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ORIGINAL PAPER

Prognostic impact of complex and/or monosomal karyotypes in post-transplant poor cytogenetic acute myeloid leukaemia: A quantitative approach

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Summary

To evaluate the prognostic impact of complex karyotype (CK) and/or monosomal karyotype (MK) in combination with various clinical factors on allogeneic stem cell transplantation (HSCT) outcomes of patients with acute myeloid leukaemia (AML), we analysed the registry database of adult AML patients who underwent allogeneic HSCT between 2000 and 2019 in Japan. Among 16 094 patients, those with poor cytogenetic risk ($N = 3345$) showed poor overall survival (OS) after HSCT (25.3% at 5 years). Multivariate analyses revealed that CK and/or MK (hazard ratio [HR], 1.31 for CK without MK; 1.27 for MK without CK; and 1.73 for both), age at HSCT ≥50 years (HR, 1.58), male sex (HR, 1.40), performance status ≥2 (HR, 1.89), HCT-CI

score ≥3 (HR, 1.23), non-remission status at HSCT (HR, 2.49), and time from diagnosis to HSCT ≥3 months (HR, 1.24) independently reduced post-HSCT OS among patients with poor cytogenetic risk AML. A risk scoring system based on the multivariate analysis successfully stratified patients into five distinct groups for OS. This study confirms the negative effects of CK and MK on post-HSCT outcomes, and offers a powerful risk scoring system for predicting prognoses after HSCT among AML patients with unfavourable cytogenetics.

KEYWORDS
acute myeloid leukaemia, allogeneic stem cell transplantation, complex karyotype, monosomal karyotype

INTRODUCTION

Outcomes of patients with acute myeloid leukaemia (AML) are strongly influenced by genetic factors. While, with the introduction of high-throughput sequencing, impact of molecular alterations, such as adverse effects of *TP53* mutations and *MECOM* rearrangements, on prognosis of patients with AML is becoming clear, conventional diagnostic karyotype remains a powerful prognostic factor that predicts responses to induction therapy and survival of these patients in clinical practice.[1–6]

The National Comprehensive Cancer Network (NCCN) guideline defines three genetic subgroups to classify AML according to the risk of relapse: favourable, intermediate and poor.[7] The unfavourable group includes patients with a heterogeneous prognostic outcomes. Among the unfavourable cytogenetic abnormalities, complex karyotype (CK) as well as monosomal karyotype (MK) are associated with worst outcomes, despite intensive chemotherapy treatment.[2,3]

Allogeneic stem cell transplantation (HSCT) is the only treatment that can achieve long-term survival of AML patients with poor cytogenetic risk, especially CK and/or MK. Clinical data on allogeneic HSCT for AML patients with CK and/or MK are limited because of the heterogeneous definition of chromosomal risk, especially that of CK, an extremely great variety of transplant procedures, and a highly limited patient cohort (for example, analysis of patients only in first complete remission) in previous reports.[8–11] Therefore, the role of allogeneic HSCT in improving the poor prognosis among patients with AML carrying CK and/or MK according to patient background has not been fully determined. Given that post-transplant outcomes are influenced not only by cytogenetics but also by various clinical parameters,[5] the prognostic impact of CK and/or MK on transplantation outcome should be evaluated comprehensively and quantitatively in conjunction with a variety of clinical factors.

Thus, using the Japanese nationwide transplant registry, we performed a retrospective cohort study, in order to (1) evaluate effects of CK and MK in combination with various clinical parameters on post-HSCT outcomes and (2) offer a sophisticated risk scoring system, which can be applied in a wide range of clinical settings, to identify AML patients with unfavourable cytogenetics who benefit from allogeneic HSCT. Our findings provide valuable information for treatment decision making and should contribute to improvements in transplantation outcomes in this patient group.

PATIENTS AND METHODS

Patients

Data on adult patients (age ≥16 years) with AML who had undergone their first allogeneic HSCT between 2000 and 2019 were obtained through the Transplant Registry Unified Management Program (TRUMP) sponsored by the Japanese Society for Transplantation and Cellular Therapy (JSTCT).[12,13] Patients without survival data or with HLA mismatches at three or more loci were excluded. The study was planned by the Adult AML Working Group of the JSTCT, approved by the data management committees of TRUMP and by the Institutional Review Board of Kyoto University Hospital, and was conducted in accordance with the Declaration of Helsinki.

Cytogenetic analysis

Cytogenetic analysis was performed on metaphase samples of bone marrow or peripheral blood obtained prior to induction therapy by using standard banding techniques. Karyotypes were determined according to the International System for Human Cytogenetic Nomenclature.[14] The karyotype analysis was based on a minimum of 20 metaphases for each sample as a routine procedure. An abnormality was considered to be clonal when at least two metaphases had the same aberration in the case of either a structural abnormality or an additional chromosome. If there was monosomy, it had to be present at least three metaphase cells to be significant. CK was defined as the presence of three or more unrelated cytogenetic abnormalities in the absence of translocation t(8;21), inversion/translocation inv(16)/t(16;16) and translocation t(15;17) at the time of diagnosis. MK was defined as two or more autosomal chromosome monosomies or a single autosomal monosomy in the presence of

at least one other structural chromosomal abnormality.[15] Cytogenetic risk was classified in accordance with criteria specified by the National Comprehensive Cancer Network Guidelines (Acute Myeloid Leukaemia. Version 1.2016), as described in detail elsewhere[7]: Favourable risk group included inv(16), t(16;16), t(8;21) and t(15;17); Intermediate risk group, normal cytogenetics, +8 alone, t(9;11), or other non-defined; Poor risk group, CK, MK, −5, 5q−, −7, 7q−, 11q23 other than t(9;11), inv(3), t(3;3), t(6;9) and t(9;22). Molecular abnormalities were not utilized in the cytogenetic classification because molecular information was not available in the majority of patients.

Study endpoints and definitions

The primary endpoint was overall survival (OS) after transplantation; death regardless of the cause was considered an event. Secondary endpoints were disease-free survival (DFS), and cumulative incidences of relapse and non-relapse mortality (NRM). Conditioning intensity was defined according to operational definitions of the National Marrow Donor Program/CIBMTR.[16] Intensified myeloablative conditioning regimens included cyclophosphamide (CY)/total body irradiation (TBI)/VP16 (VP16, total 30–40 mg/kg), and CY/TBI/high-dose cytarabine (cytarabine, total 6–12 g/m^2).[17,18] Eastern cooperative oncology group performance status scale (ECOG PS) at transplantation was evaluated according to ECOG criteria.[19] Haematopoietic cell transplantation-specific comorbidity index (HCT-CI) was determined according to the Seattle scale.[20] HLA matching was assessed using allele data for the HLA-A, -B, -C and -DRB1 loci in bone marrow and peripheral blood stem cell graft, and by using serological data for the HLA-A, -B and -DR loci in cord blood graft.[21,22] HLA mismatch was defined in the graft-versus-host disease (GVHD) vector when recipient alleles or antigens were not shared by the donor and was defined in the host-versus-graft direction when donor alleles were not shared by the recipient. In this study, complete remission (CR) referred to morphological CR, which was defined as <5% blasts in a cellular marrow with recovery of >1000/μL neutrophils, >100 000/μL platelets and no requirement of red blood cell transfusion nor evidence of extramedullary leukaemia.[23]

Statistical analysis

Categorical variables and continuous variables were compared between groups with Fisher's exact test and two-tailed unpaired Student's *t*-test, respectively. Probabilities of OS and DFS were estimated according to the Kaplan–Meier method and compared among groups with the Cox proportional-hazards model. Probabilities of relapse and NRM were estimated on the basis of cumulative incidence methods, and compared among groups with the Fine–Gray proportional-hazards model,[24] considering death without relapse as a competing event for relapse, relapse as a competing event for NRM. The following variables were considered in the multivariate analyses; patient age at the time of transplantation, sex, ECOG PS, HCT-CI, patient cytomegalovirus status, type of AML, cytogenetic risk, disease status at the time of transplantation, time from diagnosis to transplantation, donor age, donor-sex mismatch, ABO-mismatch, HLA mismatches, intensity of the conditioning, use of TBI, graft source, GVHD prophylaxis, addition of ATG to conditioning regimen, and year of transplantation.

Patients with poor cytogenetic risk AML were randomly divided into a training cohort (making up two-thirds of the patients) and a validation cohort (one-third of the patients). Regarding development of a risk-scoring system, adjusted hazard ratios (HRs) for OS, which were calculated using the training cohort, were converted to integer weights as follows; natural logistic HR values of <0.10, 0.10–0.29, 0.30–0.49, 0.50–0.69, 0.70–0.89, 0.90–1.09 were assigned respective weights of 0, 1, 2, 3, 4 and 5. The risk index was defined as the sum of these integer weights, which was used to stratify patients into distinct risk groups in terms of OS. The performance of the index was then validated for patients in the validation cohort.

All tests were two-sided and p values of <0.05 were considered statistically significant. All analyses and random cohort allocation were performed with Stata version 17 software (Stata Corp.).

RESULTS

Patient characteristics

Baseline demographic, disease characteristics and transplant procedures are summarized in Table S1. In total, 16 094 patients with a median age of 50 years (range, 16–85) underwent HSCT. Among them, 14 168 patients (88.0%) had an initial diagnosis of de novo AML, while 1132 (7.0%) had secondary AML. In terms of cytogenetic risk classification, favourable risk, intermediate risk and poor risk accounted for 2005 (12.5%), 9297 (57.8%) and 3345 patients (20.8%), respectively, while cytogenetic risk could not be evaluated in 1447 (9.0%). Regarding remission status, 6071 patients (37.7%) were transplanted in the first complete remission (CR1), 2258 (14.0%) underwent transplantation in the second complete remission (CR2), and 7027 (43.7%) were transplanted in non-CR. Conditioning regimens consisted of myeloablative conditioning in 11 095 patients (69.0%), and intensified myeloablative conditioning was selected in 1444 patients (9.0%).

Among 3345 patients with AML carrying poor risk cytogenetics, CK and/or MK was observed in 2182 patients (65.2%) (Tables 1 and 2). CK and MK coexisted in 985 patients (29.4%), while isolated CK without MK and isolated MK without CK were observed in 1086 (32.5%) and 111 (3.3%), respectively. There is a trend for older patient age at transplantation among poor cytogenetic risk patients or

TABLE 1 Patient characteristics as per presence of complex karyotype and/or monosomal karyotype.

	Poor cytogenetics (*N* = 3345)	CK– and MK– (*N* = 1163)	CK+ and MK– (*N* = 1086)	CK– and MK+ (*N* = 111)	CK+ and MK+ (*N* = 985)	*p*-value
Patient age, years						
Median (range)	54.0 (16–85)	50.0 (16–85)	54.0 (16–79)	48.0 (18–82)	57.0 (16–77)	<0.001*
<50	1342 (40.1%)	570 (49.0%)	434 (40.0%)	58 (52.3%)	280 (28.4%)	<0.001*
≥50	2003 (59.9%)	593 (51.0%)	652 (60.0%)	53 (47.7%)	705 (71.6%)	
Patient sex						<0.001*
Male	2127 (63.6%)	696 (59.8%)	689 (63.4%)	57 (51.4%)	685 (69.5%)	
Female	1217 (36.4%)	466 (40.1%)	397 (36.6%)	54 (48.6%)	300 (30.5%)	
ECOG PS						<0.001*
0–1	2736 (81.8%)	990 (85.1%)	899 (82.8%)	87 (78.4%)	760 (77.2%)	
2–4	558 (16.7%)	147 (12.6%)	172 (15.8%)	19 (17.1%)	220 (22.3%)	
HCT-CI						<0.001*
0–2	2174 (65.0%)	778 (66.9%)	740 (68.1%)	59 (53.2%)	597 (60.6%)	
≥3	721 (21.6%)	178 (15.3%)	204 (18.8%)	31 (27.9%)	308 (31.3%)	
CMV-Ab						0.377
Negative	462 (13.8%)	163 (14.0%)	151 (13.9%)	19 (17.1%)	129 (13.1%)	
Positive	2588 (77.4%)	862 (74.1%)	858 (79.0%)	77 (69.4%)	791 (80.3%)	
Type of AML						<0.001*
De novo	2862 (85.6%)	1013 (87.1%)	937 (86.3%)	84 (75.7%)	828 (84.1%)	
Secondary	390 (11.7%)	103 (8.9%)	122 (11.2%)	20 (18.0%)	145 (14.7%)	
Disease status						<0.001*
CR1	1115 (33.3%)	491 (42.2%)	360 (33.1%)	38 (34.2%)	226 (22.9%)	
CR2	119 (3.6%)	53 (4.6%)	42 (3.9%)	5 (4.5%)	19 (1.9%)	
≥CR3	10 (0.3%)	5 (0.4%)	5 (0.5%)	0 (0.0%)	0 (0.0%)	
Non-CR	2085 (62.3%)	609 (52.4%)	673 (62.0%)	67 (60.4%)	736 (74.7%)	
Time from diagnosis to transplantation, months						
Median (range)	5.1 (0.0–241.3)	5.6 (0.0–241.3)	5.1 (0.2–188.0)	5.1 (0.1–98.4)	4.4 (0.2–73.3)	<0.001*
≤3	631 (18.9%)	163 (14.0%)	188 (17.3%)	26 (23.4%)	254 (25.8%)	<0.001*
3–6	1431 (42.8%)	483 (41.5%)	460 (42.4%)	40 (36.0%)	448 (45.5%)	
≥6	1282 (38.3%)	517 (44.5%)	438 (40.3%)	45 (40.5%)	282 (28.6%)	
Donor age, years[a]						
Median (range)	39.0 (0–84)	39.0 (8–69)	40.0 (12–84)	40.0 (0–74)	40.0 (16–65)	0.311
<40	1007 (50.8%)	393 (53.9%)	324 (49.5%)	28 (49.1%)	262 (48.2%)	0.185
≥40	977 (49.2%)	336 (46.1%)	330 (50.5%)	29 (50.9%)	282 (51.8%)	
Sex mismatch						<0.001*
Matched	1601 (47.9%)	560 (48.2%)	525 (48.3%)	47 (42.3%)	469 (47.6%)	
Male to female	705 (21.1%)	277 (23.8%)	230 (21.2%)	31 (27.9%)	167 (17.0%)	
Female to male	886 (26.5%)	268 (23.0%)	280 (25.8%)	32 (28.8%)	306 (31.1%)	
ABO mismatch						0.055
Matched	1520 (45.4%)	529 (45.5%)	499 (45.9%)	51 (45.9%)	441 (44.8%)	
Minor mismatch	724 (21.6%)	248 (21.3%)	233 (21.5%)	20 (18.0%)	223 (22.6%)	
Major mismatch	706 (21.1%)	233 (20.0%)	231 (21.3%)	24 (21.6%)	218 (22.1%)	
Major-minor mismatch	324 (9.7%)	114 (9.8%)	108 (9.9%)	11 (9.9%)	91 (9.2%)	
HLA mismatch						0.334
No	1241 (37.1%)	456 (39.2%)	392 (36.1%)	39 (35.1%)	354 (35.9%)	
Yes	2104 (62.9%)	707 (60.8%)	694 (63.9%)	72 (64.9%)	631 (64.1%)	

(Continues)

TABLE 1 (Continued)

	Poor cytogenetics (*N* = 3345)	CK– and MK– (*N* = 1163)	CK+ and MK– (*N* = 1086)	CK– and MK+ (*N* = 111)	CK+ and MK+ (*N* = 985)	*p*-value
Conditioning						<0.001*
Myeloablative, standard	1952 (58.4%)	698 (60.0%)	633 (58.3%)	44 (39.6%)	577 (58.6%)	
Myeloablative, intensified	300 (9.0%)	121 (10.4%)	93 (8.6%)	15 (13.5%)	71 (7.2%)	
Reduced intensity	1069 (32.0%)	331 (28.5%)	356 (32.8%)	48 (43.2%)	334 (33.9%)	
TBI						0.028*
No	1258 (37.6%)	430 (37.0%)	390 (35.9%)	33 (29.7%)	405 (41.1%)	
Yes	2079 (62.2%)	729 (62.7%)	693 (63.8%)	77 (69.4%)	580 (58.9%)	
Graft source						<0.001*
Rel-BM	275 (8.2%)	119 (10.2%)	72 (6.6%)	9 (8.1%)	75 (7.6%)	
Rel-PBSC	784 (23.4%)	270 (23.2%)	262 (24.1%)	30 (27.0%)	222 (22.5%)	
UR-BM	947 (28.3%)	368 (31.6%)	315 (29.0%)	22 (19.8%)	242 (24.6%)	
UR-PBSC	60 (1.8%)	17 (1.5%)	23 (2.1%)	2 (1.8%)	18 (1.8%)	
UR-CB	1279 (38.2%)	389 (33.4%)	414 (38.1%)	48 (43.2%)	428 (43.5%)	
GVHD prophylaxis						<0.001*
CyA-based	1022 (30.6%)	408 (35.1%)	332 (30.6%)	34 (30.6%)	248 (25.2%)	
Tac-based	2323 (69.4%)	755 (64.9%)	754 (69.4%)	77 (69.4%)	737 (74.8%)	
Addition of ATG to conditioning regimen	299 (8.9%)	88 (7.6%)	114 (10.5%)	6 (5.4%)	91 (9.2%)	0.055
Years of transplant						<0.001*
2000–2009	927 (27.7%)	391 (33.6%)	293 (27.0%)	38 (34.2%)	205 (20.8%)	
2010–2019	2418 (72.3%)	772 (66.4%)	793 (73.0%)	73 (65.8%)	780 (79.2%)	

Abbreviations: AML, acute myeloid leukaemia; ATG, anti-thymocyte globulin; BM, bone marrow; CB, cord blood; CK, complex karyotype; CR, complete remission; CyA, cyclosporine A; ECOG PS, Eastern Cooperative Oncology Group Performance Status Scale; GVHD, graft-versus-host disease; HCT-CI, haematopoietic cell transplantation-specific comorbidity index; MK, monosomal karyotype; PBSC, peripheral blood stem cell; Rel, related; Tac, tacrolimus; TBI, total body irradiation; UR, unrelated.

*indicates $p < 0.05$.

[a]Donor age was evaluated among cases excluding CB transplantation.

TABLE 2 Distribution of complex and monosomal karyotypes among patients with poor cytogenetic risk.

	N = 3345
CK– and MK–	1163 (34.8%)
–5/5q–, isolated	92 (2.8%)
–7/7q–, isolated	53 (1.6%)
CK+ and MK–	1086 (32.5%)
CK– and MK+	111 (3.3%)
CK+ and MK+	985 (29.4%)

Abbreviations: CK, complex karyotype; MK, monosomal karyotype.

patients with CK and MK, compared with the entire cohort. While 8518 individuals (52.9%) underwent allogeneic HSCT at CR in the whole cohort, only 37.3% of patients with poor cytogenetic risk, and 24.8% of patients with CK and MK received transplantation at CR. Time from diagnosis to transplantation was shorter in patients with CK and MK (Table 1; Table S1).

Impact of CK and/or MK on transplantation outcome

As expected, patients with poor cytogenetic risk AML showed significantly lower 5-year OS (25.3%) and DFS (22.6%) as well as a higher relapse rate (51.2%) and comparable NRM (26.2%) following allogeneic HSCT, compared with those with favourable or intermediate cytogenetic risk AML (Figure 1A–D).

Next, we assessed the impact of CK and/or MK on transplantation outcomes among patients with poor cytogenetic risk AML (Figure 2A–D). While patients with poor cytogenetic risk AML lacking CK and MK had preferable 5-year OS (37.1%) and DFS (33.6%), those with either CK or MK showed poorer 5-year OS (25.5% for CK without MK; 27.7% for MK without CK) and DFS (22.3% for CK without MK; 22.3% for MK without CK) with higher relapse rate (52.5% for CK without MK; 54.1% for MK without CK) after HSCT. Importantly, coexistence of both CK and MK was associated with extremely poor OS (10.4%) and DFS (9.8%), as well as a very high relapse rate (61.9%).

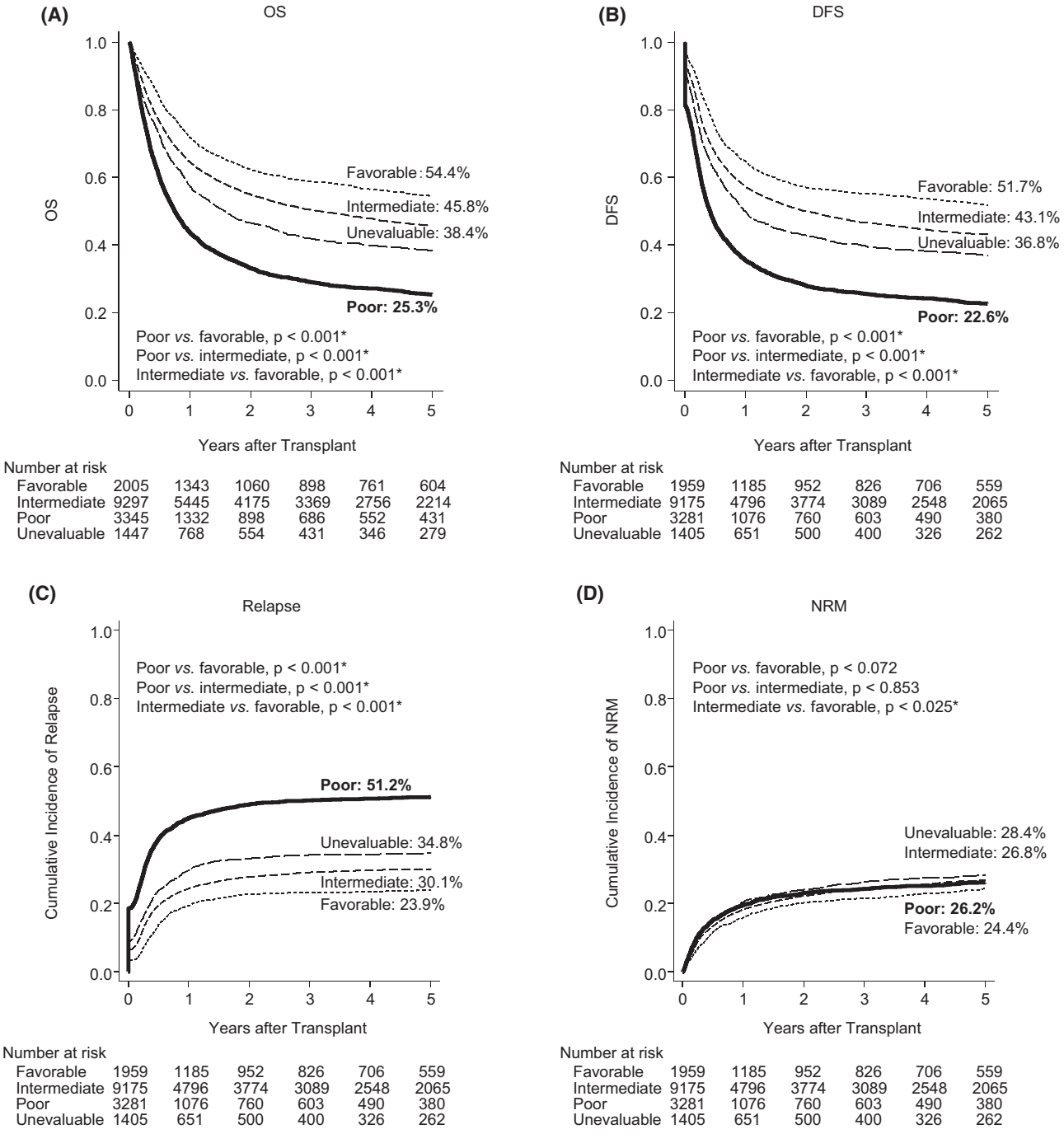

FIGURE 1 Comparison of outcomes according to cytogenetic risk group in the whole cohort. (A) Overall survival (OS). (B) Disease-free survival (DFS). (C) Cumulative incidence of relapse. (D) Cumulative incidence of non-relapse mortality (NRM). *p* Values were calculated using the log-rank test (A, B) and Fine and Gray's tests (C, D). $^*p < 0.05$.

Univariate and multivariate analysis of outcomes in the training cohort

To evaluate the significance of CK and/or MK in combination with various clinical factors on transplantation outcome, using the training cohort ($N = 2230$) that was randomly extracted from among all patients with poor cytogenetic risk AML (Table S2), we performed univariate (Table S3) and multivariate analysis (Table S4). Multivariate analysis, including all potentially related variables, revealed that CK and/or MK (hazard ratio [HR], 1.32 for CK without MK; 1.40 for MK without CK; and 1.82 for both), age at HSCT ≥50 years (HR, 1.70), male sex (HR, 1.42), performance status ≥2 (HR, 1.96), HCT-CI score ≥3 (HR, 1.27),

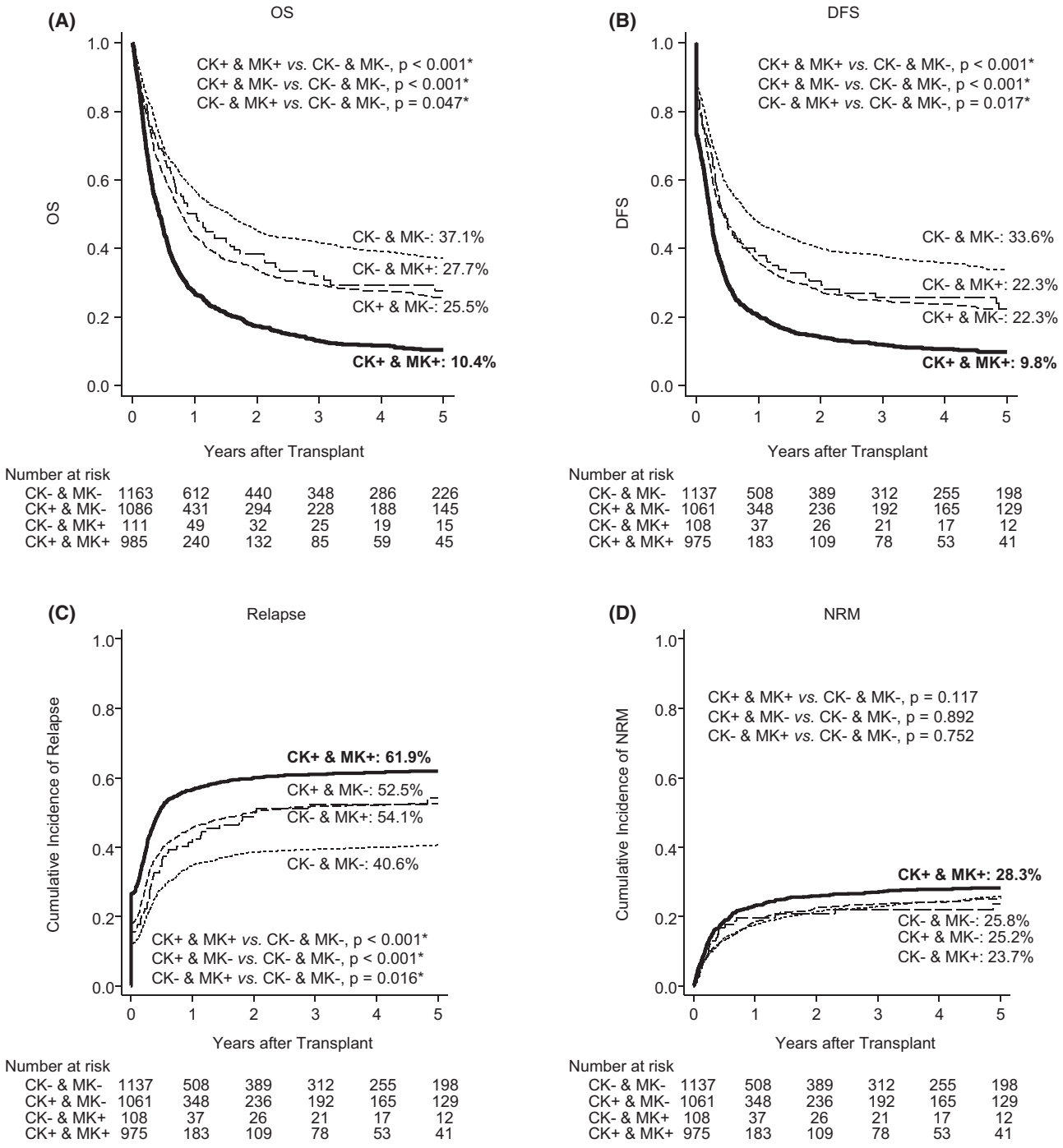

FIGURE 2 Prognostic impact of complex karyotype (CK) and/or monosomal karyotype (MK) on outcomes in the poor cytogenetic risk group. (A) Overall survival (OS). (B) Disease-free survival (DFS). (C) Cumulative incidence of relapse. (D) Cumulative incidence of non-relapse mortality (NRM). *p* Values were calculated using the log-rank test (A, B) and Fine and Gray's tests (C, D). **p* < 0.05.

non-remission status (HR, 2.66) at HSCT, and time from diagnosis to HSCT ≥3 months (HR, 1.26 for 3–6 months; 1.23 for ≥6 months) independently reduced OS after HSCT among patients with poor cytogenetic risk AML. Among these risk factors for OS, both CK and/or MK, and non-remission status at HSCT had the greatest adverse impact on OS without significant interaction (Figure S1). Intensity of conditioning, HLA mismatch or graft source were not associated with OS in the multivariate analysis (Table S4). Regarding relapse and NRM, CK and/or MK significantly increased cumulative incidence of relapse, while it did not affect NRM.

Development of a transplantation-specific risk scoring system for AML with poor cytogenetic risk (TSS-P)

Then, to weight the prognostic impact of each clinical factor clearly, a risk scoring system for use in a clinical setting was developed. On the basis of the multivariate analysis, we defined a TSS-P scoring system, including seven variables having independent prognostic impact on OS: CK and/or MK, age at transplantation, patient sex, performance status at transplantation, HCT-CI score at transplantation, disease remission status at transplantation, and time from diagnosis to HSCT (Table 3; Tables S5–S8).

One point each was assigned for CK without MK (HR, 1.305), and MK without CK (HR, 1.269), HCT-CI >3 (HR, 1.228), and time from diagnosis to transplantation >3 months (HR, 1.240); two points for age ≥50 (HR, 1.581) and male sex (HR, 1.404); three points for both CK and MK (HR, 1.731), ECOG PS ≥2 (HR, 1.893); and five points for non-CR at transplantation (HR, 2.489) (Table 4). TSS-P prognostic categories were determined by combining the scores of these seven factors. According to this score, patients were divided into the following five risk groups: very low (score 0–3), low (4–6), intermediate (7–9), high (10–14) and very high (15–17).

TABLE 3 Multivariate analysis for OS among patients with poor cytogenetic risk.

	OS		
	HR	**(95% CI)**	***p*-value**
CK/MK			
CK+ and MK− vs. CK− and MK−	1.305	(1.135–1.500)	<0.001*
CK− and MK+ vs. CK− and MK−	1.269	(0.918–1.756)	0.150
CK+ and MK+ vs. CK− and MK−	1.731	(1.506–1.991)	<0.001*
Patient age			
≥50 vs. <50	1.581	(1.407–1.777)	<0.001*
Patient sex			
Male vs. female	1.404	(1.250–1.576)	<0.001*
ECOG PS			
2–4 vs. 0–1	1.893	(1.656–2.165)	<0.001*
HCT-CI			
≥3 vs. <3	1.228	(1.085–1.389)	0.001*
Disease status			
Non-CR vs. CR	2.489	(2.183–2.837)	<0.001*
Time from diagnosis to transplantation, months			
≥3 vs. <3	1.240	(1.086–1.416)	0.002*

Abbreviations: CI, confidence interval; CK, complex karyotype; CR, complete remission; ECOG PS, Eastern Cooperative Oncology Group Performance Status Scale; HCT-CI, haematopoietic cell transplantation-specific comorbidity index; HR, hazard ratio; MK, monosomal karyotype; OS, overall survival.

*indicates $p < 0.05$.

Validation of TSS-P scoring system

The prognostic impact of the TSS-P was evaluated in an independent validation cohort of 1115 patients. There were no statistically significant differences in patient characteristics between the training and validation cohorts (Table S2). Median OS in both series was comparable (7.7 months in the training vs. 8.6 months in the validation cohort; $p = 0.056$).

Risk groups defined by the TSS-P in the validation cohort had significantly different 5-year OS (63.5%, 43.8%, 29.8%, 8.0% and 0.0%, respectively; Figure 3A; Table 5). The TSS-P also stratified patients for DFS and relapse (Figure 3B,C; Table 5). Notably, the TSS-P identified a small proportion of patients with very high risk (5.4% in the validation cohort) who had extremely poor OS after transplantation (3.9% of 1-year OS). The miserable OS of this patient population derived from both high incidence of relapse and NRM (Figure 3C,D; Table 5).

TABLE 4 Prognostic scores.

Prognostic variables	**0**	**1**	**2**	**3**	**4**	**5**
CK/MK	CK− and MK−	CK+ and MK− CK− and MK+	–	CK+ and MK+	–	–
Age at transplantation, years	<50	–	≥50	–	–	–
Sex	Female	–	Male	–	–	–
ECOG-PS	0–1	–	–	2–4	–	–
HCT-CI	0–2	3-	–	–	–	–
Stage	CR	–	–	–	–	Non-CR
Time from diagnosis to transplantation, months	<3	≥3	–	–	–	–

Note: According to this score, patients were divided into the following five risk groups: very low (score 0–3), low (score 4–6), intermediate (score 7–9), high (score 10–14) and very high (score 15–17).

Abbreviations: CK, complex karyotype; CR, complete remission; ECOG PS, Eastern Cooperative Oncology Group Performance Status Scale; HCT-CI, haematopoietic cell transplantation-specific comorbidity index; MK, monosomal karyotype.

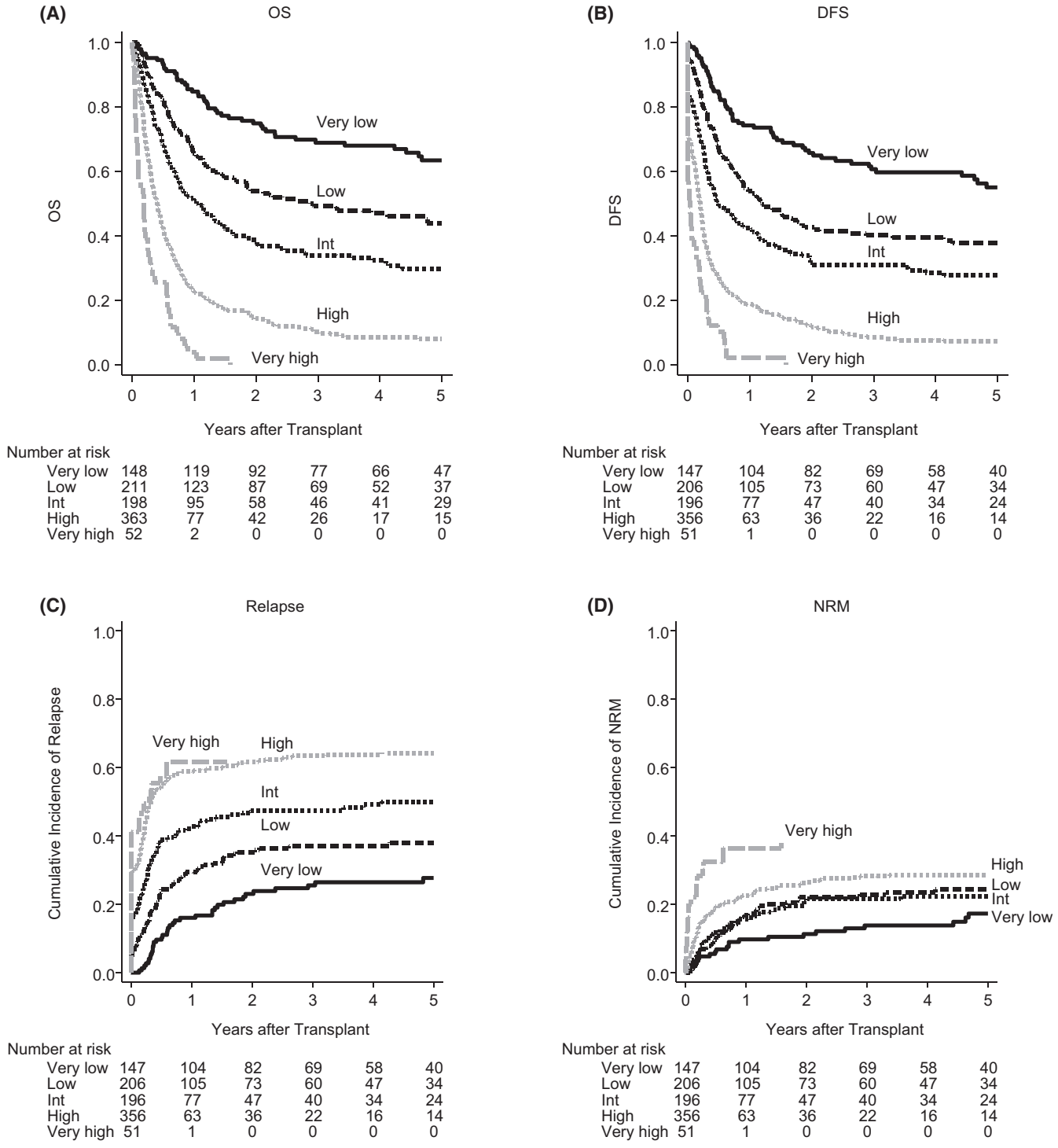

FIGURE 3 Transplantation outcomes based on TSS-P prognostic, risk-based categories in the validation cohort. (A) Overall survival (OS). $p < 0.001$. (B) Disease-free survival (DFS). $p < 0.001$. (C) Cumulative incidence of relapse. $p < 0.001$. (D) Cumulative incidence of non-relapse mortality (NRM). $p < 0.001$. p Values were calculated using the log-rank test (A, B) and Fine and Gray's tests (C, D). The number of patients in each category and their proportional representation are shown in Table S9.

Then, we evaluated the stratification performance of the TSS-P among subgroups and found that the TSS-P can fairly stratify OS in various subgroups (Figure 4; Figure S2), suggesting that this scoring system can be applied in various clinical settings with high generalizability.

DISCUSSION

Using the Japanese nationwide registry database, the present study analysed effects of CK and MK in combination with various clinical parameters on post-HSCT outcomes.

TABLE 5 Effects of risk categorization on transplantation outcomes in the validation cohort.

Risk group	No. of patients (%)	OS			DFS			Relapse			NRM		
		HR	(95% CI)	*p*-value	HR	(95% CI)	*p*-value	HR	(95% CI)	*p*-value	HR	(95% CI)	*p*-value
Very low	148 (15.2)	Reference			Reference			Reference			Reference		
Low	211 (21.7)	1.75	(1.26–2.44)	0.001*	1.76	(1.29–2.38)	<0.001*	1.61	(1.12–2.33)	0.011*	1.42	(0.89–2.27)	0.140
Intermediate	198 (20.4)	2.78	(2.02–3.82)	<0.001*	2.53	(1.87–3.42)	<0.001*	2.39	(1.67–3.42)	<0.001*	1.39	(0.86–2.24)	0.177
High	363 (37.4)	6.10	(4.55–8.2)	<0.001*	5.13	(3.89–6.75)	<0.001*	3.76	(2.72–5.20)	<0.001*	1.85	(1.20–2.84)	0.005*
Very high	52 (5.4)	14.09	(9.5–20.9)	<0.001*	9.72	(6.63–14.25)	<0.001*	3.84	(2.39–6.17)	<0.001*	2.95	(1.57–5.53)	0.001*

Abbreviations: CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NRM, non-relapse mortality; OS, overall survival.
*indicates $p < 0.05$.

There were two major findings: (1) Among adult patients with AML carrying poor cytogenetic risk, CK and/or MK was associated with significantly worse OS and DFS, as well as a higher relapse rate; (2) a novel risk stratification system, which incorporates CK and MK and clinical factors, including age, sex, performance status, HCT-CI, disease status at transplantation, and time from diagnosis to transplantation, was established to predict prognosis after HSCT among AML patients with unfavourable cytogenetics.

First, we evaluated impact of cytogenetic risk on post-transplant outcome among AML patients using an updated cohort of patients and showed that poor cytogenetic risk was significantly associated with lower OS and DFS along with a higher relapse rate, compared with those with favourable or intermediate cytogenetic risk AML. This is consistent with previous studies[7] and suggests that cytogenetic risk remains a robust prognostic factor, even with recent improvements in transplantation procedures.

Then, we assessed impact of CK and/or MK on transplantation outcomes among patients with poor cytogenetic risk AML. In this study, among AML patients with poor cytogenetic risk, patients who harboured CK and/or MK represented 65.2% of poor cytogenetic risk group and had a significantly poorer OS and DFS, along with higher relapse rate after HSCT than those without CK or MK. Also, a synergistic effect was observed in which both CK and MK were associated with a worse outcome than either alone. These observations are compatible with previous clinical studies.[25,26]

In this study, genetic alterations were not analysed. In a study that evaluated impact of both clinical factors, and genetic factors that include conventional karyotyping and comprehensive molecular analysis utilizing next generation sequencing techniques on post-transplant outcomes of myeloid neoplasms, clinical information and classical karyotyping explained about 90% of overall prognosis, but molecular abnormalities (such as *TP53* mutation) further contributed to post-transplant prognostic stratification.[5] Thus, incorporation of molecular information may improve predictive performance of our prognostic model. Recent studies have shown a significant association between cytogenetic abnormalities and prognostic genetic alterations.[27–29] For instance, CK and/or MK was reported to co-occur frequently with *TP53* mutation, which induces genetic instability, chemoresistance, with a lower CR rate and poorer OS in AML.[30–33] As G-band testing of karyotype has the advantages that it is relatively simple, inexpensive and widely used, CK and/or MK detected by G-banding can be used as a marker for unfavourable genetic alterations in clinical practice.

Patients with AML harbouring CK and/or MK are likely to have other adverse prognostic factors, including older age, poorer performance status and less controlled disease status as reported previously.[1,34] Therefore, the influence of CK and/or MK on transplantation outcome is confounded by these clinical factors. Thus, in order to assess the precise impact of CK and/or MK by adjusting for clinical factors, we performed multivariate analyses in a training cohort and showed that CK and/or MK, as well as sex, performance

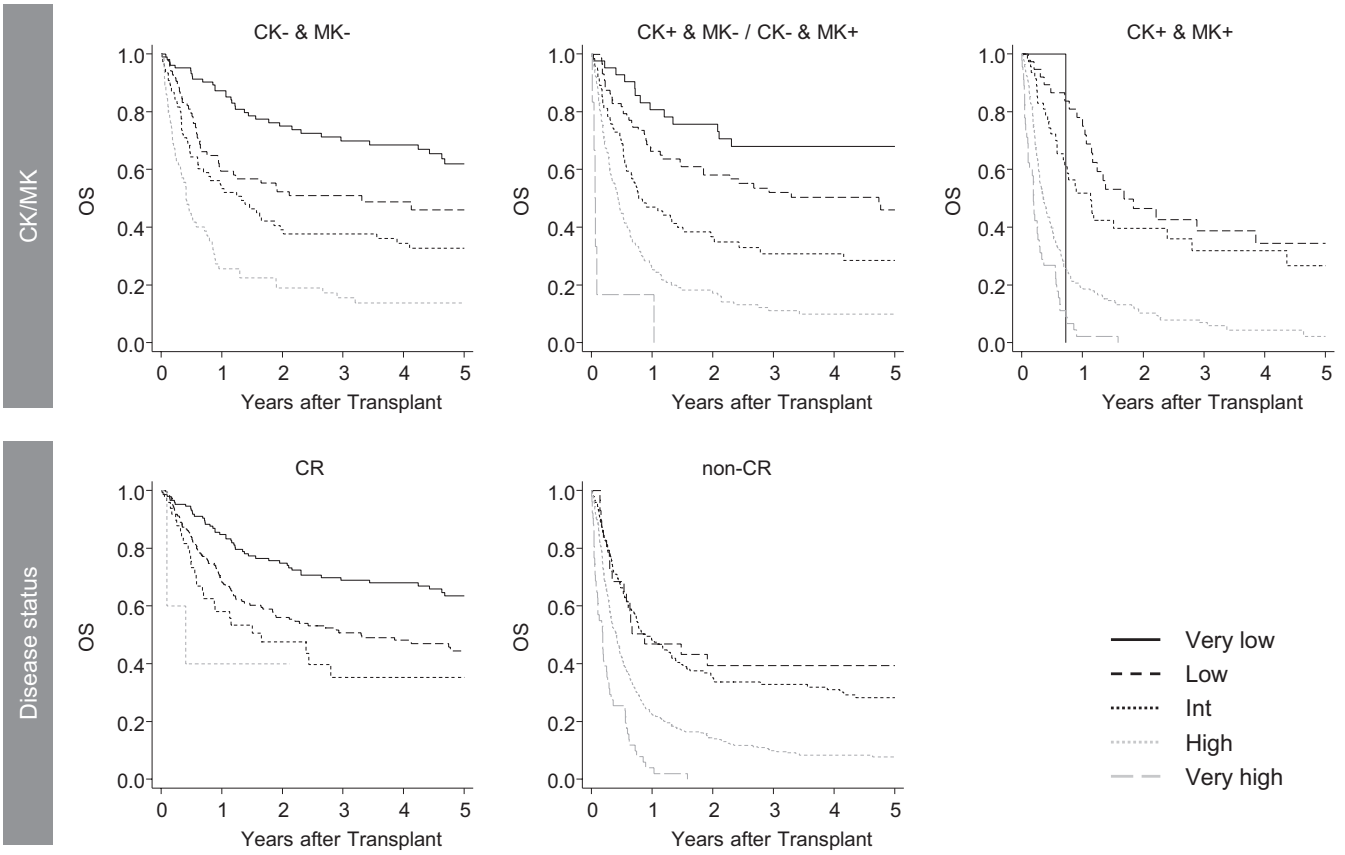

FIGURE 4 Overall survival (OS) among subgroups based on TSS-P prognostic, risk-based categories. OS stratification according to TSS-P in each subgroup related to complex karyotype (CK)/monosomal karyotype (MK) and disease status at transplantation. The number of patients in each category and their proportional representation are shown in Table S9. CR, complete remission.

status, HCT-CI, disease status at transplantation, and time from diagnosis to transplantation, independently reduced OS and DFS along with high relapse rate. While disease status at transplantation was a strong predictor for OS, it did not interact significantly with CK and/or MK regarding OS, suggesting that patients with poor cytogenetic risk AML are likely to benefit from allo-HSCT if disease status is controlled before transplantation, irrespective of CK and/or MK.

Next, to apply these findings in clinical practice, where a wide variety of situations must be considered, we developed a novel risk stratification system, TSS-P, based on multivariate analyses. TSS-P successfully stratified patients into five distinct groups for OS in a validation cohort, thereby identifying patients who are most or least likely to derive benefits from HSCT. According to TSS-P, even in patients who have AML with CK and MK, and have not achieved CR before transplantation, HSCT can offer long survival if all other factors are favourable (intermediate group). In contrast, patients who have multiple unfavourable factors and are categorized in the high risk or very-high risk groups are likely to experience high rates of early relapse and NRM, and are less likely to enjoy a survival benefit of HSCT. In particular, 1-year OS in the very-high risk group was 3.9%, indicating that allo-HSCT for this population might not be a suitable treatment option, compared with other treatments or best supportive care, if TSS-P score cannot be improved before transplantation. Novel therapeutic strategies for this patient group, including molecular targeted therapies and cellular therapies, should be investigated.

While the strength of the study includes detailed analyses using real-world data, limitations of the study should be acknowledged. First, it was a retrospective, multicenter registry study, with various protocols. Therefore, patient pre-transplant characteristics cannot be completely adjusted among different cytogenetic risk groups, even though we utilized multivariate analyses. Second, molecular information was not available in the majority of patients of this study cohort. Given that evaluation of genetic alterations requires standardized methods, optimization of genetic analysis and data collection for registry data in a real-world setting is required. Third, in the present study, each variable was grouped by a threshold in the TSS-P model for the purpose of clinical applicability. While significance of each variable in post-transplant outcome was consistent in all multivariate analysis models treating variables in different patterns, arbitrariness in grouping has not been completely eliminated. For age, because the difference is greatest when 50 years is used as the threshold (Table 3; Tables S5–S8), 50 years was adopted as the threshold in the final model. Given that advances in transplantation procedures and the introduction of novel targeted therapies enables us to perform HSCT in older populations overtime, we consider that weight of age and threshold in the prognostic stratification should

be continuously evaluated. Fourth, our results suggested that sooner HSCT is recommended. In the meantime, disease status at HSCT was also a significant prognostic factor. In relation with disease status, post-treatment response parameters, including CR with incomplete count recovery and morphologic leukaemia-free state, which have drawn attention in the context of novel targeted therapies, were not included in this study. As impact of incomplete count recovery on prognosis of AML patients have been conflicting depending patient background,[35,36] optimal timing of HSCT for AML patients with unfavourable cytogenetics should be further studied incorporating these new response parameters. Fifth, because HLA-haploidentical transplantation with high-dose cyclophosphamide (PTCy-haplo) accounted only a small fraction of the total (1.8%) in this study, the prognostic impact of PTCy-haplo in patients with poor cytogenetic risk AML should be assessed in the future.

In conclusion, CK and/or MK has poor prognostic effect on transplantation outcomes of adult AML patients. At the same time, our analysis indicates that prognosis is determined not only by CK and/or MK but also by a combination of clinical factors. Our novel risk scoring system, TSS-P, reliably estimates transplantation outcomes in adult AML patients with unfavourable cytogenetic risk and helps treatment decision-making for this patient population.

AUTHOR CONTRIBUTIONS

Tomoyasu Jo, Yasuyuki Arai, Shinichiro Oshima and Masamitsu Yanada designed the study. Tomoyasu Jo and Yasuyuki Arai performed the statistical analysis. Tomoyasu Jo, Yasuyuki Arai, Shinichiro Oshima, Tadakazu Kondo, Kaito Harada and Masamitsu Yanada interpreted the data. Tomoyasu Jo and Yasuyuki Arai wrote the manuscript. Noriko Doki, Takahiro Fukuda, Masatsugu Tanaka, Yukiyasu Ozawa, Takuro Kuriyama, Kazuhiro Ikegame, Yuta Katayama, Shuichi Ota, Takahide Ara, Toshiro Kawakita and Makoto Onizuka provided the patient data. Makoto Onizuka, Tatsuo Ichinohe and Yoshiko Atsuta collected patient data, and all authors reviewed and provided critiques on the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing financial interests.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study is not openly available due to reasons of sensitivity (patient privacy) and are available from the corresponding author upon reasonable request such as application of novel drugs.

ETHICS APPROVAL STATEMENT

The study was planned by the Adult AML Working Group of the JSTCT, approved by the data management committees of TRUMP and by the Institutional Review Board of Kyoto University Hospital.

PATIENT CONSENT STATEMENT

Written informed consent was obtained from all the patients.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

CLINICAL TRIAL REGISTRATION (INCLUDING TRIAL NUMBER)

Not applicable.

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SUPPORTING INFORMATION

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

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