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ARTICLE

Acute myeloid leukemia

Prognostic index for patients with relapsed or refractory acute myeloid leukemia who underwent hematopoietic cell transplantation: a KSGCT multicenter analysis

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Abstract

A multicenter retrospective study was performed to explore a prognostic scoring index in order to identify a population who are least likely to benefit from allogeneic hematopoietic cell transplantation (HCT) in patients with relapsed or refractory acute myeloid leukemia (AML). The cohort included 519 patients with AML, who received HCT between 2005 and 2015 at a status of relapse or primary induction failure. Multivariate analysis demonstrated five independent predictors for OS, including C-reactive protein ≥ 1 mg/dL, peripheral blood blast fraction ≥ 20%, poor-risk karyotype, performance status ≥ 2, and bone marrow unrelated donor as a stem cell source. A prognostic scoring index was explored based on these predictors, and successfully separated the cohort into four groups. At 2 years, OS was 47%, 24%, 8%, and 0% for Good (Score 0, 1: $n = 118$), Intermediate-1 (Score 2: $n = 75$), Intermediate-2 (Score 3: $n = 39$), and Poor (Score 4: n = 24), respectively ($P < 0.001$). The predicting value of the index was confirmed in a validation cohort. Although a further validation study is warranted, the scoring index may be useful to predict survival and to identify the population with the lowest survival prior to HCT in patients with relapsed or refractory AML.

Introduction

The outcomes of allogeneic hematopoietic cell transplantation (HCT) in patients with non-remission acute myeloid leukemia (AML) remain unsatisfactory. Numerous studies have documented various strategies predicting transplant outcomes [1–26]. However, it has been suggested that non-remission AML consisted of quite heterogenous patient population. Alternatively, an ambiguous definition for non-remission makes the implications of the results difficult, leading to diverse outcomes. The detection of cohorts which possess extremely poor prognosis after HCT is particularly important, from the viewpoint of proper use of medical and human resources, including stem cell donors. Potential approaches include abandoning HCT and the development of new therapeutic strategies. However, few studies have clearly documented the prognostic factors or indices to identify the population which possess extremely poor prognosis after HCT [1–8]. The purpose of this retrospective study was to develop a prognostic scoring index identifying patients with non-remission AML, in whom HCT was least beneficial.

Methods

Study design

A multicenter retrospective study was performed to evaluate outcomes, construct a scoring system, and to detect the population with lowest survival for patients with non-remission AML. Patients with non-remission AML who received HCT between 2005 and 2015 at participating institutions in Kanto Study of Group for Cell Therapy (KSGCT) were included in this study. After screening the

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registry data, further clinical information, such as the detailed description of non-remission status and biomarkers prior to HCT, was collected using a clinical research form from each participating center. Data on the white blood cell count and blast fraction in the peripheral blood, lactate dehydrogenase (LDH), and C-reactive protein (CRP) were obtained at the start of the conditioning regimen, while data on the blast fraction and nuclear cell count (NCC) in the bone marrow were obtained at the latest examination before the start of the conditioning regimen.

Relapse was defined as detection of ≥ 5% blast in the BM or a circulating blast in the peripheral blood during chemotherapy. Primary induction failure was defined as the absence of a history of complete remission (CR) after at least one course of induction therapy. Eligibility criteria were defined primarily based on blast cell fractions in the bone marrow and peripheral blood. Inclusion criteria were the blasts in bone marrow ≥ 5% or detection of blast cell in peripheral blood prior to HCT. Patients with a bone marrow blast fraction < 5% and the absence of blast cells in peripheral blood were excluded from this study. Of note, other factors, such as extramedullary sarcoma without bone marrow involvement (EMNR), incomplete hematologic recovery, and the detection of measurable residual diseases, led to exclusion if hematological blast cell fractions did not meet the inclusion criteria. Untreated disease was also excluded. Selection process of the study cohort from registry data is shown in Fig. 1. A total of 639 patients with non-remission AML were found in the registry data. After excluding 120 patients, 519 patients were included in the analysis.

Classification of karyotype and hematopoietic cell transplantation-comorbidity index (HCT-CI) was based on that used in previous reports [27, 28]. Conditioning regimens were classified into two categories: myeloablative conditioning (MAC) regimen and reduced conditioning (RIC) regimen. MAC includes more than 8 Gy of total body irradiation or a busulfan plus cyclophosphamide regimen, whereas RIC includes other regimens such as a fludarabine-containing regimen [29]. Acute graft-versus-host disease (GVHD) was defined by consensus criteria, whereas chronic GVHD was classified according to standard criteria [30, 31].

Registration data were obtained from the KSGCT data center, and all patients provided informed consent for data reporting. This study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the institutional review board of each participating site.

Statistical analysis

The Fisher exact test and Mann–Whitney U test were performed to assess categorical and continuous variables, respectively. Pearson's correlation test was employed to assess the relationship between biomarkers. The

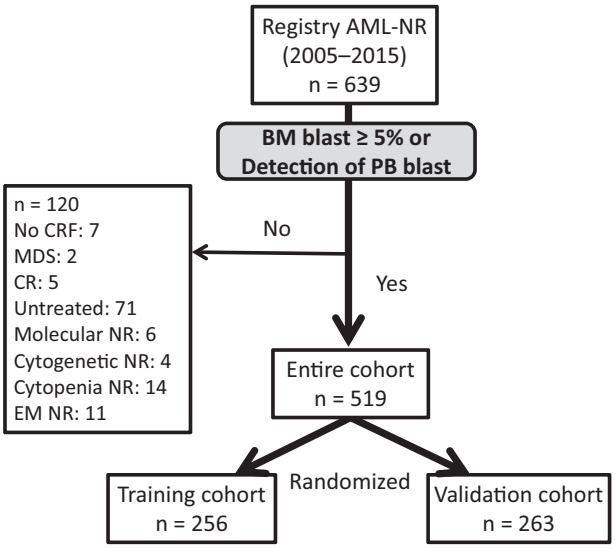

Fig. 1 Selection process of the study cohort from registry data. AML acute myeloid leukemia, NR non-remission, BM bone marrow, PB peripheral blood, CRF clinical research form, MDS myelodysplastic syndrome, CR complete remission, EM extramedullary sarcoma

Kruskal–Wallis test was performed to compare distribution of a biomarker between the groups. Follow-up intervals were calculated from the day of HCT to the last hospital visit. The Kaplan–Meier method was used to assess overall survival (OS) using the log-rank test. Univariate and multivariate analysis were performed to identify potential prognostic factors. The Cox proportional hazards method was used for the multivariate analysis to assess OS. Gray's test and the Fine–Gray test were used to assess the cumulative incidence of relapse. Competing risks were relapse, or relapse mortality (RM) and non-relapse mortality (NRM).

Regarding the design of the prognostic scoring index, the whole cohort was first equally assigned to the training and the validation cohort. The patients were randomly allocated to either the test or validation cohort, using computer-generated random numbers. The following variables were considered in univariate analysis: age, sex, disease status, duration from diagnosis to HCT, duration of complete remission, risk of karyotype, AML subtype, peripheral blood blast fraction at the time of HCT, NCC in bone marrow, LDH level and CRP, performance status, HCT-CI, donor source, presence of human leukocyte antigen (HLA) mismatch, conditioning intensity, and GVHD prophylaxis. Peripheral blood blast fractions, not those in the bone marrow, were incorporated into analysis, because the blast fraction in the bone marrow was not available in a significant proportion of the cohort. The cutoff value of continuous variables was set based on comprehensive evaluations, including median values, results of univariate analysis or receiver-operating characteristic curve, and simplicity. Univariate analyses detected covariates with a

significant P-value of < 0.1. Prognostic predictors were calculated based on multivariate analysis, using the stepwise method. Based on the value of hazard risk, a point was given to each of the predictors. The total points of the predictors were summed for each patient, and the cohort was stratified into risk groups.

Analyses were performed using EZR version 1.36 statistical software, a graphical user interface for R version 3.4.1 [32].

Results

Patient characteristics

Patient characteristics are shown in Table 1. The median age was 51 years (range: 16–71). Disease status included primary induction failure in 282 patients and relapse after remission in 237 patients. The median blast fraction in the bone marrow and peripheral blood prior to HCT was 22% (range: 0–100) and 3% (range: 0–100), respectively. The median duration from diagnosis to HCT was 7 months (range: 0–124). An HLA antigen-mismatched donor, including a single unit of umbilical cord blood, was used for 242 patients.

The Pearson's test showed a weak correlation between CRP and blast fraction in the bone marrow ($r = 0.337$). The Kruskal–Wallis test found an association between elevation of CRP and poorer performance status ($P < 0.001$). There was no deviation between the training and the validation cohort, except for donor source.

Outcomes and results of univariate and multivariate analyses in the training cohort

Univariate and multivariate analyses were performed using the training cohort to determine the prognostic factors. The median follow-up period was 36.7 months (range: 2.5–129). OS, NRM, relapse, and RM rates at 1 year were 42%, 36%, 53%, and 41%, respectively (Table 2). Univariate analysis for OS demonstrated that adverse factors included duration of complete remission (CR) < 6 months, duration from diagnosis to HCT < 7 months, HCT-CI ≥ 1 point, poor-risk karyotype, peripheral blood blast fraction ≥ 20%, performance status ≥ 2, CRP ≥ 1 mg/dL, LDH ≥ upper limit of normal, HLA-matched graft, RIC regimen, bone marrow from unrelated donor, and GVHD prophylaxis with tacrolimus. NCC in bone marrow ($\geq 10 \times 10^4/\mu L$) did not remain significant ($P = 0.13$). The results of multivariate analyses are shown in Table 3. Independent predictors for OS included CRP ≥ 1 mg/dL, peripheral blood blast fraction ≥ 20%, poor-risk karyotype, performance status ≥ 2, and bone marrow from unrelated donor. Independent predictors for relapse included CRP ≥ 1 mg/dL, CR duration < 6 months, poor-risk karyotype, and HLA mismatch donor. Regarding NRM, HCT-CI ≥ 1 was identified as the only predictor.

Prognostic scoring index and validation

One point was assigned for all adverse factors, and points were summed for each patient. Summed scores were classified into four risk groups, and a prognostic scoring index was created. Outcomes according to the index are shown in Table 4. At 2 years, OS was 47%, 24%, 8%, and 0% for Good (Score 0, 1: $n = 118$), Intermediate-1 (Score 2: $n = 75$), Intermediate-2 (Score 3: $n = 39$), and Poor (Score 4: $n = 24$), respectively ($P < 0.001$) (Fig. 2a). Applying the index to the validation cohort, OS at 2 years was 40%, 18%, 12%, and 0% for Good ($n = 133$), Intermediate-1 ($n = 61$), Intermediate-2 ($n = 49$), and Poor ($n = 20$), respectively ($P < 0.001$) (Fig. 2b). The predictive value of the index in the training cohort was confirmed in the validation cohort.

Cause of death

The cause of death for the training cohort is shown in Table 5. A total of 184 patients were dead. RM was found in 104 patients (55%) and NRM was in 80 patients (45%). The most common cause of NRM was infection (16%).

Discussion

A multicenter retrospective study was performed to evaluate outcomes, design a prognostic scoring index, and detect the population with lowest survival in patients with relapsed or refractory AML after allogeneic HCT. To overcome the limitation of registry data, definitive eligibility criteria were set, and an additional clinical research form was used. Ambiguous non-remission status, such as measurable residual disease by cytogenetics and molecular techniques, complete remission with incomplete hematologic recovery, and untreated leukemia were excluded. Regarding untreated leukemia, survival risk is not always worse, and the evaluation of outcomes has been unclear [33, 34]. With these strict criteria, the true cohort of relapsed or refractory AML was selected from the registry database. Using the clinical research form, additional information concerning the disease status, including biomarkers or bone marrow examination, further refined this cohort.

Many previous reports confirmed that overall survival of patients with relapsed or refractory AML was generally poor [1–8]. The high rate of both NRM and RM contributed to the low rate of OS. Various variables regarding disease status and risk, tumor burden, patient status, donor condition, and transplant regimen were comprehensively included in multivariate analysis. Based on simplification and

Table 1 Patient characteristics

	Entire cohort n = 519	Training cohort n = 256	Validation cohort n = 263	*P*
Age				
Median (range), years	51 (16–71)	50 (16–70)	51 (16–71)	0.80
Sex				
Male	325	155	170	0.38
Female	194	101	93	
Subtype				
De novo AML	321	153	168	0.26
Following MDS	109	62	47	
Therapy-related AML	18	10	8	
Without antecedent MDS	71	31	40	
Status				
Primary induction failure	282	145	137	0.35
First relapse	194	93	101	
Second or later relapse	43	18	25	
Extramedullary lesion				
None	452	224	228	0.96
CNS involvement	13	6	7	
Other	54	26	28	
Karyotype				
Good	43	16	27	0.43
Intermediate	246	124	122	
Poor	224	113	111	
Other	6	3	3	
CR duration				
Median (range), months	7 (1–48)	7 (1–48)	7 (1–48)	0.64
Duration from diagnosis to HCT				
Median (range), months	7 (0–124)	7 (0–78)	7 (1–124)	0.38
Blast in PB prior to HCT (n=516)				
Median (range) [%]	3 (0–100)	3 (0–99)	3 (0–100)	0.96
Blast in BM prior to HCT (n=479)				
Median (range) [%]	22 (0–100)	20 (0–99)	24 (0–100)	0.37
CRP prior to HCT				
Median (range) [mg/dL]	0.57 (0–42.1)	0.6 (0–26.6)	0.5 (0–42.1)	0.57
Performance status				
0-1	437	215	222	1
2-4	81	40	41	
HCT-CI				
0	294	144	150	0.97
1-3	169	83	86	
4-7	55	28	27	
Donor source				
Related BM	48	26	22	0.047
Related PB	106	50	56	
Unrelated BM	204	113	91	
Unrelated PB	2	2	0	
Umbilical CB	159	65	94	
HLA antigen match				
6/6 match	277	150	127	0.02
Other	242	106	136	
HLA antigen match in related donor and CB (n=313)				
6/6 match	107	51	56	0.84
5/6 match	58	26	32	
4/6 match	130	57	73	
3/6 match	18	7	11	

Table 1 (continued)

	Entire cohort n = 519	Training cohort n = 256	Validation cohort n = 263	*P*
HLA allele match in unrelated donor (n=206)				
8/8 match	113	68	45	0.38
7/8 match	63	32	31	
6/8 match	26	12	14	
5/8 match	4	3	1	
Conditioning regimen				
Myeloablative	313	150	163	0.47
TBI base	213	101	112	
BuCy	94	47	47	
Other	6	2	4	
Reduced indensity	206	106	100	
FluMel base	110	57	53	
FluBu4 base	39	16	23	
FluBu2 base	42	26	16	
FluCy base	12	5	7	
Other	3	2	1	
GVHD prophylaxis				
Cyclosporine base	218	109	109	0.93
Tacrolimus base	299	146	153	
Other	2	1	1	

AML acute myeloid leukemia, *MDS* myelodysplastic syndrome, *CNS* central nervous system, *CR* complete remission, *HCT* hematopoietic cell transplantation, *WBC* white blood cell count, *PB* peripheral blood, *NCC* nuclear cell count, *BM* bone marrow, *LDH* lactate dehydrogenase, *CRP* C-reactive protein, *HCT-CI* hematopoietic cell transplantation-comorbidity index, *CB* cord blood, *HLA* human leukocyte antigen, *TBI* total body irradiation, *Bu* busulfan, *Cy* cyclophosphamide, *Flu* fludarabine, *Mel* melphalan, *Bu4* busulfan of 12.8 mg/kg, *Bu2* busulfan of 6.4 mg/kg, *GVHD* graft-versus-host disease

Table 2 Outcomes in the training cohort

Outcomes	*n* = 256 [%] (95% CI)
Median days of engraftment (range)	20 days (9–65)
Engraftment at 50 days	85.5 (80.5–89.3)
Acute GVHD (grade II to IV) at 100 days	48.3 (41.5–54.8)
Chronic GVHD at 1 year	34.9 (28.3–41.6)
Relapse at 1 year	52.5 (45.9–58.6)
Relapse mortality at 1 year	41.4 (35.1–47.7)
Non-relapse mortality at 1 year	35.7 (29.5–41.9)
GRFS at 1 year	17.2 (12.9–22.1)
GRFS at 2 years	13.2 (9.3–17.8)
Median overall survival (days)	239 days (189–335)
Overall survival at 1 year	42.1 (35.9–48.1)
Overall survival at 2 years	30.1 (24.4–35.9)

GVHD graft-versus-host disease, *GRFS* graft-versus-host disease-free relapse-free survival, *CI* confidence interval

Table 3 Multivariate analyses in the training cohort

	HR	95% CI	*P*	Point
OS				
CRP ≥ 1 mg/dL	1.84	1.35–2.50	<0.001	1
Blast in PB ≥ 20%	1.99	1.48–2.69	<0.001	1
Poor-risk karyotype	1.75	1.30–2.35	<0.001	1
Performance status ≥ 2	1.74	1.17–2.57	0.006	1
BM from unrelated donor	1.56	1.16–2.09	0.003	1
Relapse				
CRP ≥ 1 mg/dL	1.48	1.02–2.13	0.037	
CR duration < 6 months	1.65	1.01–2.69	0.046	
Poor-risk karyotype	1.78	1.23–2.56	0.002	
HLA mismatch donor	0.50	0.35–0.73	<0.001	
NRM				
HCT-CI ≥ 1	1.84	1.21–2.80	0.004	

OS overall survival, *CRP* C-reactive protein, *PB* peripheral blood, *BM* bone marrow, *CR* complete remission, *HLA* human leukocyte antigen, *HCT-CI* hematopoietic cell transplantation-comorbidity index, *HR* hazard ratio, *CI* confidence interval

comprehensiveness, the cutoff value was simply set, and factors were mainly stratified into two groups. Based on multivariate analysis, independent prognostic predictors for poor OS included poor-risk karyotype, peripheral blood blast fraction ≥ 20%, CRP ≥ 1 mg/dL, performance status ≥ 2, and bone marrow from unrelated donor. These predictors were associated with disease risk, tumor burden, patient status, and transplant regimen.

Table 4 Outcomes according to the prognostic index in the training cohort

Score	Good	Intermediate-1	Intermediate-2	Poor	*P*
	n = 118	*n* = 75	*n* = 39	*n* = 24	
	0,1	2	3	4,5	
	[%] (95% CI)	[%] (95% CI)	[%] (95% CI)	[%] (95% CI)	
Median days of engraftment (range)	20 days (18–21)	19 days (18–21)	24 days (19–33)	23 days (19–NA)	0.003
Engraftment at 50 days	89.7 (82.5–94.1)	93.3 (84.2–97.3)	71.8 (54.4–83.5)	62.5 (39.1–79.1)	0.003
Acute GVHD (grade II to IV) at 100 days	46.8 (36.6–56.3)	53.9 (41.0–65.2)	44.3 (26.8–60.5)	43.6 (20.9–64.4)	0.78
Chronic GVHD at 1 year	44.4 (34.2–54.1)	33.7 (22.0–45.8)	NA	NA	0.030
Relapse at 1 year	31.5 (23.3– 40.0)	57.3 (45.2–67.7)	62.8 (44.5–76.6)	58.3 (34.5–76.1)	<0.001
Relapse mortality at 1 year	17.1 (10.9–24.6)	41.3 (30.0–52.3)	51.0 (33.3–66.1)	50.0 (27.9–68.6)	<0.001
Non-relapse mortality at 1 year	18.7 (12.2–26.2)	24.0 (15.0–34.2)	37.5 (21.8–53.1)	45.8 (23.9–65.3)	0.089
GRFS at 1 year	32.3 (24.0–40.9)	7.9 (3.2–15.3)	0	0	<0.001
Overall survival at 1 year	64.2 (54.8–72.1)	34.7 (24.2–45.4)	11.6 (3.7–24.3)	4.2 (0.3–17.6)	<0.001
Overall survival at 2 years	46.3 (36.8–55.3)	24.0 (15.1–34.1)	7.7 (1.6–20.3)	0	<0.001

GVHD graft-versus-host disease, *GRFS* graft-versus-host disease-free relapse-free survival, *CI* confidential interval, *NA* not available

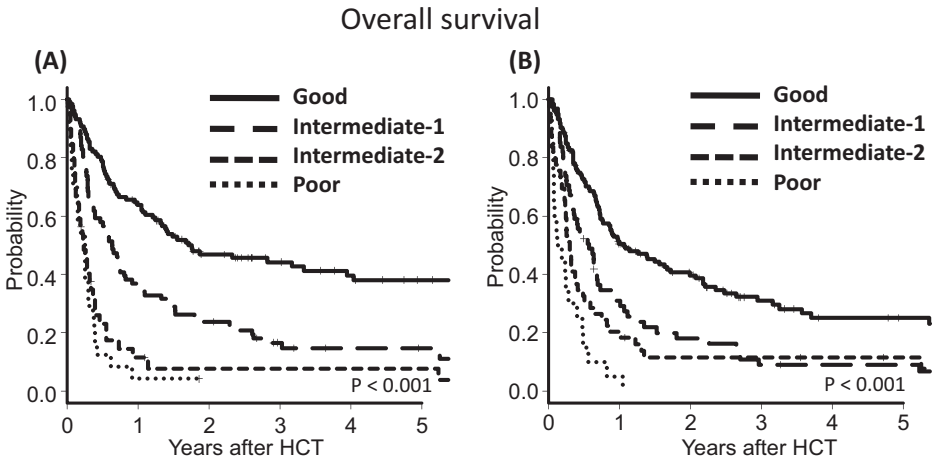

Fig. 2 Overall survival according to the prognostic index. **a** Patients in the training cohort. **b** Patients in the validation cohort. HCT hematopoietic cell transplantation

Table 5 Cause of death in the training cohort

Factors	*n* = 184 (%)
Relapse mortality	104 (55)
Non-relapse mortality	80 (45)
Infection	31(16)
Graft failure	8 (4)
Organ failure	5 (3)
TMA	5 (3)
Acute GVHD	4 (2)
Chronic GVHD	8 (4)
VOD	4 (2)
Hemorrhage	5 (3)
Interstitial pneumonitis	3 (2)
CNS event	3 (2)
ARDS	4 (2)

TMA thrombotic microangiopathy, *VOD* veno-occlusive disease, *GVHD* graft-versus-host disease, *CNS* central nervous system, *ARDS* acute respiratory distress syndrome

Although peripheral blood blast fraction, performance status, and karyotype were previously reported as risk factors [1, 3–5, 8], CRP level, a simple and useful biomarker, emerged as a novel risk factor. In the conventional HCT setting, a pre-HCT inflammatory status is known to be one of the adverse predictors [35–37]. This study found that the value of CRP prior to HCT had correlation to blast fraction of the bone marrow and association with performance status, suggesting that elevation of CRP may have associated with tumor burden and patient manifestation, such as the presence of tumor fever or active infection.

Interestingly, HLA mismatch donor was demonstrated as the most favorable predictor for relapse, suggesting the possibility of graft-versus-leukemia effect [38–40]. In the univariate analysis, HLA-mismatched donor showed significantly favorable OS compared with HLA-matched donor ($P = 0.045$; data not shown). However, in the multivariate analysis, it did not remain as a favorable predictor for OS. It is plausible that a higher NRM rate may have canceled out the favorable impact

of HLA mismatch on relapse. A mismatched donor is expected to have a graft-versus-leukemia effect and reduce the relapse risk. Therefore, reducing the NRM, such as controlling GVHD or infection, may improve the OS.

Based on simplification, comprehensiveness, and stratification, a prognostic scoring index, composed of five survival predictors and stratifying the cohort into four risk groups, was designed. Particularly, the ability of the index to predict survival was confirmed in the independent validation cohort, suggesting that the present index could be reliable and useful to predict survival or to identify a population with least benefit from HCT for patients who undergo HCT with relapsed or refractory status.

Considering the balance of the number of patients and outcomes, it might have been better to combine the poor and intermediate-2 risks together. However, another goal of the study was detection of the population with extremely poor survival. Therefore, these unfavorable groups were rather divided. Finally, by setting strict eligibility criteria and designing the prognostic scoring index, groups with the lowest survival rate were successfully extracted. For these groups with least benefit from HCT, not performing HCT is one of the meaningful options, and there are other novel strategies, such as participating in the clinical trial of new agents. Recently, new strategies prior to HCT for non-remission leukemia have been attempted. Namely, to reduce or not to increase tumor burden, preconditioning interventions, such as sequential chemotherapy or chemotherapy with inducing nadir, have been reported [24–26]. A combination of these interventions and the present index may improve outcomes. Innovative cellular therapies, such as chimeric antigen T cells, or viral-specific cytotoxic T cells, together with the approaches providing post-transplant immunosuppression-free technology, such as post-transplant high-dose cyclophosphamide, may also contribute to further improvement of the results.

Previous studies with a large cohort and independent subgroup analysis are extremely limited. Duval et al. documented outcomes in patients with relapse or primary induction failure for acute leukemia [3], comprehensively and profoundly analyzing a large cohort, focusing on the MAC regimen. Moreover, a prognostic scoring system for patients with AML was successfully designed and partially matched that of this study. However, there are differences between the studies, including the analyzed variables, transplantation techniques, including the conditioning regimen, medical background, and racial characteristics.

There are several limitations of this study. First, the strict eligibility criteria prevented comprehensive analysis for non-remission acute leukemia. Since non-remission was defined based on the results from bone marrow and peripheral blood examinations, outcomes in patients with extramedullary lesions were unknown. As previously mentioned, patients with untreated leukemia were also excluded, due to ambiguous evaluations, and should be investigated in future studies. Second, owing to the retrospective nature of the study, available data were heterogeneous and incomplete. For example, the result of the FLT3-ITD test was available in only 21% of the entire cohort. Moreover, although data from peripheral blood or biochemistry were obtained in all patients, available data of bone marrow examination was 92% of the entire cohort and the timing was not uniform. Treatment strategies were also heterogeneous, including decisions regarding the timing of when to start HCT or donor availability. Furthermore, whether the treatment was planned to achieve disease remission or to preserve patient comorbidities without achieving remission was also unknown. Accordingly, classification of patient characteristics, such as the conditioning regimen or donor availability, was relatively rough, due to heterogeneous characteristics and statistical power. Moreover, evaluation of HLA matching at HLA-A, -B, -C, and -DRB1 alleles, instead of HLA-A, -B, and -DR antigen evaluation in this study, may be desirable. However, HLA mismatch had no impact even on antigen-level matching in this study. Therefore, we speculated that HLA mismatch might not have a strong impact on allele-level matching. Third, the majority of patients registered from transplant centers located in metropolitan cities. Thus, the differences in sociomedical background may influence the results of the analysis. Therefore, another validation study with an independent cohort is warranted.

In conclusion, the present index was useful to predicting survival in patients with AML who underwent HCT and who either had a status of relapse or primary induction failure. Further studies are warranted to assess the scoring system with an independent cohort.

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Author contributions TT was the primary investigator, managed the study, performed biomedical statistics, and wrote the paper. JK, TI, and YK contributed to managing and supporting the study as a working member of the group. YN, MT, ND, S Fujiwara, SK, MO, ST, TS, TM, S Fujisawa, EM, KM, NA, MG, RW, KS, KU, and NT contributed to collecting research forms as a representative of the institution. SO supervised the study.

Compliance with ethical standards

Conflict of interest Dr. Usuki reports grants and personal fees from MSD K.K., Sumitomo Dainippon Pharma, Pfizer Japan, and Celgene Corporation, grants from Astellas Pharma, Otsuka, Kyowa Kirin, GlaxoSmithKline K.K., Sanofi K.K., Shire Japan, SymBio Pharmaceuticals Limited, Daiichi Sankyo, Boehringer-Ingelheim Japan, and Janssen Pharmaceutical K.K., and personal fees from Novartis, Ono Pharmaceutical, Takeda Pharmaceuticals, Chugai Pharmaceutical,

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