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Risk Stratification and Prognosticators of Acute Myeloid Leukemia with Myelodysplasia-Related Changes in Patients Undergoing Allogeneic Stem Cell Transplantation: A Retrospective Study of the Adult Acute Myeloid Leukemia Working Group of the Japan Society for Hematopoietic Cell Transplantation

Kaito Harada[1,*], Takaaki Konuma[2], Shinichiro Machida[1], Jinichi Mori[3], Jun Aoki[4], Naoyuki Uchida[5], Kazuteru Ohashi[6], Takahiro Fukuda[7], Masatsugu Tanaka[8], Kazuhiro Ikegame[9], Yukiyasu Ozawa[10], Koji Iwato[11], Tetsuya Eto[12], Makoto Onizuka[1], Tatsuo Ichinohe[13], Yoshiko Atsuta[14,15], Shingo Yano[16]

[1] *Department of Hematology and Oncology, Tokai University School of Medicine, Isehara, Japan*
[2] *Department of Hematology/Oncology, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan*
[3] *Department of Hematology, Jyoban Hospital, Tokiwakai, Fukushima, Japan*
[4] *Department of Hematology, Yokohama City University Medical Center, Yokohama, Japan*
[5] *Department of Hematology, Federation of National Public Service Personnel Mutual Aid Associations Toranomon hospital, Tokyo, Japan*
[6] *Hematology Division, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan*
[7] *Department of Hematopoietic Stem Cell Transplantation, National Cancer Center Hospital, Tokyo, Japan*
[8] *Department of Hematology, Kanagawa Cancer Center, Yokohama, Japan*
[9] *Division of Hematology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan*
[10] *Department of Hematology, Japanese Red Cross Nagoya First Hospital, Nagoya, Japan*
[11] *Department of Hematology, Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital, Hiroshima, Japan*
[12] *Department of Hematology, Hamanomachi Hospital, Fukuoka, Japan*
[13] *Department of Hematology and Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan*
[14] *Japanese Data Center for Hematopoietic Cell Transplantation, Nagoya Japan*
[15] *Department of Healthcare Administration, Nagoya University Graduate School of Medicine, Nagoya, Japan*
[16] *Division of Clinical Oncology and Hematology, The Jikei University School of Medicine, Tokyo, Japan*

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A B S T R A C T

Although the prognosis of acute myeloid leukemia with myelodysplasia-related changes (AML-MRC) is worse than that of AML not otherwise specified (AML-NOS), transplantation outcomes and prognosticators of AML-MRC patients undergoing allogeneic stem cell transplantation (allo-SCT) remain unclear. Transplantation outcomes of AML-MRC (n = 4091) were compared with those of AML-NOS (n = 3964) in patients who underwent allo-SCT between 2003 and 2016 using a nationwide registration database. The 3-year overall survival (OS; 35.5% versus 50.6%) was lower and the relapse (42.3% versus 32.1%) and nonrelapse mortality (26.3% versus 22.0%) rates were higher in the AML-MRC group than in the AML-NOS group. Based on the hierarchical AML-MRC classification, myelodysplasia as the sole criterion was associated with better OS compared with AML-NOS, whereas monosomal or complex karyotype and −5/del(5q) were associated with poor OS. A history of myelodysplastic syndrome and −7/del(7q) did not affect OS. Accordingly, AML-MRC with complex karyotype or −5/del(5q) and that with monosomal karyotype were classified as intermediate and high risks, respectively, whereas the remaining cases were classified as low risk. The 3-year OS rates were 50.7%, 36.9%, and 13.8% in the low-, intermediate-, and high-risk groups, respectively ($P < .001$). Risk classification, older age, and low performance status score were significant risk factors for survival in AML-MRC, independently of the disease status. Grades I to II acute graft-versus-host disease significantly reduced the 3-year relapse (24.7% versus 31.6%), leading to better survival (hazard ratio, .64). Our prognostic risk stratification can potentially aid in elucidating the diverse transplantation outcomes in patients with AML-MRC.

INTRODUCTION

Acute myeloid leukemia with myelodysplasia-related changes (AML-MRC) is a distinct entity defined by the World

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* Correspondence and reprint requests: Kaito Harada, MD, Department of Hematology and Oncology, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa, 259-1143, Japan.
E-mail address: haradakaito1986@gmail.com (K. Harada).

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Health Organization (WHO) in 2008 by the presence of multilineage dysplasia (MLD), and/or myelodysplastic syndrome (MDS)-related cytogenetics, and/or a history of MDS or MDS/myeloproliferative neoplasm (MPN) [1]. In the 2016 WHO classification, AML-MRC was preserved as a distinct entity, with some minor revisions in MDS-related cytogenetics [2]. Most patients in studies reporting that the prognosis of AML-MRC was worse than that of AML not otherwise specified (NOS) [3–8] had undergone chemotherapy rather than allogeneic stem cell transplantation (allo-SCT). Similarly, the known prognostic factors of AML-MRC, including MLD as the sole AML-MRC criterion (MLD-solo) [6,8–10], are based on studies including patients who did not undergo transplantation.

Allo-SCT is a potentially curative therapy for patients with AML. Following the recommendations for allo-SCT in patients with AML with intermediate or poor cytogenetic risk [11,12], most fit patients with AML-MRC undergo allo-SCT. Because AML-MRC is a heterogeneous disease, transplantation outcomes in these patients can be highly variable; however, data on transplantation outcomes in patients with AML-MRC are sparse [13], and detailed transplantation outcomes in a large-scale cohort fulfilling the WHO classification criteria for AML-MRC have not been reported. Therefore, the prognostic factors for patients with AML-MRC undergoing allo-SCT remain to be elucidated.

We used a nationwide registration database to compare the transplantation outcomes between patients with AML-MRC and AML-NOS and analyzed the prognostic impact of MLD, specific MDS-related cytogenetic abnormalities, and a history of MDS or MDS/MPN. We further determined the prognostic factors based on patient and transplantation characteristics in patients with AML-MRC undergoing allo-SCT.

METHODS

Study Design and Data Collection

Clinical data were provided by the Transplant Registry Unified Management Program 2 of the Japanese Data Center for Hematopoietic Cell Transplantation [14,15]. Patients aged ≥ 18 years with AML-MRC or AML-NOS who underwent their first allo-SCT between 2003 and 2016 were eligible for inclusion in the study. All patients with AML-MRC and AML-NOS were diagnosed at participating institutions, and the diagnoses were reviewed by the first author in accordance with the criteria provided by the WHO in 2016 [2]. Patients with therapy-related myeloid neoplasms, acute erythroid leukemia, and with AML harboring t(8;21), inv(16), t(16;16), or 11q23 abnormalities were excluded from this study. In addition, patients with del(9q) were also excluded because these patients were not defined as AML-MRC according to the WHO criteria in 2016. Patients with MLD-solo harboring *NPM1* or *CEBPα* mutations were not excluded from study because of the lack of molecular data in our registry database. In the cohort focusing on AML-MRC, patients lacking data on WBC count at the time of diagnosis, blast percentage in the bone marrow (BM) and peripheral blood (PB) at the time of transplantation, and other patient and transplant characteristics were excluded. Accordingly, 8055 and 1687 patients were eligible to be included in the overall and AML-MRC cohorts, respectively. The study protocol complied with the principles of the Declaration of Helsinki, and approval for this retrospective study was obtained from the Institutional Review Board of Tokai University School of Medicine.

Study Endpoints and Definitions

The study endpoints were overall survival (OS), leukemia-free survival (LFS), relapse, and nonrelapse mortality (NRM). OS was defined as the time between transplantation and death or the time of last contact. LFS was

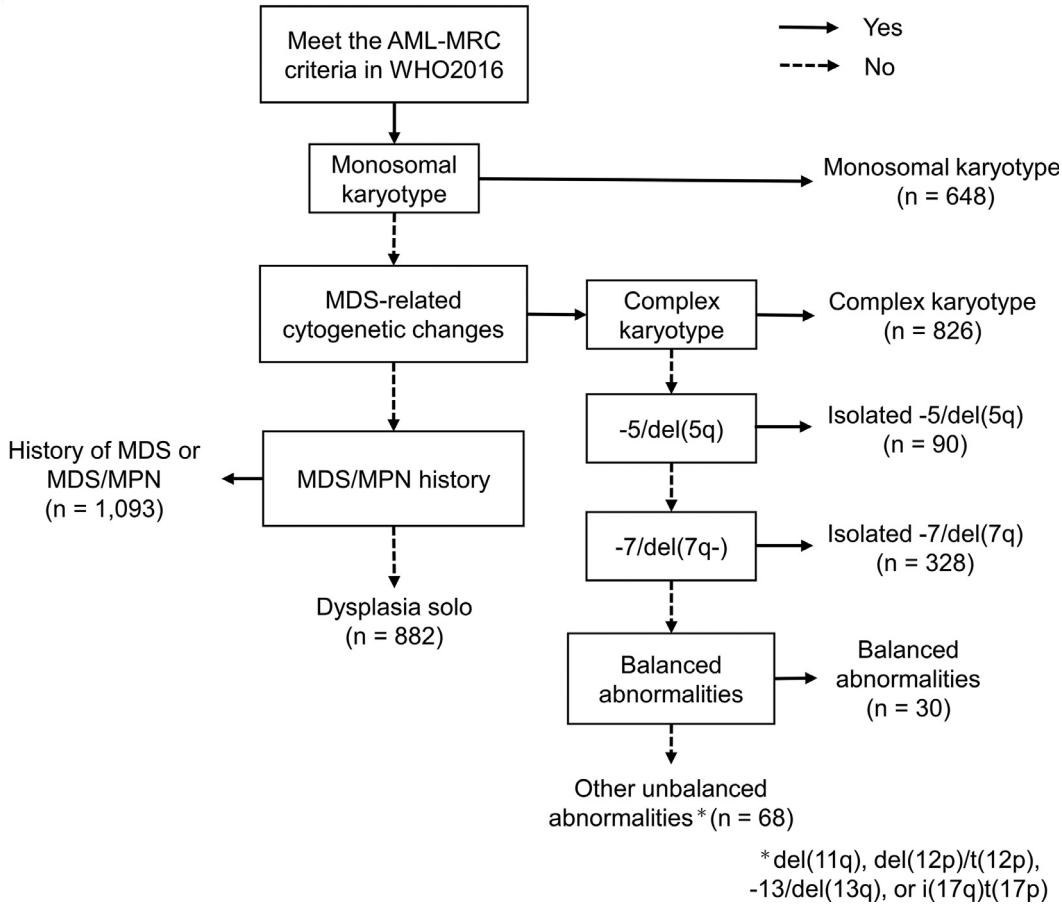

Figure 1. The hierarchical classification system used for patients with AML-MRC in the current study. For example, patients with a monosomal karyotype were classified into the monosomal karyotype group, regardless of whether they had specific MDS-related cytogenetic changes or not.

defined as the time between transplantation and the first event (either relapse or death). Relapse was defined as hematologic evidence of disease. Patients who failed to achieve complete remission (CR) after allo-SCT were categorized as relapse cases at day 0. NRM was defined as death without relapse. Given that monosomal karyotype (MK), complex karyotype (CK: ≥3 clonal chromosomal abnormalities), and chromosome 5 or 7 abnormalities are overlapping categories [16–18], we used a hierarchical classification system based on the WHO classification criteria to classify patients with AML-MRC in the current study (Figure 1). The conditioning intensity was classified in line with the published criteria [19,20]. Acute graft-versus-host disease (GVHD) was diagnosed and graded at each center according to the criteria reported previously [21]. HLA disparity was defined as a mismatch when a mismatch of at least 1 serologic level in related BM or PB SCT or allele level in unrelated BM or PB SCT was detected between the recipient and donor.

Statistical Analysis

Distributions of patient characteristics were compared using Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. OS and LFS probabilities were estimated using the Kaplan-Meier method, and differences between groups were analyzed using the log-rank test. The incidence rate of relapse and NRM were determined using a cumulative incidence method, and differences between the groups were analyzed using Gray's test by considering each risk as a competing risk. Multivariate analyses were performed with the Cox proportional hazard regression model for OS and LFS or the Fine-Gray proportional hazards model for relapse and NRM. Those factors that demonstrated significance at $P < .05$ in the univariate analysis were included in the multivariate analyses, and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated.

The covariates considered in the univariate models for each analysis included age (<55 versus ≥55 years), sex (male versus female), performance status (PS; 0 to 1 versus 2 to 4), hematopoietic cell transplant–specific comorbidity index (HCT-CI; 0 to 2 versus ≥3), WHO classification (AML-MRC versus AML-NOS), WBC count at the time of diagnosis (<20,000 versus ≥20,000/μL), disease status at the time of transplantation (CR versus not CR), conditioning intensity (myeloablative versus reduced-intensity conditioning), donor source (matched related versus mismatched related versus matched unrelated versus mismatched unrelated donor versus cord blood), GVHD prophylaxis (cyclosporine- versus tacrolimus-based), cytomegalovirus serostatus of the donor–recipient pair (donor [D]+/recipient [R]+ versus D+/R− versus D−/R+ versus D−/R−), ABO incompatibility (ABO-matched versus ABO-mismatched donor), year of the transplantation (2003 to 2007 versus 2008 to 2012 versus 2013 to 2016), and days from the diagnosis to the transplantation (at least median versus less than median days). In the analysis focusing on the patients with AML-MRC, risk classification (low versus intermediate versus high) and proportion of blasts in BM (<20% versus ≥20%) and PB (<5% versus ≥5%) at transplantation were also included as variables.

For multiple comparisons, P values were corrected using Holm's method. All P values were 2-sided, and all statistical analyses were performed using EZR, a graphic user interface for R software (version 2.13.0; R Foundation for Statistical Computing, Vienna, Austria) [22].

RESULTS

Patient Characteristics and Transplant Outcomes in the Overall Cohort

Among the 8055 patients who met the study criteria for inclusion, 3964 and 4091 patients were classified into the AML-MRC and AML-NOS groups, respectively. Table 1 summarizes the patient and transplant characteristics of the groups. Specifically, the distributions of the diagnostic criteria for AML-MRC were as follows: MLD-solo (n = 882, 22.3%), a history of MDS or MDS/MPN (n = 1093, 27.6%), and MDS-related cytogenetic abnormalities (n = 1976, 49.8%). Among the 648 patients with MK, 642 (99.1%), 363 (56.0%), and 358 (55.2%) harbored CK, −5/del(5q), and −7/del(7q), respectively. Patients with AML-MRC were older and more likely men. They also had worse PS score, higher HCT-CI score, and lower WBC count at diagnosis and were less likely to be in CR. Regarding the transplant characteristics, patients with AML-MRC were more likely to receive reduced-intensity conditioning, cord blood as a stem cell source, and tacrolimus-based GVHD prophylaxis and less likely to have donor- and recipient-positive cytomegalovirus serostatus. The time from diagnosis to transplantation was significantly shorter in the AML-MRC group than in the AML-NOS group (170 versus 234 days, $P < .001$). The median follow-up period for survivors was 45 months (range, 0 to 176).

The OS and LFS were significantly shorter in the AML-MRC group than in the AML-NOS group (3-year OS, 35.5% versus 50.6%, $P < .001$; 3-year LFS, 31.3% versus 45.9%, $P < .001$, respectively) (Figure 2A, B). After adjusting for other covariates, AML-MRC was significantly associated with poor OS (HR, 1.11; 95% CI, 1.01 to 1.21; $P = .029$) and LFS (HR, 1.17; 95% CI, 1.09 to 1.26; $P < .001$) (Supplementary Table S1). The cumulative incidence rates of relapse and NRM were significantly higher in the AML-MRC group than in the AML-NOS group (3-year relapse rate, 42.3% versus 32.1%, $P < .001$; 3-year NRM, 26.3% versus 22.0%, $P < .001$, respectively) (Figure 2C, D). In the multivariate analyses, AML-MRC was significantly associated with relapse (HR, 1.22; 95% CI, 1.11 to 1.34; $P < .001$) but not with NRM (HR, .99; 95% CI, .86 to 1.13; $P = .85$) (Supplementary Table S1).

Given the heterogeneity of AML-MRC, we next divided patients in the AML-MRC group into subgroups: MLD-solo, MDS or MDS/MPN history, MK, CK, isolated −5/del(5q), isolated −7/del(7q), other unbalanced abnormalities, and balanced abnormalities groups, according to the AML-MRC fulfillment criteria of the WHO. Figure 2E, F show the OS and relapse rates in the entire AML-NOS group and in the subgroups. At 3 years the OS rates were 51.7%, 40.3%, 12.1%, 35.8%, 32.9%, 38.0%, 47.5%, and 50.7% in the MLD-solo, MDS or MDS/MPN history, MK, CK, isolated −5/del(5q), isolated −7/del(7q), other unbalanced abnormalities, and balanced abnormalities groups, respectively (Figure 2E). After adjusting for other covariates, MLD-solo (HR, .81; 95% CI, .71 to .94; $P = .005$) was associated with better OS compared with AML-NOS, whereas a history of MDS or MDS/MPN (HR, .88; 95% CI, .77 to 1.01; $P = .061$), isolated −7/del(7q) (HR, .99; 95% CI, .81 to 1.22; $P = .96$), other unbalanced abnormalities (HR, .88; 95% CI, .56 to 1.39; $P = .59$), and balanced abnormalities (HR, .90; 95% CI, .45 to 1.82; $P = .77$) were not associated with OS. In contrast, MK (HR, 2.30; 95% CI, 2.00 to 2.64; $P < .001$), CK (HR, 1.28; 95% CI, 1.08 to 1.52; $P = .005$), and isolated −5/del(5q) (HR, 1.47; 95% CI, 1.05 to 2.06; $P = .024$) were associated with poor OS (Table 2). Although the number of patients in other unbalanced abnormalities groups was small, we performed the multivariate analysis additionally considering each rare chromosomal change as an independent group. No significant differences in OS were found between AML-NOS and isolated del(11q) (HR, .85; 95% CI, .32 to 2.27; $P = .74$), isolated del(12p)/t(12p) (HR, .99; 95% CI, .47 to 2.08; $P = .97$), isolated −13/del(13q) (HR, 1,92; 95% CI, .72 to 5.12; $P = .20$), and isolated i(17q)/t(17p) groups (HR, .53; 95% CI, .20 to 1.41; $P = .20$).

The cumulative incidence rates of relapse at 3 years were 29.0%, 32.8%, 64.1%, 46.9%, 51.9%, 42.2%, 21.9%, and 41.2% in the MLD-solo, MDS or MDS/MPN history, MK, CK, isolated −5/del(5q), isolated −7/del(7q), other unbalanced abnormalities, and balanced abnormalities groups, respectively (Figure 2F). After adjusting for other covariates, a history of MDS or MDS/MPN (HR, .86; 95% CI, .75 to 1.00; $P = .043$) and other unbalanced abnormalities (HR, .34; 95% CI, .15 to .77; $P = .010$) were significantly associated with a lower relapse rate compared with AML-NOS, whereas MLD-solo (HR, .91; 95% CI, .79 to 1.06; $P = .24$) and balanced abnormalities (HR, 1.19; 95% CI, .67 to 2.11; $P = .56$) did not exhibit an association with a lower relapse rate. In contrast, MK (HR, 2.19; 95% CI, 1.90 to 2.52; $P < .001$), CK (HR, 1.37; 95% CI, 1.15 to 1.62; $P < .001$), isolated −5/del(5q) (HR, 1.94; 95% CI, 1.37 to 2.75; $P < .001$), and isolated −7/del(7q) (HR, 1.24; 95% CI, 1.01 to 1.52; $P = .043$) were associated with a higher relapse rate (Table 2).

Table 1
Patient and Transplant Characteristics according to the WHO Classification

Characteristic	Subcategory	AML-MRC (n = 3964)	AML-NOS (n = 4091)	*P*
Median age, yr [IQR]		56 [45-62]	49 [37-58]	<.001
Age	<55 yr	1842 (46.5)	2652 (64.8)	<.001
	≥55 yr	2122 (53.5)	1439 (35.2)	
Sex	Male	2591 (65.4)	2222 (54.3)	<.001
	Female	1373 (34.6)	1869 (45.7)	
PS	0-1	3318 (83.7)	3740 (91.4)	<.001
	≥2	591 (14.9)	334 (8.2)	
	Missing	55 (1.4)	17 (.4)	
HCT-CI	0-2	2735 (69.0)	3096 (75.7)	<.001
	≥3	634 (16.0)	372 (9.1)	
	Missing	595 (15.0)	623 (15.2)	
Median WBC count at diagnosis, /μL [IQR]		3400 [1700-11,187]	20,000 [3780-69,250]	<.001
Disease status at transplantation	CR	1482 (37.4)	2640 (64.5)	<.001
	Non-CR	2482 (62.6)	1451 (35.5)	
Conditioning	Myeloablative	2467 (62.2)	2883 (70.5)	<.001
	Reduced intensity	1492 (37.8)	1208 (29.5)	
Donor source	MRD	774 (19.5)	983 (24.0)	<.001
	MMRD	381 (9.6)	359 (8.8)	
	MUD	779 (19.7)	943 (23.1)	
	MMUD	609 (15.4)	646 (15.8)	
	CB	1421 (35.8)	1160 (28.4)	
GVHD prophylaxis	Tac-based	2592 (65.4)	2542 (62.1)	.002
	CyA-based	1294 (32.6)	1483 (36.3)	
	Others	78 (2.0)	66 (1.6)	
Cytomegalovirus serostatus	D+/R+	1268 (32.0)	1459 (35.7)	<.001
	D+/R−	169 (4.3)	242 (5.9)	
	D−/R+	992 (25.0)	922 (22.6)	
	D−/R−	252 (6.4)	317 (7.7)	
	Missing	1283 (32.4)	1151 (28.1)	
ABO incompatibility	Match	1850 (46.7)	1967 (48.1)	.23
	Major mismatch	823 (20.8)	777 (19.0)	
	Minor mismatch	837 (21.1)	907 (22.)	
	Major and minor mismatch	406 (10.2)	416 (10.2)	
	Missing	48 (1.2)	24 (.6)	
Year of the transplantation	2003-2007	851 (21.5)	887 (21.7)	0.95
	2008-2012	1615 (40.7)	1671 (40.8)	
	2013-2016	1498 (37.8)	1533 (37.5)	
Median days from diagnosis to transplantation [IQR]		170 [111-265]	234 [157-445]	<.001
Fulfilled criteria for AML-MRC	MLD-solo	882 (22.3)		
	History of MDS or MDS/MPN	1093 (27.6)		
	MDS-related cytogenetics	1976 (49.8)		
	MK	648 (16.3)		
	CK	432 (10.9)		
	CK without precise data	394 (9.9)		
	Isolated −5/del(5q)	90 (2.3)		
	Isolated −7/del(7q)	328 (8.3)		
	Other unbalanced abnormalities	68 (1.7)		
	Del(11q)	24 (.6)		
	Del(12p)/t(12p)	20 (.5)		
	−13/del(13q)	10 (.3)		
	i(17q)/t(17p)	14 (.4)		
	Balanced abnormalities	30 (.8)		

Values are n (%) unless otherwise defined. IQR indicates interquartile range; MRD, matched related donor; MMRD, mismatched related donor; MUD, matched unrelated donor; MMUD, mismatched unrelated donor; CB, cord blood; Tac, tacrolimus; CyA, cyclosporine A.

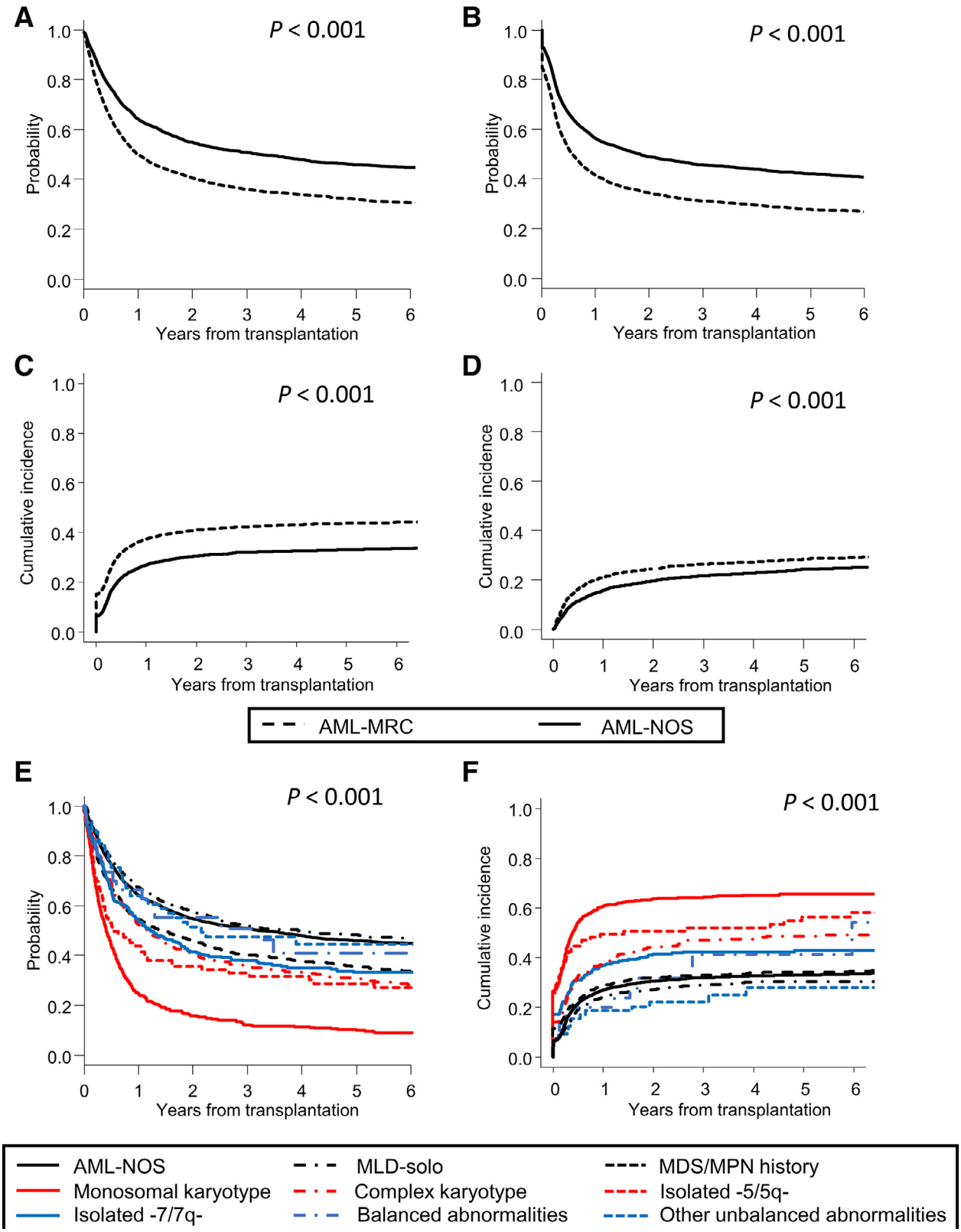

Figure 2. OS (A), LFS (B), relapse rate (C), and NRM (D) in the overall cohort. Patients were dichotomized into AML-MRC and AML-NOS groups in accordance with the WHO classification. OS (E) and relapse rate (F) in the overall cohort stratified according to the subgroups used for AML-MRC.

Transplant Outcomes and Risk Factors for Survival in the AML-MRC Cohort

We next focused on the AML-MRC cohort (n = 1687) to identify the prognostic factors for transplantation outcomes. Based on the prognostic impact of the WHO classification criteria on OS (Table 2), we reclassified the AML-MRC cohort into the following 3 groups: a low-risk group comprising the MLD-solo, history of MDS or MDS/MPN, isolated −7/del(7q), other

Table 2
Prognostic Impact of the AML-MRC Fulfillment Criteria of the WHO on OS, LFS, Relapse, and NRM in the Overall Cohort

	OS			LFS			Relapse			NRM		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Fulfillment criteria for AML-MRC (vs. NOS)												
MLD-solo	.81	.71-.94	.005	.91	.81-1.01	.08	.91	.79-1.06	.24	.94	.77-1.15	.57
History of MDS or MDS/MPN	.88	.77-1.01	.061	.96	.86-1.06	.43	.86	.75-1.00	.043	1.10	.90-1.33	.35
MK	2.30	2.00-2.64	<.001	2.14	1.92-2.39	<.001	2.19	1.90-2.52	<.001	.93	.72-1.19	.55
CK	1.28	1.08-1.52	.005	1.28	1.11-1.46	<.001	1.37	1.15-1.62	<.001	1.06	.81-1.38	.69
Isolated −5/del(5q)	1.47	1.05-2.06	.024	1.49	1.14-1.96	.004	1.94	1.37-2.75	<.001	.71	.36-1.41	.33
Isolated −7/del(7q)	.99	.81-1.22	.96	1.12	.96-1.32	.16	1.24	1.01-1.52	.043	.95	.69-1.31	.75
Other unbalanced abnormalities	.88	.56-1.39	.59	.76	.52-1.12	.17	.34	.15-.77	.010	1.73	.98-3.08	.06
Balanced abnormalities	.90	.45-1.82	.77	1.19	.70-2.02	.52	1.19	.67-2.11	.56	.29	.04-2.12	.22
Age, <55 vs. ≥55 yr	1.42	1.30-1.56	<.001	1.29	1.20-1.39	<.001	.98	.89-1.07	.61	1.56	1.35-1.81	<.001
Male vs. female	1.18	1.09-1.29	<.001	1.13	1.06-1.21	<.001	1.01	.93-1.10	.81	1.21	1.06-1.37	.005
PS, ≥2 vs. 0-1	2.11	1.87-2.37	<.001	1.80	1.64-1.98	<.001	1.31	1.16-1.49	<.001	1.50	1.23-1.83	<.001
HCT-CI ≥3 vs. 0-2	1.16	1.04-1.29	.008	1.08	.99-1.18	.10	.83	.73-.94	.003	1.27	1.08-1.50	.004
WBC count ≥20,000 vs. <20,000	1.16	1.05-1.27	.002	1.17	1.09-1.25	<.001	1.42	1.29-1.56	<.001	.83	.72-.95	.008
Disease status, non-CR vs. CR	2.31	2.11-2.54	<.001	2.31	2.15-2.49	<.001	3.05	2.78-3.36	<.001	.95	.83-1.09	.46
RIC vs. MAC	1.03	.94-1.13	.57	1.07	1.00-1.16	.058	1.16	1.05-1.27	.004	.90	.78-1.05	.17
Donor source (vs. MRD)												
MMRD	1.41	1.20-1.66	<.001	1.07	.94-1.21	.32	.84	.72-.99	.038	1.72	1.32-2.23	<.001
MUD	1.17	1.01-1.35	.032	.90	.81-1.00	.05	.84	.74-.96	.01	1.33	1.06-1.67	.014
MMUD	1.37	1.17-1.60	<.001	1.00	.89-1.12	.98	.70	.61-.81	<.001	2.01	1.58-2.55	<.001
CB	1.25	1.06-1.46	.008	1.00	.91-1.09	.97	.70	.62-.79	<.001	2.11	1.65-2.69	<.001
Tac-based vs. CyA-based	.82	.73-.91	<.001							.78	.66-.91	.002
Cytomegalovirus serostatus (vs. D+/R+)												
D+/R−	.97	.82-1.14	.71							.97	.76-1.24	.82
D−/R+	1.00	.90-1.11	.99							.97	.83-1.14	.72
D−/R−	1.01	.87-1.17	.88							.96	.76-1.20	.69
Year of the transplantation (vs. 2003-2007)												
2008-2012							1.03	.88-1.21	.72			
2013-2016							.92	.78-1.09	.34			
Days from diagnosis to transplantation, at least median vs. less than median	.96	.88-1.04	.31	1.03	.96-1.11	.36	.97	.88-1.06	.45	1.02	.90-1.17	.71

RIC indicates reduced-intensity conditioning; MAC, myeloablative conditioning.

unbalanced abnormalities, and balanced abnormalities groups (n = 1088, 64.5%); an intermediate-risk group comprising the CK and isolated −5/del(5q) groups (n = 273, 16.2%); and a high-risk group comprising the MK group (n = 326, 19.3%). In the AML-MRC cohort, the median age at transplantation was 56 years, and 64.7% of the cohort were men. The median WBC count at diagnosis was 3440/μL, and 757 (44.9%) were in CR, whereas the remaining 930 patients (55.1%) were not in CR at transplantation. Of those not in CR, 514 (30.5%), 208 (12.3%), and 208 (12.3%) patients had refractory, relapsed, and untreated AML-MRC, respectively. The median proportions of blasts in the BM and PB at transplantation for those not in CR were 22% and 4%, respectively (Table 3). With a median follow-up of 42 months (range, 1 to 169), the 3-year OS and LFS rates were 41.5% and 35.9%, respectively (Figure 3A). The cumulative 3-year incidence of relapse and NRM were 39.9% and 24.2%, respectively (Figure 3B). According to the risk stratification, the 3-year OS rates were 50.7%, 26.9%, and 13.8% in the low-, intermediate-, and high-risk groups, respectively ($P < .001$; Figure 3C). The cumulative 3-year relapse incidence rates were 31.2%, 46.5%, and 64.0% in the low-, intermediate-, and high-risk groups, respectively ($P < .001$; Figure 3D). The multivariate analysis revealed that intermediate risk, compared with low risk, was significantly associated with poor OS (HR, 1.58; 95% CI, 1.33 to 2.88; $P < .001$) and a high relapse rate (HR, 1.58; 95% CI, 1.29 to 1.93; $P < .001$). The same was true with high risk regarding OS (HR, 2.71; 95% CI, 2.32 to 3.16; $P < .001$) and relapse rate (HR, 2.70; 95% CI, 2.26 to 3.22; $P < .001$; data not shown).

Because approximately half of the patients with AML-MRC underwent allo-SCT while not in CR, we performed a subgroup analysis according to disease status at transplantation. Among the patients in CR at transplantation, the 3-year OS rates were 64.9%, 52.6%, and 33.4% in the low-, intermediate-, and high-risk groups, respectively ($P < .001$; Figure 4A). The cumulative incidence of 3-year relapse rates were 20.1%, 36.0%, and 54.4% in the low-, intermediate-, and high-risk groups, respectively ($P < .001$; Figure 4B). In the multivariate analysis, the risk stratification was associated with poor OS and LFS (Table 4). Other significant risk factors for OS were older age and a low PS score, and the latter was also associated with poor LFS. Regarding relapse, the risk classification was associated significantly with relapse (Table 4). In contrast, allo-SCT from matched unrelated donors, mismatched unrelated donors, or cord blood were associated with a significantly reduced relapse rate. The risk classification did not affect the NRM, whereas older age, a low PS score, a high HCT-CI score, and allo-SCT from mismatched unrelated donors or cord blood were associated with high NRM.

Among the patients not in CR at transplantation, the 3-year OS rates were 36.3%, 25.0%, and 5.7% in the low-, intermediate-, and high-risk groups, respectively ($P < .001$; Figure 4C). The cumulative 3-year relapse incidence rates were 42.3%, 54.8%, and 67.8% in the low-, intermediate-, and high-risk groups, respectively ($P < .001$; Figure 4D). After adjusting for covariates, intermediate and high risks were associated with worse OS, LFS, and relapse rate (Table 5). Other significant risk factors for OS were older age, male sex, a low PS score, and ≥5% blast percentage in PB; the latter 3 were also associated with poor LFS. In contrast, allo-SCT from matched unrelated donors or cord blood were good prognostic factors for LFS, associated with a reduced relapse rate (Table 5). A low PS score and ≥5% blast percentage in PB were other significant risk factors for relapse. Regarding NRM, the risk classification did not have a significant prognostic

Table 3
Patient and Transplant Characteristics in the AML-MRC Cohort

Characteristic	Subcategory	AML-MRC (n = 1687)
Median age, yr [IQR]		56 [45-62]
Age	<55 yr	773 (45.8)
	≥55 yr	914 (54.2)
Sex	Male	1092 (64.7)
	Female	595 (35.3)
PS	0-1	1482 (87.8)
	≥2	205 (12.2)
HCT-CI	0-2	1353 (80.2)
	≥3	334 (19.8)
MRC risk classification	Low risk	1088 (64.5)
	MLD-solo	440 (26.1)
	History of MDS or MDS/MPN	447 (26.5)
	Isolated −7/del(7q)	153 (9.1)
	Other unbalanced	abnormalities
	33 (2.0)	
	Balanced	abnormalities
	15 (.9)	
	Intermediate risk	273 (16.2)
	CK	228 (13.5)
	Isolated −5/del(5q)	45 (2.7)
High risk	326 (19.3)	
MK	326 (19.3)	
Median WBC count at diagnosis, /μL [IQR]		3440 [1755-12,025]
Disease status at transplantation	CR	757 (44.9)
	Non-CR	930 (55.1)
	Refractory	514 (30.5)
	Relapsed	208 (12.3)
	Untreated	208 (12.3)
Median proportion of blasts in BM at SCT [IQR]		22 [8.4-41.8]
	≥20%	510 (54.8)
Median proportion of blasts in PB at SCT [IQR]		4 [0-21]
	≥5%	447 (48.1)
Conditioning	Myeloablative	
	1116 (66.2)	
Reduced-intensity	571 (33.8)	
Donor source	MRD	348 (20.6)
	MMRD	171 (10.1)
	MUD	422 (25.0)
	MMUD	341 (20.2)
	CB	405 (24.0)
GVHD prophylaxis	Tac-based	1171 (69.4)
	CyA-based	490 (29.0)
	Others	26 (1.5)
Cytomegalovirus serostatus	D+/R+	747 (44.3)
	D+/R−	110 (6.5)
	D−/R+	655 (38.8)
	D−/R−	175 (10.4)
ABO incompatibility	Match	839 (49.7)
	Major mismatch	343 (20.3)
		327 (19.4)

(continued)

Table 3 (*Continued*)

Characteristic	Subcategory	AML-MRC (n = 1687)
	Minor mismatch	
	Major and minor mismatch	178 (10.6)
Year of the transplant	2003-2007	115 (6.8)
	2008-2012	837 (49.6)
	2013-2016	735 (43.6)
Media days from diagnosis to transplant [IQR]		174 [114-255]

Values are n (%) unless otherwise defined.

impact, and a low PS score was the only significant risk factor for NRM.

Effect of Acute GVHD on Transplant Outcomes in the AML-MRC Cohort

Finally, we investigated the effect of acute GVHD (aGVHD) on transplantation outcomes in the AML-MRC cohort. The cumulative incidence rates of grades I to II and III to IV aGVHD at day +100 were 42.0% (95% CI, 39.6% to 44.3%) and 14.0% (95% CI, 12.4% to 15.7%), respectively. Among patients who survived over 100 days without a relapse, the landmark analysis revealed that the relapse rate was significantly lower in those with grades I to II aGVHD than in those without aGVHD, whereas the difference in relapse rates was not significant between those with grades I to II and III to IV aGVHD (31.6%, 24,7%, and 25.1% at 3 years for patients without aGVHD, those with grades I to II aGVHD, and those with grades III to IV aGVHD, respectively; $P = .015$) (Figure 5A). The NRM was not significantly different between patients with grades I to II aGVHD and those without aGVHD, although the NRM in patients with grades III to IV aGVHD was significantly higher than that in patients with grades I to II aGVHD (14.7%, 18.8%, and 44.3% at 3 years for patients without aGVHD, those with grades I to II aGVHD, and those with grades III to IV aGVHD, respectively; $P < .001$) (Figure 5B). The Cox proportional regression model with grades I to II or III to IV aGVHD as time-dependent covariates showed that grades I to II aGVHD was significantly associated with better OS (HR, .66; 95% CI, .57 to .77; $P < .001$); however, grades III to IV aGVHD was associated with worse OS (HR, 1.80; 95% CI, 1.50 to 2.15; $P < .001$; data not shown). The subgroup Cox proportional regression model stratified by disease status at transplantation revealed that the beneficial effects of grades I to II aGVHD on survival was more evident in patients not in CR at transplantation (HR, .55; 95%

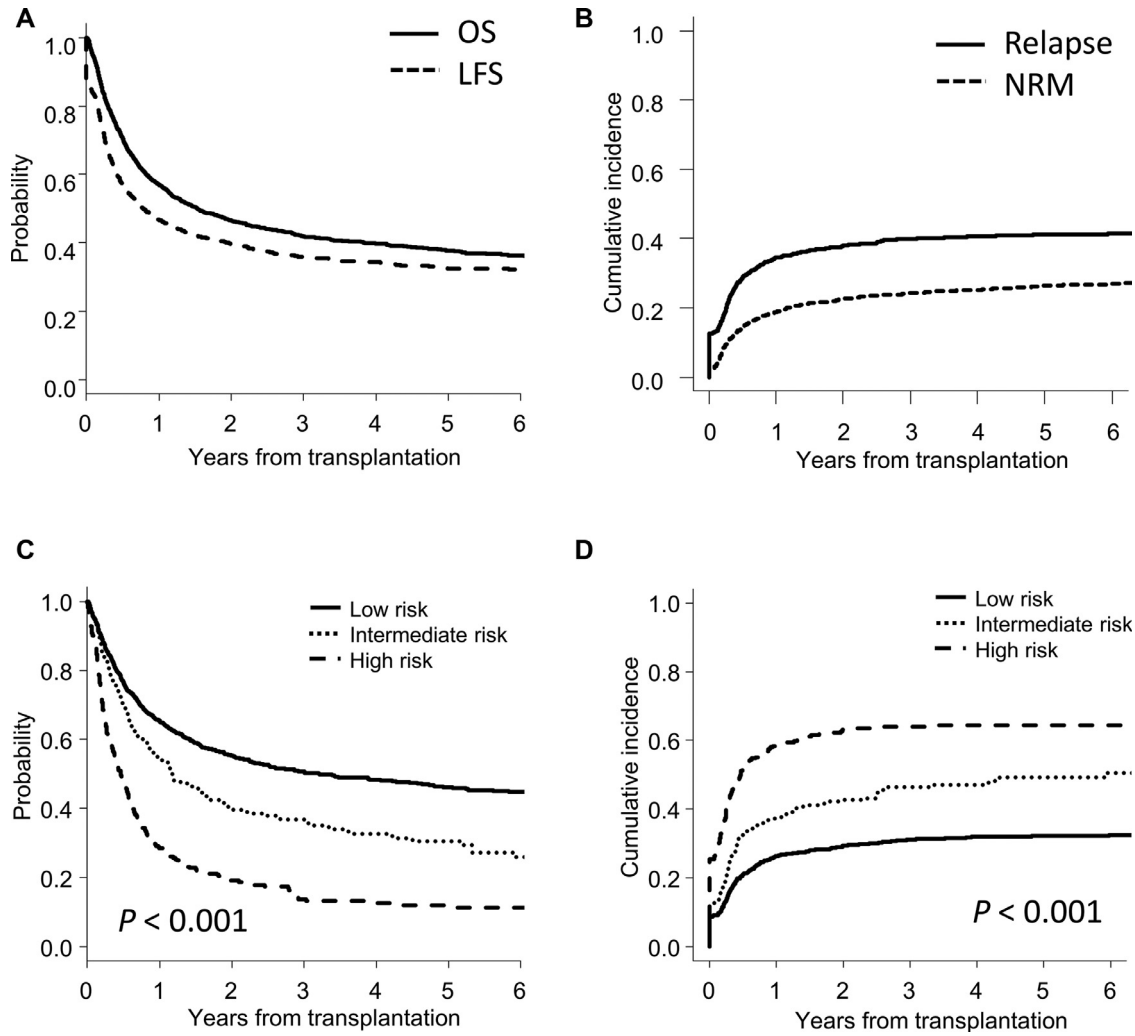

Figure 3. OS and LFS (A) and relapse rate and NRM (B) in the AML-MRC cohort. OS (C) and relapse rate (D) stratified by the MRC risk stratification.

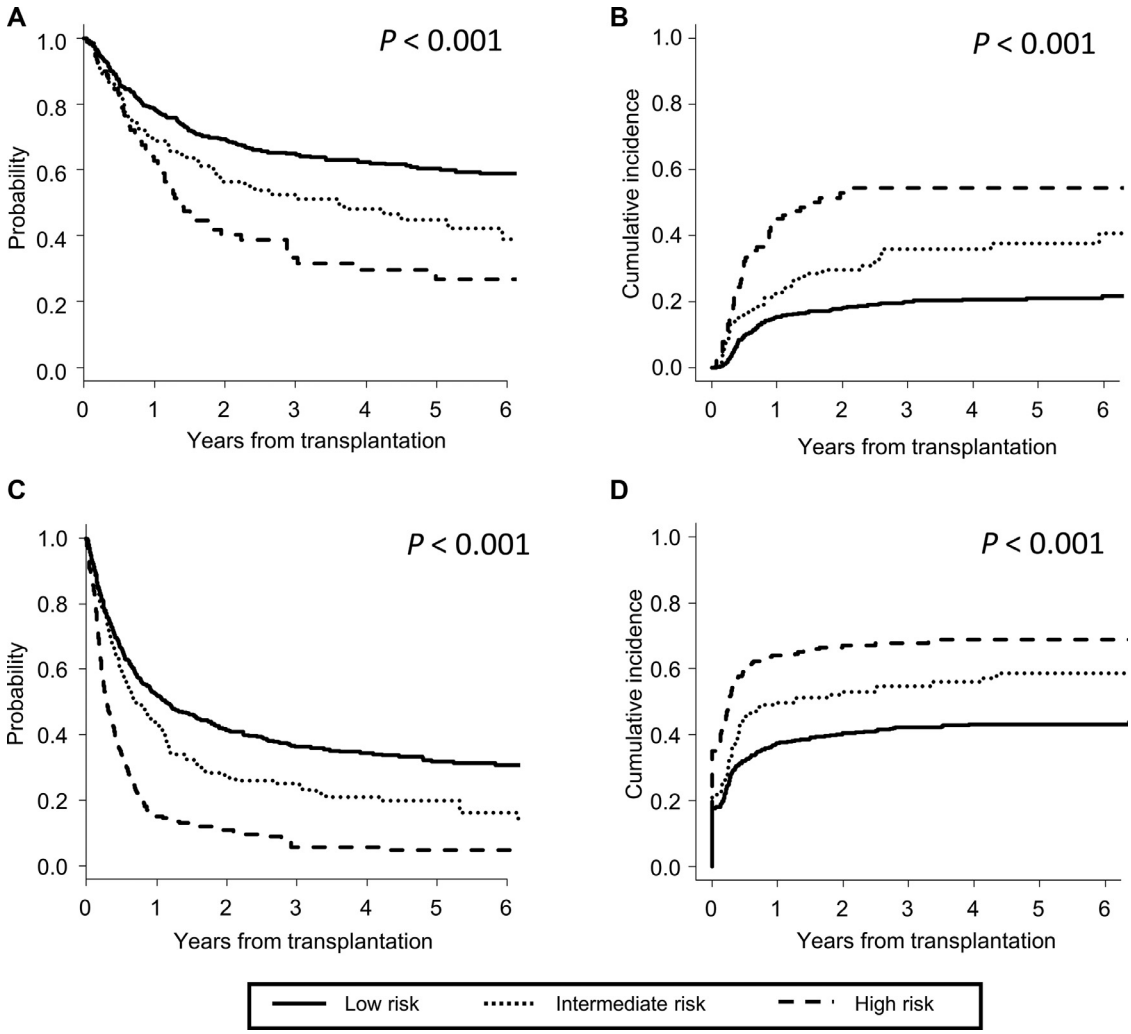

Figure 4. OS and relapse rate according to the MRC risk stratification among patients in CR (A and B) and those not in CR (C and D).

CI, .46 to .67; $P < .001$) than in those in CR at transplantation (HR, .82; 95% CI, .63 to 1.07; $P = .14$) (Supplementary Table S2). Figure 5C, D shows the adjusted OS rates according to the development of aGVHD stratified by the disease status at transplantation.

DISCUSSION

The present study demonstrated that transplant outcomes were worse in patients with AML-MRC than in those with AML-NOS. In contrast, a single-center study reported that transplant outcomes were similar between patients with AML-MRC and AML-NOS [13]. The inconsistency in the findings of the 2 studies might be attributed mainly to the smaller number of patients included in the previous study or to the disparity in MDS-related cytogenetic abnormalities and the donor source. Thus, we subdivided patients with AML-MRC according to the WHO classification criteria and found that transplant outcomes were highly diversified in patients with AML-MRC. We developed a new risk stratification system that properly stratified the outcomes of patients with AML-MRC using conventional cytogenetic data. This risk stratification can be applied to all patients with AML-MRC regardless of the disease status at allo-SCT. In addition, the differences in survival or relapse rate between the intermediate- and high-risk groups were also significant (data not shown). This risk stratification system can help clinicians predict survival after allo-SCT in a clinical setting.

As expected, AML-MRC harboring CK or MK was associated with worse outcomes than AML-NOS. In contrast, the OS of patients with isolated −7/del(7q), who are classified as poor risk in the National Comprehensive Cancer Network guidelines for AML [11], surprisingly did not differ from that of patients with AML-NOS. However, it should be noted that the isolated −7/del(7q) group did not include patients with CK or MK in the current study because of the hierarchical classification of patients into the CK or MK groups, and the relapse rate remained significantly higher than those with AML-NOS in the multivariate analysis. In fact, approximately half of the patients with MK concurrently harbored −7/del(7q), and their outcome were worse than those of isolated −7/del(7q). Thus, these results can be applicable only to chromosome 7 abnormalities not harboring CK or MK, such as a single 7 chromosome monosomy. Given the dismal outcome of patients with AML-MRC harboring isolated −7/del(7q) who did not undergo allo-SCT [23,24], allo-SCT might, at least partially, alleviate that outcome. Our results were consistent with a previous study reporting acceptable transplant outcomes in patients with MDS or secondary AML harboring a single 7 chromosome monosomy [16].

Regarding chromosome 5 abnormalities, although the inconsistency of the impact of −5/del(5q) on survival among patients

Table 4
Multivariate Analysis for OS, LFS, Relapse, and NRM in the AML-MRC Cohort Focusing on Patients in CR at the Time of Transplantation

	OS			LFS			Relapse			NRM		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
MRC risk classification (vs. low risk)												
Intermediate risk	1.64	1.21-2.21	.001	1.65	1.25-2.18	<.001	1.88	1.30-2.70	<.001	1.14	.74-1.77	.55
High risk	2.38	1.76-3.21	<.001	2.56	1.93-3.39	<.001	3.55	2.50-5.02	<.001	.93	.56-1.53	.76
Age, <55 vs. ≥55 yr	1.50	1.15-1.95	.003	1.24	.97-1.58	.086				1.45	1.03-2.03	.033
Male vs. female	1.26	.99-1.60	.063	1.14	.91-1.42	.26	.94	.70-1.26	.68	1.27	.91-1.77	.16
PS, ≥2 vs. 0-1	3.31	2.05-5.33	<.001	2.89	1.80-4.65	<.001	2.07	.98-4.35	.055	2.26	1.16-4.40	.016
HCT-CI, ≥3 vs. 0-2	1.20	.88-1.63	.26	1.02	.75-1.39	.89				1.54	1.04-2.30	.032
RIC vs. MAC	.97	.75-1.26	.82	1.05	.82-1.34	.71	1.26	.93-1.69	.14			
Donor source (vs. MRD)												
MMRD	1.27	.80-2.00	.31	1.01	.66-1.54	.97	.57	.32-1.01	.053	1.87	.98-3.59	.059
MUD	.94	.68-1.30	.70	.85	.64-1.14	.28	.67	.46-.98	.038	1.33	.84-2.09	.22
MMUD	1.12	.79-1.59	.53	.91	.67-1.25	.58	.55	.35-.88	.012	1.88	1.16-3.04	.011
CB	1.08	.71-1.64	.73	.77	.54-1.10	.15	.40	.24-.67	<.001	2.08	1.17-3.68	.012
Cytomegalovirus serostatus (vs. D+/R+)												
D+/R−	1.11	.73-1.69	.63							1.43	.84-2.42	.18
D−/R+	.89	.67-1.20	.45							.81	.55-1.21	.31
D−/R−	1.18	.81-1.73	.39							1.30	.79-2.13	.31
Days from diagnosis to transplantation, ≥174 vs. <174	.90	.71-1.15	.40	.85	.68-1.07	.17	.84	.61-1.15	.27			

Table 5
Multivariate Analysis for OS, LFS, Relapse, and NRM in the AML-MRC Cohort Focusing on Patients Not in CR at the Time of Transplantation

	OS			LFS			Relapse			NRM		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
MRC risk classification (vs. low risk)												
Intermediate risk	1.39	1.12-1.73	.003	1.24	1.01-1.53	.044	1.36	1.07-1.73	.012	.91	.64-1.29	.59
High risk	2.64	2.19-3.17	<.001	2.26	1.89-2.70	<.001	2.12	1.75-2.59	<.001	.85	.62-1.17	.32
Age, <55 vs. ≥55 yr	1.29	1.09-1.53	.003	1.15	.98-1.36	.088				1.12	.85-1.47	.43
Male vs. female	1.31	1.11-1.56	.002	1.28	1.09-1.51	.003	1.17	.97-1.42	.10	1.05	.80-1.39	.71
PS, ≥2 vs. 0-1	2.18	1.82-2.63	<.001	1.78	1.48-2.13	<.001	1.28	1.03-1.59	.025	1.41	1.04-1.90	.025
HCT-CI, ≥3 vs. 0-2	.98	.81-1.18	.83	.92	.76-1.10	.35				1.33	1.00-1.78	.054
Proportion of blasts in PB ≥5% at SCT	1.32	1.13-1.56	<.001	1.32	1.13-1.55	<.001	1.21	1.01-1.46	.040	1.11	.86-1.44	.41
RIC vs. MAC	1.06	.89-1.26	.50	1.10	.93-1.30	.25	1.09	.91-1.31	.35			
Donor source (vs. MRD)												
MMRD	.92	.69-1.23	.57	.86	.65-1.13	.28	.82	.61-1.10	.19	1.20	.73-1.98	.47
MUD	.92	.71-1.20	.54	.78	.61-.99	.045	.74	.57-.97	.029	1.16	.75-1.81	.50
MMUD	1.00	.77-1.32	.97	.87	.68-1.12	.28	.81	.62-1.05	.11	1.14	.71-1.82	.58
CB	.89	.67-1.18	.42	.78	.62-.98	.030	.52	.41-.68	<.001	1.61	.99-2.60	.053
Cytomegalovirus serostatus (vs. D+/R+)												
D+/R−	1.11	.78-1.56	.57							.85	.48-1.54	.60
D−/R+	1.17	.94-1.45	.16							1.10	.77-1.57	.59
D−/R−	1.04	.78-1.39	.78							.73	.43-1.24	.25
Days from diagnosis to transplantation, ≥174 vs. <174	1.06	.90-1.25	.46	1.12	.95-1.31	.17	1.17	.97-1.40	.094			

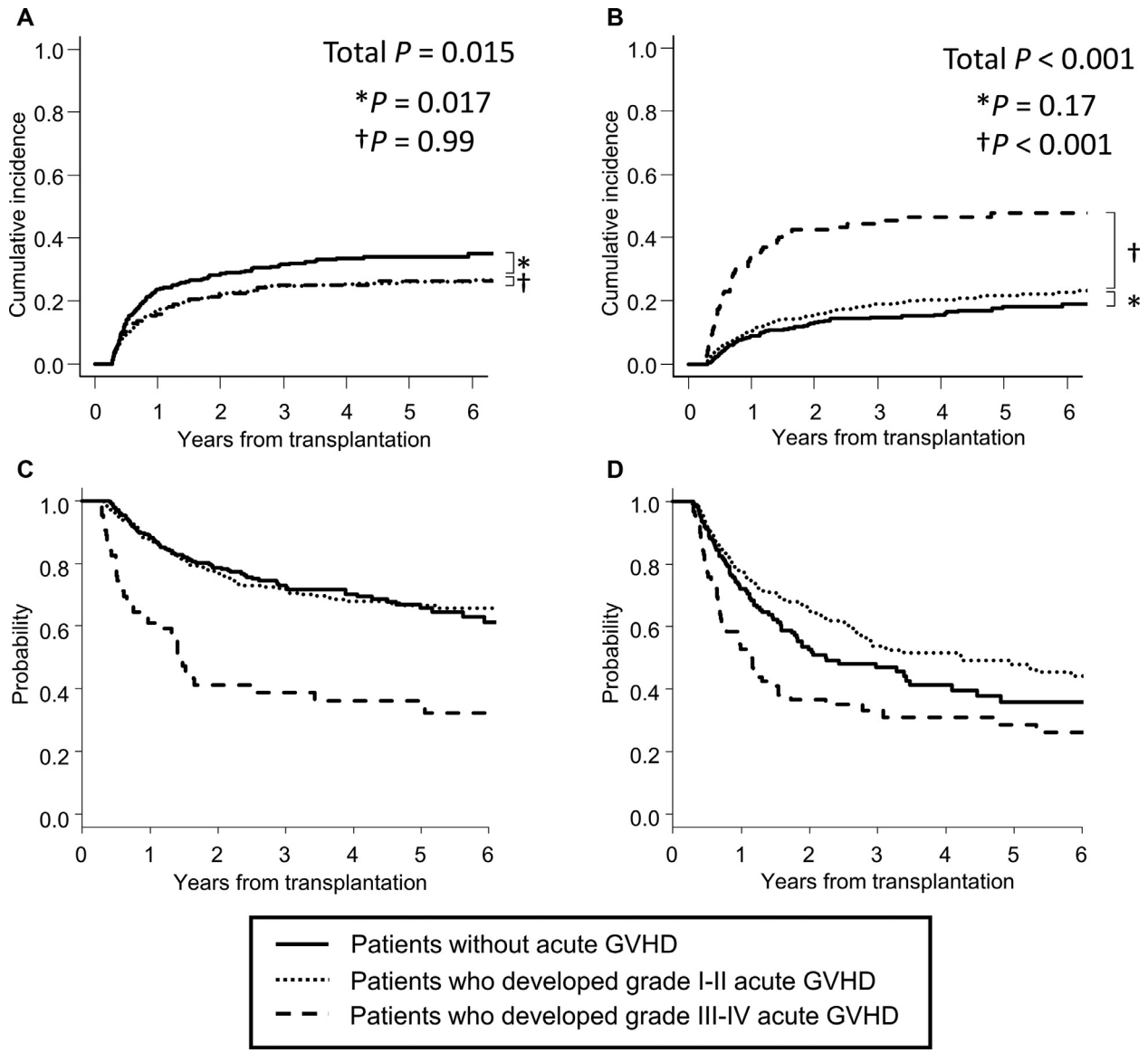

Figure 5. Relapse rate (A) and NRM (B) according to the development of grades I to II and III to IV aGVHD in the AML-MRC cohort. (C and D) OS in patients in CR and those not in CR adjusted for confounding factors.

harboring MK was previously reported [17,25], their impact on survival in patients without MK undergoing allo-SCT was not fully evaluated. The previous study showed the dismal transplant outcome of patients with isolated −5/del(5q) in which only 1 of 6 patients were alive after allo-SCT [17]. However, the authors were unable to draw a conclusion on the prognostic impact of isolated −5/del(5q) because of the small number of patients. Our study included 90 patients with isolated −5/del(5q), and for the first time we demonstrated that patients with AML-MRC harboring isolated −5/del(5q) also exhibited worse outcomes than those with AML-NOS, suggesting the limited beneficial effect of allo-SCT in these patients.

The subgroup analysis showed that the 3-year OS rates of intermediate- or high-risk patients undergoing allo-SCT in CR at transplantation were 53% and 34%, respectively. Although this outcome might be because of a patient selection bias, these results were markedly better than those reported in patients who did not undergo allo-SCT [23,26], and similar outcomes were reported in several studies [27,28]. Taken together, urgent allo-SCT should be considered in fit patients with intermediate- or high-risk AML-MRC who have achieved CR. In contrast, the outcomes were modest or even dismal in intermediate- or high-risk patients not in CR at transplantation, suggesting the minimal beneficial effect of allo-SCT in these patients. Therefore, indication for allo-SCT in those patients should be carefully reviewed. MK and CK were reported to be associated with *TP53* mutations [18,29]. Recent studies demonstrated that patients with *TP53* mutations were likely to respond to DNA methylation inhibitors [30]. However, whether treatment with DNA methylation inhibitors followed by allo-SCT could improve outcomes in those with *TP53* mutations remains to be elucidated.

The proportion of blasts in PB but not in BM at transplantation was associated with relapse and poor survival in patients not in CR at transplantation. Previous studies also reported the prognostic relevance of blasts in PB [31,32]. The circulating blasts might reflect the disease burden especially in patients with a low blast percentage in BM [32] or those associated with certain molecular abnormalities. Regarding the donor

source for patients with AML-MRC in CR at transplantation, allo-SCT from a donor other than a matched related donor, which was associated with a lower relapse, was, however, also associated with NRM, consequently resulting in comparable OS rates with patients receiving allo-SCT from a matched related donor. Notably, in patients not in CR at transplantation, cord blood and matched unrelated donor also were associated with a lower relapse, which led to a better LFS rate. In contrast, against our expectations, the intensity of the conditioning regimen did not affect the transplant outcomes in the multivariate analysis. Undergoing allo-SCT at the appropriate time, while taking into account CR achievement, patient condition, and donor source, could be the key factors to improve outcomes in AML-MRC.

We also found that grades I to II aGVHD was associated with a significantly reduced relapse, suggesting the graft-versus-leukemia effects accompanying aGVHD development. With a negligible adverse effect on NRM, grades I to II aGVHD was associated with a significantly improved survival. The beneficial effects of grades I to II aGVHD were reported previously in patients with acute leukemia or MDS who underwent cord blood transplantation [33]. Importantly, the present study demonstrated the prognostic relevance of grades I to II aGVHD in disease-specific and disease status–specific situations. Surprisingly, patients with AML-MRC not in CR at transplantation but not those in CR clearly benefited from the development of grades I to II aGVHD. Considering the dismal outcomes of patients with AML-MRC not in CR at transplantation, the approach to induce aGVHD but to control it in a grade of I to II might be considered to improve the outcomes of AML-MRC.

The current study has several limitations. First, this retrospective study was based on a registered database, which did not contain data on genetic abnormalities, although some mutations, such as in *ASXL1* and *TP53*, were shown to be associated with survival [29,34,35]. In addition, AML with MLD-solo were not classified as AML-MRC when a mutation of *NPM1* or biallelic mutation of *CEBPA*was present, according to the WHO criteria in 2016; however, patients with MLD-solo harboring those mutations were not specifically excluded from our study. Thus, our study might overestimate the transplant outcomes of patients with MLD-solo. However, a large-scale analysis including genetic and clinical factors in patients with MDS and secondary AML reported that clinical patient characteristics were predominant determinants of post-transplant outcomes, accounting for approximately 90% of the total hazards when combined with cytogenetic abnormalities [29]. Second, the median age of patients in our study was lower than those reported in previous studies [6,10,35], because only those who underwent allo-SCT were included. Thus, there could be a patient selection bias, and our results should be carefully interpreted. Third, the data on treatment before and after allo-SCT were not fully available. As noted above, treatment with DNA methylation inhibitors followed by allo-SCT might improve the transplant outcomes in patients with high-risk AML-MRC [30], and a clinical trial targeting AML with CK and/or MK is now ongoing (ClinicalTrials.gov: NCT03080766). In addition, upfront allo-SCT is an alternative option for some patients with AML-MRC, because whether pretransplant induction chemotherapy can improve outcomes in AML-MRC remains unclear [32,36]. This strategy also deserves further investigation, and we have previously reported the advantages of upfront allo-SCT [37].

In conclusion, we demonstrated that the transplant outcomes were highly diversified in patients with AML-MRC based on the presence of MLD, MDS-related cytogenetic changes, and a history of MDS or MDS/MPN. Our prognostic risk stratification can potentially aid in elucidating the diverse transplant outcomes in patients with AML-MRC. Performing allo-SCT at the appropriate time while taking into consideration the disease status, clinical condition of the patient, and donor source and by controlling aGVHD can potentially improve outcomes in patients with AML-MRC.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi: 10.1016/j.bbmt.2019.04.025.

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