at 5 year, % (95% CI)		at 5 year, % (95% CI)		at 5 year, % (95% CI)		at 5 year, % (95% CI)	
Age at HSCT								
0–9 years	47.9 (42.7–52.8)	0.626	52.8 (47.5–57.7)	0.411	37.5 (32.6–42.3)	0.957	14.7 (11.3–18.5)	0.518
10–19 years	45.7 (40.0–51.2)		50.2 (44.4–55.8)		38.7 (33.3–44.1)		15.6 (11.8–20.0)	
Patient sex								
Male	46.6 (41.2–52.4)	0.651	49.2 (43.7–54.5)	0.213	37.1 (32.1–42.2)	0.762	16.3 (12.6–20.4)	0.368
Female	47.2 (41.8–52.4)		54.0 (48.5–59.2)		38.9 (33.7–44.0)		13.9 (10.4–17.8)	
PS								
0–1	52.1 (47.5–56.4)	< 0.001	56.8 (52.1–61.2)	< 0.001	34.5 (30.3–38.7)	< 0.001	13.5 (10.5–16.7)	0.134
≥2	20.8 (11.7–31.8)		22.2 (12.4–33.8)		58.9 (45.9–69.7)		20.3 (11.2–31.3)	
Unknown	41.0 (32.8–49.0)		46.7 (38.2–54.7)		40.3 (32.0-48.3)		18.7 (12.7–25.7)	
HCT-CI								
0–2	50.7 (45.8–55.5)	0.020	55.4 (50.3–60.2)	0.002	36.2 (31.6–40.7)	0.464	13.1 (10.0-16.6)	0.173

AML-DD acute myeloid leukemia, defined by differentiation; *AML-MR* acute myeloid leukemia, myelodysplasia-related; *CB* cord blood; *CK* complex karyotype; *CR* complete remission; *GVHD* graft-versus-host disease; *HCT-CI* hematopoietic cell transplant-specific comorbidity index; *HSCT* hematopoietic stem cell transplantation; *LFS* leukemia-free survival; *MAC* myeloablative conditioning; *MDS* myelodysplastic neoplasms; MK monosomal karyotype; *MMRD* mismatched related donor; *MMUD* mismatched unrelated donor; *MPN* myeloproliferative neoplasms; *MRD* matched related donor; *MUD* matched unrelated donor; *NR* no remission; *NRM* non-relapse mortality; *OS* overall survival; *PS* performance status; *RIC* reduced intensity conditioning.

Variable	LFS	*P*	OS	*P*	Relapse	*P*	NRM	*P*
	at 5 year, % (95% CI)		at 5 year, % (95% CI)		at 5 year, % (95% CI)		at 5 year, % (95% CI)	
≥3	32.9 (13.0-54.6)		32.7 (12.9–54.4)		43.6 (20.1–65.1)		23.5 (6.6–46.2)	
Unknown	41.1 (35.0-47.1)		46.1 (39.8–52.1)		40.6 (34.5–46.6)		18.3 (13.8–23.4)	
AML type								
DD	48.2 (43.4–52.7)	0.108	51.1 (46.2–55.7)	0.023	37.6 (33.1–42.0)	0.101	14.3 (11.2–17.7)	0.878
History of MDS or MDS/MPN	56.4 (36.1–72.5)		67.5 (46.7–81.6)		25.5 (11.0–43.0)		18.0 (6.4–34.4)	
Isolated − 5/del(5q)	44.9 (17.7–69.0)		59.8 (28.5–81.0)		30.8 (8.7–56.6)		24.4 (5.0-51.4)	
Isolated − 7/del(7q)	52.5 (38.7–64.6)		60.3 (46.1–71.8)		29.4 (18.2–41.6)		18.0 (9.2–29.3)	
MK with − 7/del(7q)	51.3 (20.8–75.3)		71.1 (39.8–88.1)		34.4 (8.8–62.6)		14.4 (2.1–37.8)	
MK without − 7/del(7q)	32.7 (18.0-48.2)		31.0 (16.3–47.0)		55.7 (37.5–70.4)		11.7 (3.5–25.1)	
CK	40.7 (30.0–51.0)		49.7 (38.5–60.0)		43.3 (32.6–53.8)		15.9 (8.9–24.8)	
Others	30.0 (7.1–57.8)		34.3 (8.2–63.3)		50.0 (15.9–77.0)		20.0 (2.3–50.5)	

AML-DD acute myeloid leukemia, defined by differentiation; *AML-MR* acute myeloid leukemia, myelodysplasia-related; *CB* cord blood; *CK* complex karyotype; *CR* complete remission; *GVHD* graft-versus-host disease; *HCT-CI* hematopoietic cell transplant-specific comorbidity index; *HSCT* hematopoietic stem cell transplantation; *LFS* leukemia-free survival; *MAC* myeloablative conditioning; *MDS* myelodysplastic neoplasms; MK monosomal karyotype; *MMRD* mismatched related donor; *MMUD* mismatched unrelated donor; *MPN* myeloproliferative neoplasms; *MRD* matched related donor; *MUD* matched unrelated donor; *NR* no remission; *NRM* non-relapse mortality; *OS* overall survival; *PS* performance status; *RIC* reduced intensity conditioning.

Variable	LFS	*P*	OS	*P*	Relapse	*P*	NRM	*P*
	at 5 year, % (95% CI)		at 5 year, % (95% CI)		at 5 year, % (95% CI)		at 5 year, % (95% CI)	
Disease status at HSCT								
CR	61.3 (56.4–65.8)	< 0.001	67.2 (62.3–71.6)	< 0.001	26.4 (22.3–30.8)	< 0.001	12.3 (9.3–15.7)	0.009
NR	24.6 (19.5–29.9)		27.6 (22.2–33.2)		56.1 (50.0-61.7)		19.4 (14.9–24.4)	
Donor source								
MRD	53.3 (44.9–61.1)	< 0.001	59.1 (50.5–66.7)	0.001	37.7 (29.9–45.5)	0.001	8.9 (5.0-14.3)	0.011
MMRD	32.9 (24.5–41.4)		38.7 (29.7–47.7)		48.5 (39.3–57.1)		18.6 (12.1–26.2)	
MUD	48.4 (39.2–56.9)		54.1 (44.8–62.5)		34.9 (26.5–43.4)		16.8 (10.8–23.9)	
MMUD	52.5 (40.4–63.3)		56.2 (44.0-66.8)		22.8 (14.0–33.0)		24.7 (15.4–35.2)	
CB	47.5 (40.8–54.0)		50.5 (43.5–57.1)		39.1 (32.8–45.3)		13.3 (9.2–18.3)	
Conditioning								
MAC	47.9 (43.8–51.9)	0.040	51.9 (47.7–55.9)	0.796	37.3 (33.4–41.1)	0.392	14.8 (12.1–17.8)	0.350
RIC	41.6 (31.3–51.6)		49.2 (38.2–59.2)		41.6 (31.5–51.4)		16.8 (9.8–25.4)	

AML-DD acute myeloid leukemia, defined by differentiation; *AML-MR* acute myeloid leukemia, myelodysplasia-related; *CB* cord blood; *CK* complex karyotype; *CR* complete remission; *GVHD* graft-versus-host disease; *HCT-CI* hematopoietic cell transplant-specific comorbidity index; *HSCT* hematopoietic stem cell transplantation; *LFS* leukemia-free survival; *MAC* myeloablative conditioning; *MDS* myelodysplastic neoplasms; MK monosomal karyotype; *MMRD* mismatched related donor; *MMUD* mismatched unrelated donor; *MPN* myeloproliferative neoplasms; *MRD* matched related donor; *MUD* matched unrelated donor; *NR* no remission; *NRM* non-relapse mortality; *OS* overall survival; *PS* performance status; *RIC* reduced intensity conditioning.

Variable	LFS	*P*	OS	*P*	Relapse	*P*	NRM	*P*
	at 5 year, % (95% CI)		at 5 year, % (95% CI)		at 5 year, % (95% CI)		at 5 year, % (95% CI)	
Unknown	20.0 (0.8–58.2)		60.0 (12.6–88.2)		60.0 (4.8–91.8)		20.0 (0.2–65.0)	
GVHD prophylaxis								
Cyclosporine-based	46.2 (39.5–52.6)	0.895	51.3 (44.4–57.7)	0.821	41.8 (35.4–48.2)	0.185	12.0 (8.1–16.6)	0.035
Tacrolimus-based	47.4 (42.5–52.0)		52.0 (46.9–56.7)		37.0 (32.4–41.5)		15.7 (12.4–19.4)	
Others	47.1 (30.3–62.2)		49.7 (32.5–64.7)		25.2 (12.3–40.3)		27.8 (14.2–43.1)	
HSCT year								
2000–2009	43.6 (38.5–48.5)	0.132	47.4 (42.2–52.4)	0.022	39.3 (34.3–44.2)	0.700	17.1 (13.5–21.1)	0.154
2010–2018	50.6 (44.9–56.1)		56.7 (50.7–62.3)		36.1 (30.9–41.3)		13.3 (9.6–17.6)	

AML-DD acute myeloid leukemia, defined by differentiation; *AML-MR* acute myeloid leukemia, myelodysplasia-related; *CB* cord blood; *CK* complex karyotype; *CR* complete remission; *GVHD* graft-versus-host disease; *HCT-CI* hematopoietic cell transplant-specific comorbidity index; *HSCT* hematopoietic stem cell transplantation; *LFS* leukemia-free survival; *MAC* myeloablative conditioning; *MDS* myelodysplastic neoplasms; MK monosomal karyotype; *MMRD* mismatched related donor; *MMUD* mismatched unrelated donor; *MPN* myeloproliferative neoplasms; *MRD* matched related donor; *MUD* matched unrelated donor; *NR* no remission; *NRM* non-relapse mortality; *OS* overall survival; *PS* performance status; *RIC* reduced intensity conditioning.

Next, we assessed the transplantation outcomes according to the AML-MR subgroup (Table 2). There were no significant differences in relapse rates among the AML-MR subgroups and AML-DD ($P = 0.101$); however, OS differed significantly ($P = 0.023$) (Fig. 3). In the multivariate analysis (Table 3), patients with MK without − 7/del(7q) had worse OS (HR, 1.65; 95% CI, 1.08–2.53; $P = 0.021$) than those with AML-DD did. Notably, MK with − 7/del(7q) was not associated with poor OS, similar to isolated − 7/del(7q). Therefore, we compared transplantation outcomes according to the presence or absence of -7/del(7q) within the MK group. Patients with MK and − 7/del(7q) had better OS (71.1% vs. 31.0%, $P = 0.023$) than those with MK without − 7/del(7q), suggesting that transplantation outcomes within the MK group varied according to the − 7/del(7q) status (Fig. 4A). The relapse rate was slightly lower in patients with MK and

− 7/del(7q) than in those with MK without − 7/del(7q), although the difference was not statistically significant (34.4% vs. 55.7%, *P* = 0.066) (Fig. 4B). Patients with a history of MDS or MDS/MPN had marginally better LFS (HR, 0.59; 95% CI, 0.33–1.06; *P* = 0.078) and OS (HR, 0.53; 95% CI, 0.28–1.01; *P* = 0.053); however, this was not statistically significant.

Table 3
Multivariate analysis of the transplantation outcomes in children and adolescents with AML-MR or AML-DD (total patients, n = 732)

Variable	LFS	*P*	OS	*P*	Relapse	*P*	NRM	*P*
	HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)	
PS (vs. 0–1)								
≥2	1.75 (1.27–2.42)	< 0.001	1.87 (1.34–2.60)	< 0.001	1.59 (1.07–2.35)	0.021	1.39 (0.71–2.73)	0.335
Unknown	1.13 (0.81–1.60)	0.470	1.17 (0.82–1.67)	0.379	1.10 (0.77–1.56)	0.601	1.54 (0.90–2.64)	0.116
HCT-CI (vs. 0–2)								
≥3	0.74 (0.40–1.36)	0.332	0.94 (0.51–1.75)	0.856				
Unknown	1.10 (0.78–1.54)	0.605	1.06 (0.74–1.51)	0.761				
AML type (vs. DD)								
History of MDS or MDS/MPN	0.59 (0.33–1,06)	0.078	0.53 (0.28–1.01)	0.053	0.50 (0.23–1.09)	0.080	1.04 (0.39–2.76)	0.944
Isolated −5/del(5q)	1.34 (0.65–2.73)	0.425	0.93 (0.38–2.24)	0.866	0.81 (0.29–2.26)	0.684	2.44 (1.03–5.76)	0.042
Isolated −7/del(7q)	0.78 (0.52–1.16)	0.221	0.73 (0.47–1.13)	0.159	0.72 (0.43–1.20)	0.206	1.18 (0.61–2.27)	0.630
MK with −7/del(7q)	0.56 (0.24–1.27)	0.164	0.50 (0.19–1.36)	0.175	0.55 (0.22–1.39)	0.208	1.23 (0.29–5.18)	0.774

AML-DD acute myeloid leukemia, defined by differentiation; *AML-MR* acute myeloid leukemia, myelodysplasia-related; *CB* cord blood; *CK* complex karyotype; *CR* complete remission; *GVHD* graft-versus-host disease; *HCT-CI* hematopoietic cell transplant-specific comorbidity index; *HSCT* hematopoietic stem cell transplantation; *LFS* leukemia-free survival; *MAC* myeloablative conditioning; *MDS* myelodysplastic neoplasms; MK monosomal karyotype; *MMRD* mismatched related donor; *MMUD* mismatched unrelated donor; *MPN* myeloproliferative neoplasms; *MRD* matched related donor; *MUD* matched unrelated donor; *NR* no remission; *NRM* non-relapse mortality; *OS* overall survival; *PS* performance status; *RIC* reduced intensity conditioning.

Variable	LFS	*P*	OS	*P*	Relapse	*P*	NRM	*P*
	HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)	
MK without −7/del(7q)	1.40 (0.92–2.13)	0.119	1.65 (1.08–2.53)	0.021	1.51 (0.96–2.39)	0.076	0.85 (0.32–2.27)	0.740
CK	1.20 (0.88–1.63)	0.252	1.18 (0.85–1.64)	0.327	1.18 (0.80–1.72)	0.407	1.09 (0.60–1.99)	0.776
Others	1.65 (0.77–3.54)	0.200	1.84 (0.80–4.20)	0.150	1.12 (0.41–3.05)	0.819	2.76 (0.63-12.00)	0.176
Disease status, NR vs. CR	2.93 (2.35–3.64)	< 0.001	3.12 (2.47–3.94)	< 0.001	2.96 (2.30–3.80)	< 0.001	1.53 (1.01–2.29)	0.043
Donor source (vs. MRD)								
MMRD	1.48 (1.06–2.08)	0.022	1.47 (1.03–2.11)	0.035			2.18 (1.02–4.67)	0.046
MUD	1.06 (0.74–1.51)	0.753	1.21 (0.83–1.76)	0.323			2.29 (1.02–5.15)	0.045
MMUD	0.91 (0.60–1.39)	0.664	1.09 (0.70–1.70)	0.709			3.10 (1.34–7.15)	0.008
CB	1.10 (0.81–1.50)	0.531	1.20 (0.86–1.66)	0.281			1.53 (0.78-3.00)	0.219
Conditioning (vs. MAC)								
RIC	1.10 (0.82–1.48)	0.543	1.00 (0.73–1.37)	0.999	1.04 (0.71–1.52)	0.841	1.30 (0.76–2.22)	0.339
Unknown	3.40 (1.32–	0.011	1.05 (0.30–	0.936	2.96 (1.03–	0.044	1.11 (0.23–	0.898

AML-DD acute myeloid leukemia, defined by differentiation; *AML-MR* acute myeloid leukemia, myelodysplasia-related; *CB* cord blood; *CK* complex karyotype; *CR* complete remission; *GVHD* graft-versus-host disease; *HCT-CI* hematopoietic cell transplant-specific comorbidity index; *HSCT* hematopoietic stem cell transplantation; *LFS* leukemia-free survival; *MAC* myeloablative conditioning; *MDS* myelodysplastic neoplasms; MK monosomal karyotype; *MMRD* mismatched related donor; *MMUD* mismatched unrelated donor; *MPN* myeloproliferative neoplasms; *MRD* matched related donor; *MUD* matched unrelated donor; *NR* no remission; *NRM* non-relapse mortality; *OS* overall survival; *PS* performance status; *RIC* reduced intensity conditioning.

Variable	LFS	*P*	OS	*P*	Relapse	*P*	NRM	*P*
	HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)	
	8.77)		3.71)		8.49)		5.27)	
GVHD prophylaxis (vs. cyclosporine-based)								
Tacrolimus-based							0.94 (0.54–1.64)	0.828
Others							2.88 (1.34–6.18)	0.007
HSCT year, 2010–2018 vs. 2000–2009	0.83 (0.63–1.11)	0.215	0.71 (0.52–0.96)	0.024	0.94 (0.71–1.24)	0.660	0.79 (0.49–1.26)	0.324
Acute GVHD, grade II-IV vs. 0-I	1.10 (0.88–1.39)	0.404	1.17 (0.93–1.47)	0.194	0.83 (0.62–1.11)	0.204	2.14 (1.42–3.22)	< 0.001

AML-DD acute myeloid leukemia, defined by differentiation; *AML-MR* acute myeloid leukemia, myelodysplasia-related; *CB* cord blood; *CK* complex karyotype; *CR* complete remission; *GVHD* graft-versus-host disease; *HCT-CI* hematopoietic cell transplant-specific comorbidity index; *HSCT* hematopoietic stem cell transplantation; *LFS* leukemia-free survival; *MAC* myeloablative conditioning; *MDS* myelodysplastic neoplasms; MK monosomal karyotype; *MMRD* mismatched related donor; *MMUD* mismatched unrelated donor; *MPN* myeloproliferative neoplasms; *MRD* matched related donor; *MUD* matched unrelated donor; *NR* no remission; *NRM* non-relapse mortality; *OS* overall survival; *PS* performance status; *RIC* reduced intensity conditioning.

In the multivariate analysis (Table 3), patients with PS ≥ 2 had worse LFS (HR, 1.75; 95% CI, 1.27–2.42; $P < 0.001$) and OS (HR, 1.87; 95% CI, 1.34–2.60; $P < 0.001$) and a higher relapse rate (HR, 1.59; 95% CI, 1.07–2.35; $P = 0.021$) than those with PS 0–1. Allo-HSCT performed during NR was associated with inferior LFS (HR, 2.93; 95% CI, 2.35–3.64; $P < 0.001$) and OS (HR, 3.12; 95% CI, 2.47–3.94; $P < 0.001$), an increased relapse rate (HR, 2.96; 95% CI, 2.30–3.80; $P < 0.001$), and higher NRM (HR, 1.53; 95% CI, 1.01–2.29; $P = 0.043$). Recipients transplanted with MMRD had worse LFS (HR, 1.48; 95% CI, 1.06–2.08; $P = 0.022$), inferior OS (HR, 1.47; 95% CI, 1.03–2.11; $P = 0.035$), and a higher NRM (HR, 2.18; 95% CI, 1.02–4.67; $P = 0.046$). Recipients transplanted with MUD (HR, 2.29; 95% CI, 1.02–5.15; $P = 0.045$) or MMUD (HR, 3.10; 95% CI, 1.34–7.15; $P = 0.008$) had higher NRM. Patients who underwent transplantation after

2010 had better OS (HR, 0.71; 95% CI, 0.52–0.96; *P* = 0.024). Grade II–IV aGVHD was associated with higher NRM (hazard ratio (HR), 2.14; 95% CI, 1.42–3.22; *P* < 0.001).

Prognostic factors in the total patient group

The associations between clinical characteristics and outcomes are summarized in Table 2. In the univariate analysis, transplantation outcomes did not differ significantly between patients with AML-MR and those with AML-DD (Fig. 2). In contrast, PS ≥ 2 and NR at HSCT were associated with worse LFS, inferior OS, and a higher relapse rate. Other factors associated with outcomes included hematopoietic cell transplant-specific comorbidity index, donor source, conditioning intensity, GVHD prophylaxis, HSCT year, and GVHD.

Next, we assessed the transplantation outcomes according to the AML-MR subgroup (Table 2). There were no significant differences in relapse rates among the AML-MR subgroups and AML-DD (*P* = 0.101); however, OS differed significantly (*P* = 0.023) (Fig. 3). In the multivariate analysis (Table 3), patients with MK without − 7/del(7q) had worse OS (HR, 1.65; 95% CI, 1.08–2.53; *P* = 0.021) than those with AML-DD did. Notably, MK with − 7/del(7q) was not associated with poor OS, similar to isolated − 7/del(7q). Therefore, we compared transplantation outcomes according to the presence or absence of -7/del(7q) within the MK group. Patients with MK and − 7/del(7q) had better OS (71.1% vs. 31.0%, *P* = 0.023) than those with MK without − 7/del(7q), suggesting that transplantation outcomes within the MK group varied according to the − 7/del(7q) status (Fig. 4A). The relapse rate was slightly lower in patients with MK and − 7/del(7q) than in those with MK without − 7/del(7q), although the difference was not statistically significant (34.4% vs. 55.7%, *P* = 0.066) (Fig. 4B). Patients with a history of MDS or MDS/MPN had marginally better LFS (HR, 0.59; 95% CI, 0.33–1.06; *P* = 0.078) and OS (HR, 0.53; 95% CI, 0.28–1.01; *P* = 0.053); however, this was not statistically significant.

In the multivariate analysis (Table 3), patients with PS ≥ 2 had worse LFS (HR, 1.75; 95% CI, 1.27–2.42; *P* < 0.001) and OS (HR, 1.87; 95% CI, 1.34–2.60; *P* < 0.001) and a higher relapse rate (HR, 1.59; 95% CI, 1.07–2.35; *P* = 0.021) than those with PS 0–1. Allo-HSCT performed during NR was associated with inferior LFS (HR, 2.93; 95% CI, 2.35–3.64; *P* < 0.001) and OS (HR, 3.12; 95% CI, 2.47–3.94; *P* < 0.001), an increased relapse rate (HR, 2.96; 95% CI, 2.30–3.80; *P* < 0.001), and higher NRM (HR, 1.53; 95% CI, 1.01–2.29; *P* = 0.043). Recipients transplanted with MMRD had worse LFS (HR, 1.48; 95% CI, 1.06–2.08; *P* = 0.022), inferior OS (HR, 1.47; 95% CI, 1.03–2.11; *P* = 0.035), and a higher NRM (HR, 2.18; 95% CI, 1.02–4.67; *P* = 0.046). Recipients transplanted with MUD (HR, 2.29; 95% CI, 1.02–5.15; *P* = 0.045) or MMUD (HR, 3.10; 95% CI, 1.34–7.15; *P* = 0.008) had higher NRM. Patients who underwent transplantation after 2010 had better OS (HR, 0.71; 95% CI, 0.52–0.96; *P* = 0.024). Grade II–IV aGVHD was associated with higher NRM (hazard ratio (HR), 2.14; 95% CI, 1.42–3.22; *P* < 0.001).

Prognostic factors in the AML-MR cohort

We then assessed the prognostic factors in the AML-MR cohort. Before this analysis, AML-MR was reclassified into three risk groups based on the prognostic impact of AML-MR subgroups on OS (Supplementary Fig. 1): a low-risk group (*n* = 104), including patients with a history of MDS or MDS/MPN, isolated − 7/del(7q), and MK with − 7/del(7q); an intermediate-risk group (*n* = 101), including isolated − 5/del(5q) and CK; and a high-risk group (*n* = 47), including MK without − 7/del(7q) and others. This risk stratification effectively stratified the outcomes of the AML-MR cohort. The 5-year LFS rates were 53.8%, 41.1%, and 32.0% in the low-, intermediate-, and high-risk groups, respectively (*P* = 0.005). The corresponding 5-year OS rates were 63.6%, 51.1%, and 31.8%, respectively (*P* < 0.001; Fig. 4C), and the cumulative 5-year relapse incidence rates were 28.6%, 41.9%, and 54.5%, respectively (*P* = 0.005; Fig. 4D). In the multivariate analysis (Fig. 5), relative to the low-risk group, the intermediate- and high-risk groups were associated with higher relapse rates (HR, 1.77; *P* = 0.023 and HR, 2.40; *P* = 0.001, respectively), inferior LFS (HR, 1.84; *P* = 0.008 and HR, 2.62; *P* < 0.001, respectively), and inferior OS (HR, 1.64; *P* = 0.016 and HR, 2.05; *P* = 0.002, respectively). Allo-HSCT performed during NR was associated with poorer LFS (HR, 3.22; *P* < 0.001) and OS (HR, 2.80; *P* < 0.001) and a higher relapse rate (HR, 2.43; *P* < 0.001).

Discussion

We retrospectively analyzed data from 732 children and adolescents with AML-MR or AML-DD who received allo-HSCT, focusing on the outcomes and prognostic factors of AML-MR, based on nationwide registry data. Our results demonstrated that overall transplantation outcomes did not differ significantly between patients with AML-MR and those with AML-DD; however, the subgroup analysis of AML-MR revealed significant heterogeneity in outcomes. Patients with MK without − 7/del(7q) had significantly worse OS than those with AML-DD did. Notably, within the MK subgroup, patients with − 7/del(7q) had better OS than those without − 7/del(7q). Moreover, based on the heterogeneity of AML-MR subgroups, we developed a risk stratification model that effectively distinguished transplantation outcomes in the AML-MR cohort.

Few studies have reported transplantation outcomes in AML-MR [9, 10, 20], particularly in children and adolescents [4]. Prior studies have shown lower remission induction rates [3] and a higher proportion of patients transplanted in NR among adults with AML-MRC than AML-NOS [9, 10]. However, adverse outcomes also reflect the underlying disease biology, particularly MDS-related cytogenetic abnormalities such as MK and CK, which are associated with high post-transplant relapse rates, even in patients who achieve remission [10, 21]. In contrast, the present study found no significant differences in transplantation outcomes between children and adolescents with AML-MR and those with AML-DD. In comparison to adults [10], pediatric AML-MR is characterized by a lower proportion of patients with a history of MDS or MDS/MPN and a higher proportion of those with CK or isolated − 7/del(7q). In adults, a history of MDS or MDS/MPN is associated with a more favorable prognosis, whereas CK is associated with adverse outcomes [10, 22]. These findings suggest that the prognostic impact of AML-MR subgroups differs between children and adults.

AML-MR is a heterogeneous disease category, and transplantation outcomes vary substantially among subgroups. CK is an established adverse prognostic factor, and MK has been proposed as an even poorer-risk cytogenetic subgroup among adults with AML [10, 23]. In this context, the co-occurrence of -7/del(7q) is generally regarded as particularly unfavorable [24]. In contrast, the present study showed that among children with MK, those with − 7/del(7q) had more favorable transplantation outcomes than those without − 7/del(7q), and their outcomes were similar to those of patients with isolated − 7/del(7q). This discrepancy may reflect the fundamental biological differences between pediatric and adult AML-MR. In adults, MK is characterized by extensive genomic instability, almost universal CK, and frequent co-occurrence of *TP53* alterations and loss of chromosomes, such as 5 and 7 [25]. In adult AML with − 7/del(7q), *TP53* variants are detected in approximately 30% of the cases. Clonality analyses have shown that *TP53* variants are predominantly disease-initiating events, whereas − 7/del(7q) appears as a subclonal event in approximately one-third of cases [24]. Together, these findings indicate that MK and − 7/del(7q) observed in adult AML are closely linked to *TP53*-driven genomic instability. In children, hematologic disorders with − 7 have been associated with germline *SAMD9*/*SAMD9L* or *GATA2* variants [26, 27]. The prognostic impact of -7/del(7q) within the MK group may therefore differ between pediatric and adult AML-MR, reflecting underlying biological heterogeneity, although germline testing and genetic analysis of *TP53* were not performed in this study.

Based on the heterogeneity of the AML-MR subgroups, we developed a risk stratification model that effectively distinguished transplantation outcomes in the AML-MR cohort. The main difference from adult risk stratification [10] was that patients with MK with − 7/del(7q) were assigned to the low-risk group; otherwise, the composition was largely the same. Umeda et al. proposed a novel classification of pediatric AML based on comprehensive genomic profiling that correlates with clinical outcomes and is therefore useful [13]; however, because it requires a comprehensive genomic analysis, it is not readily applicable in all countries or institutions. In contrast, our risk stratification for pediatric AML-MR is based primarily on cytogenetic findings, which may facilitate a broader clinical adoption.

Outcomes in the high-risk group remain unsatisfactory, with a 5-year OS of only 31.8%. Consistent with the strong prognostic impact of disease status at allo-HSCT, these findings underscore the importance of achieving CR before transplantation whenever possible. Relapse was the principal driver of failure in the high-risk group; therefore, prospective studies evaluating more effective pretransplant disease control and post-transplant maintenance strategies are warranted.

This study has several limitations. First, it was a retrospective analysis based on registry data. Second, information on measurable residual disease levels, which can affect outcomes, was not available for patients transplanted in the CR group. Third, data on myelodysplasia-related gene variants defining AML-MR were not captured in the registry and, therefore, could not be incorporated into our analyses. However, such myelodysplasia-related gene variants are rare in pediatric AML, accounting for only 0.1–2.1% of cases overall, and have been reported not to form a distinct prognostic category because they frequently co-occur with other abnormalities [13]. Thus, their absence is unlikely to have substantially affected the present analyses.

In conclusion, allo-HSCT outcomes in children and adolescents with AML-MR were comparable to those with AML-DD; however, AML-MR was biologically and prognostically heterogeneous. In particular, MK without − 7/del(7q) was associated with markedly inferior OS, whereas MK with − 7/del(7q) was not, a pattern that differed from that in adult AML-MR. Our cytogenetics-based risk stratification effectively distinguished transplantation outcomes within the AML-MR cohort and may aid in risk-adapted management. Disease status at allo-HSCT and performance status remained important prognostic factors, reinforcing the need for transplantation in CR, whenever possible. Further studies are warranted to refine the pediatric AML-MR-specific risk classification and develop more effective pre- and post-transplant strategies, especially for high-risk subgroups.

Declarations

Acknowledgments

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Author contributions

YKa is the principal investigator and takes the principal responsibility for the paper. YKa, AH, MY, KH, YO, and HS designed this study. YKa, YAr, MS, YKo, NY, KW, MI, KO, YT, MY, AW, TK, KU, SY, MH, and YAt recruited the patients and collected the data. YKa analyzed the data and wrote the manuscript. All authors discussed the results, commented on the manuscript, and provided their final approval of the manuscript.

Conflict of interest

The authors declare no conflicts of interest in association with the present study.

Data Availability Statement

The data of this study are not publicly available due to ethical restrictions that exceed the scope of the recipient/donor’s consent for research use in the registry.

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Figures

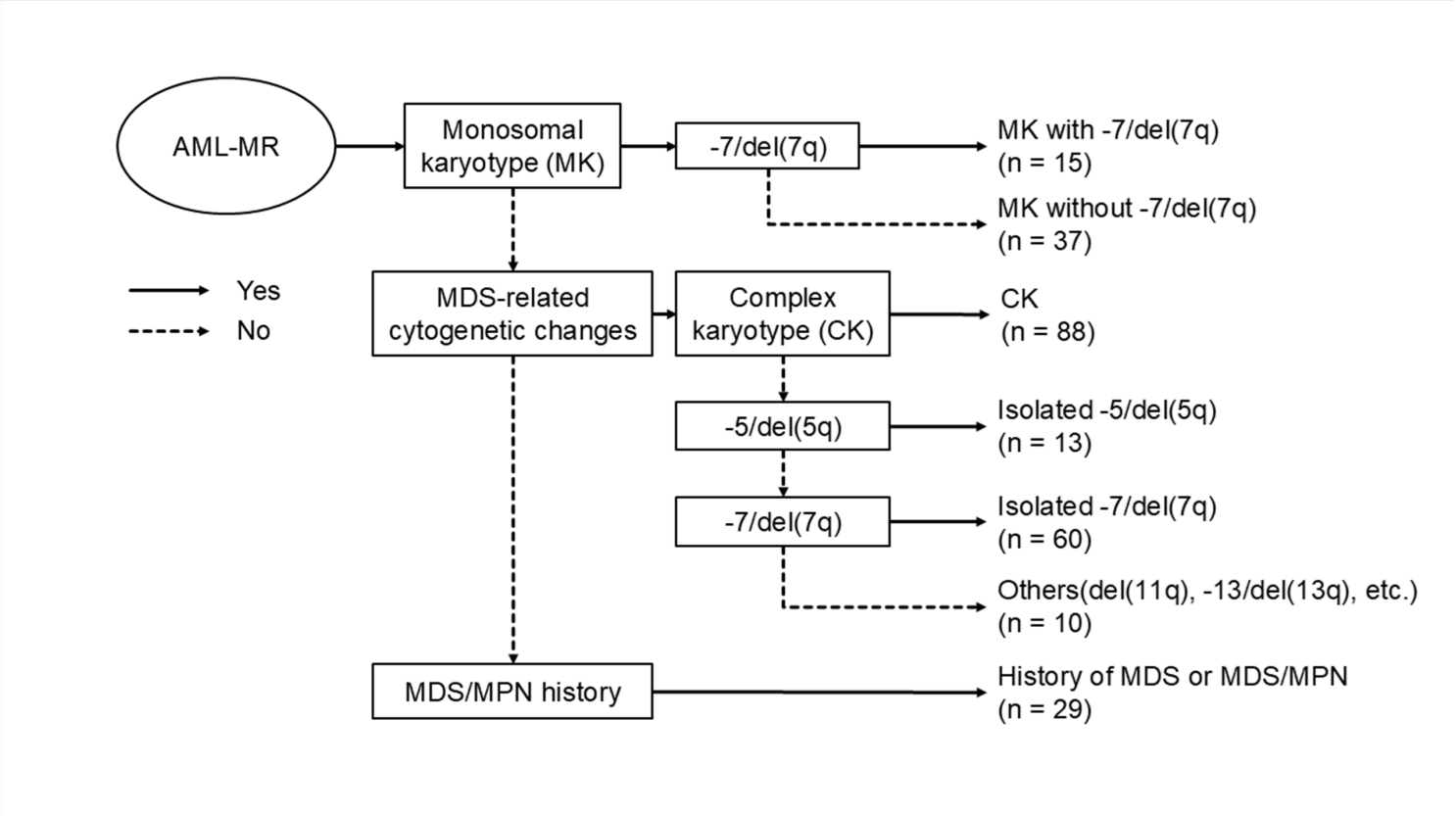


Figure 1

The hierarchical classification system used for children and adolescents with AML-MR.

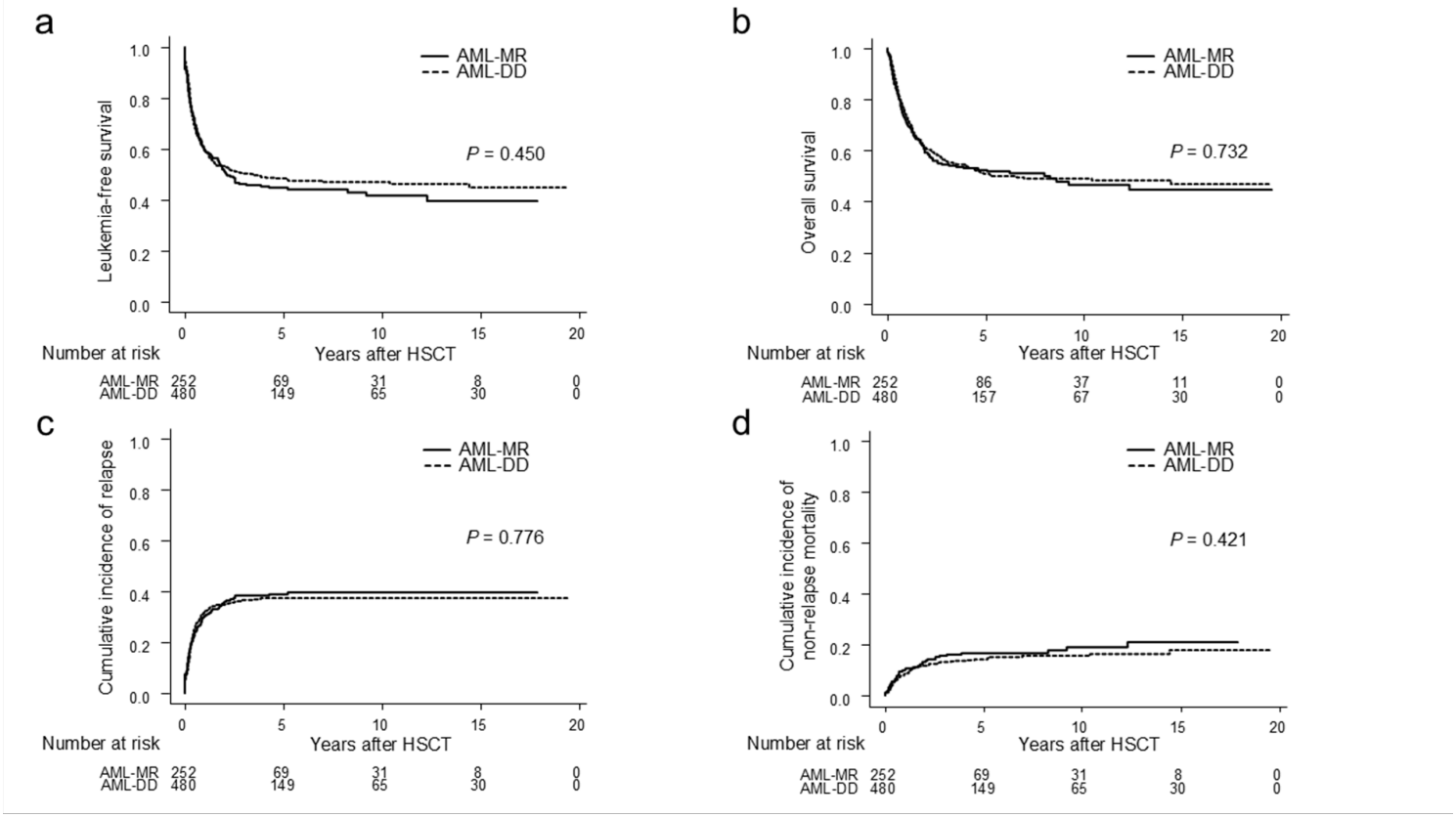


Figure 2

Outcomes of children and adolescents with AML-MR or AML-DD after allo-HSCT.

a Leukemia-free survival. **b** Overall survival. **c** Cumulative incidence of relapse. **d** Cumulative incidence of non-relapse mortality.

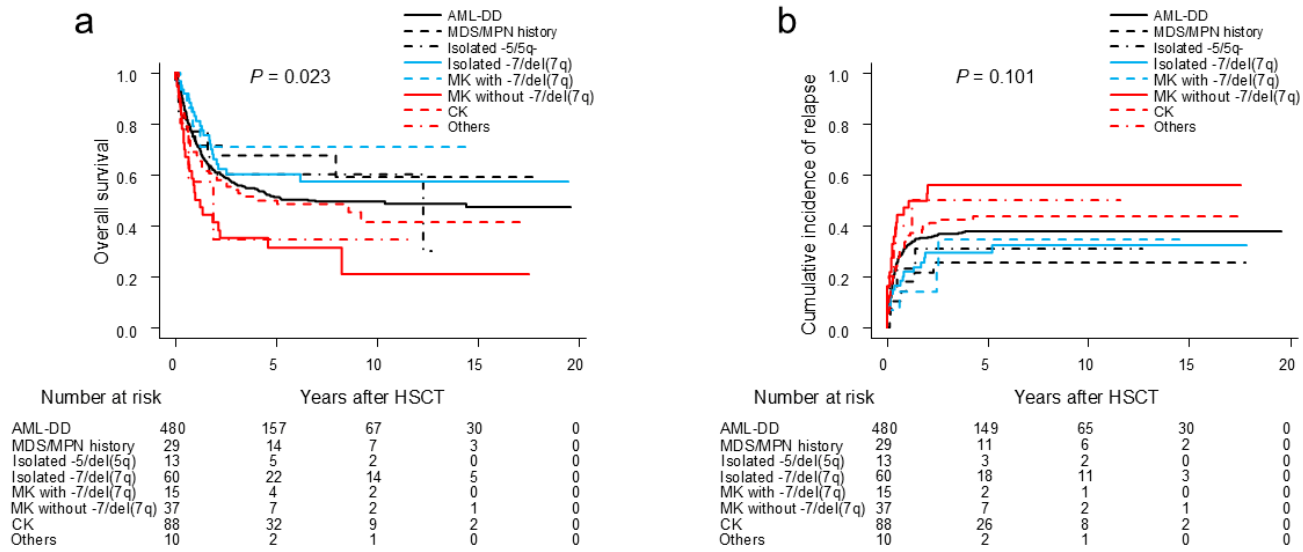


Figure 3

Outcomes of children and adolescents with AML-MR or AML-DD after allo-HSCT.

Outcomes are shown according to the AML-MR subgroups. **a** Overall survival. **b** Cumulative incidence of relapse.

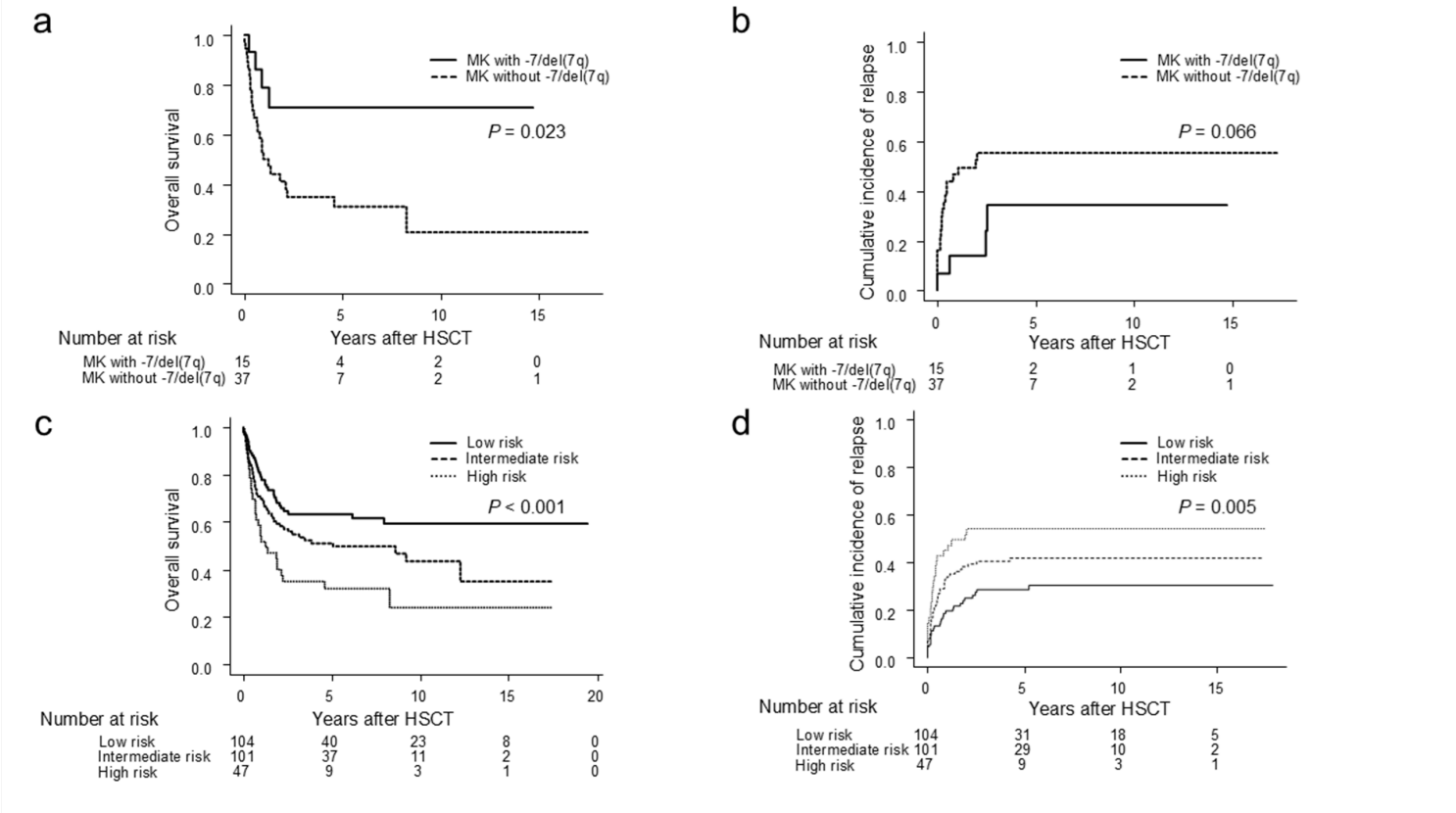


Figure 4

Outcomes of children and adolescents in the AML-MR cohort after allo-HSCT.

Outcomes are shown according to the presence of -7/del(7q) in MK (a, b) and AML-MR risk stratification (c, d). **a and c** Overall survival. **b and d** Cumulative incidence of relapse.

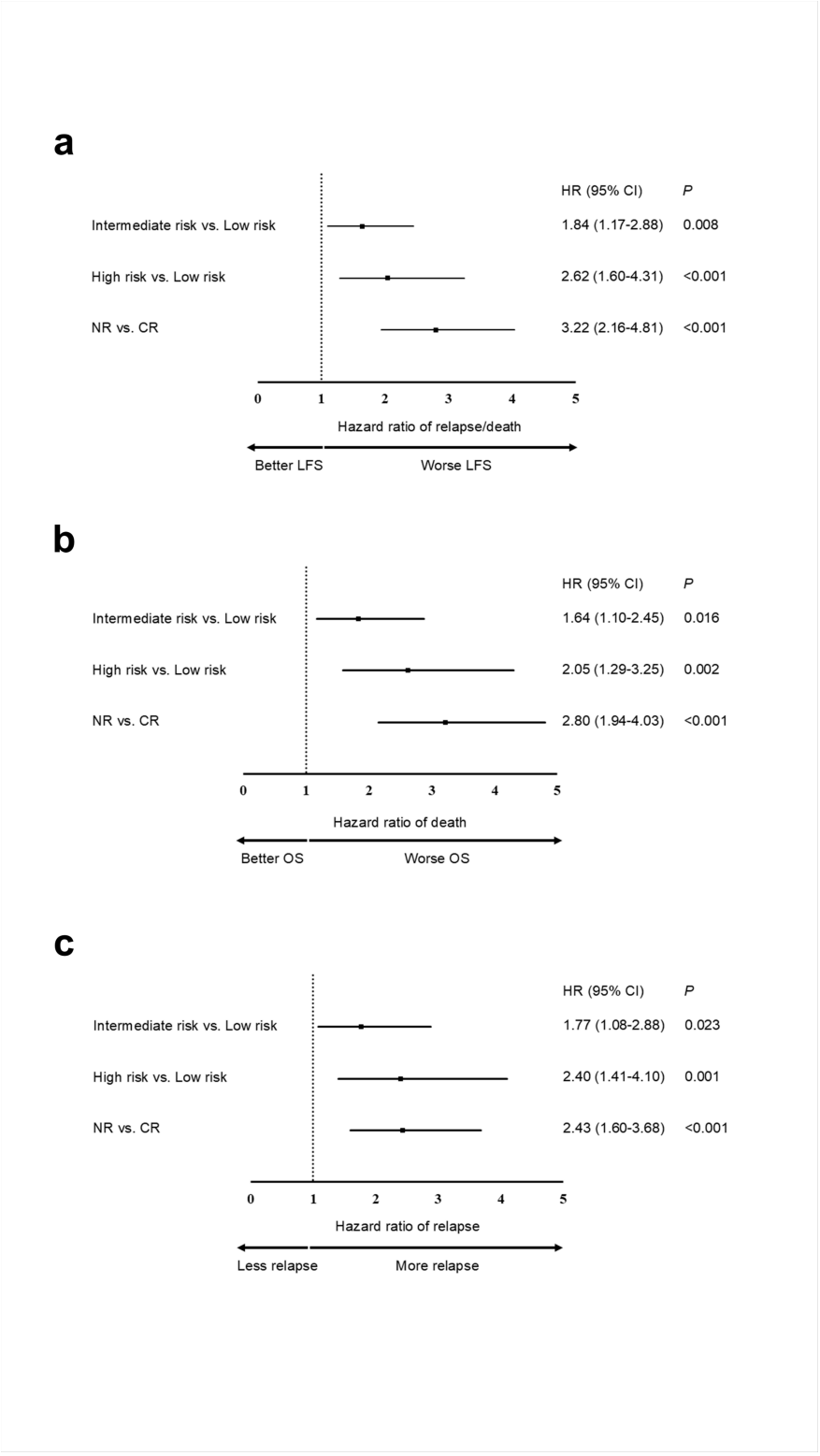


Figure 5

Multivariate analysis of children and adolescents in the AML-MR cohort after allo-HSCT.

a Leukemia-free survival. **b** Overall survival. **c**Cumulative incidence of relapse.

Supplementary Files

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- SupplementaryFigure1.tif