Personalized prediction of overall survival in patients with AML in non-complete remission undergoing allo-HCT

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Abstract
Allogenic hematopoietic stem cell transplantation (allo-HCT) is the standard treatment for acute myeloid leukemia (AML) in non-complete remission (non-CR); however, the prognosis is inconsistent. This study aimed to develop and validate nomograms and a web application to predict the overall survival (OS) of patients with non-CR AML undergoing allo-HCT (cord blood transplantation [CBT], bone marrow transplantation [BMT], and peripheral blood stem cell transplantation [PBSCT]).
1 | INTRODUCTION

The prognosis of acute myeloid leukemia (AML) in non-complete remission (non-CR) is poor and poses a challenge with respect to the selection of the optimal treatment for patients. Approximately 10%-20% of patients with refractory or relapsed AML exhibit long-term survival.1-4 Although chimeric antigen receptor T-cell therapy5 and several targeted therapies using FLT3 inhibitors,6 IDH1/IDH2 inhibitors,7,8 and CD33 antibodies9 have been developed, survival outcomes have not been sufficiently improved. Consequently, allogeneic hematopoietic stem cell transplantation (allo-HCT) remains the most effective treatment to cure refractory or relapsed AML. Recently, it was reported that for acute leukemia or myelodysplastic syndrome, patients with minimal residual disease (MRD) who underwent cord blood transplantation (CBT) showed a more favorable prognosis than those who underwent bone marrow transplantation (BMT) or peripheral blood stem cell transplantation (PBSCT).10 Despite the emerging importance of CBT in hematological malignancies with MRD, no large scale studies have been conducted on CBT in patients with AML in non-CR.

Here, we aimed to identify the prognostic factors and to develop and validate nomograms11,12 and a web application for predicting the overall survival (OS) of patients with AML in non-CR undergoing allo-HCT, including CBT. Furthermore, we constructed and evaluated prognostic models for BMT and PBSCT. Therefore, our models can simultaneously simulate the prognosis of CBT, BMT, and PBSCT as per the clinicopathological characteristics of each patient and can be helpful in selecting an optimal treatment.

2 | MATERIAL AND METHODS

2.1 | Study design and population

In this multicenter, retrospective cohort study, three nomograms and a web application were developed to predict the OS of patients with AML in non-CR undergoing single-unit CBT, BMT, and PBSCT. We included consecutive patients undergoing allo-HCT with AML aged ≥16 years who had ≥5% blasts in the bone marrow or who had ≥20% blasts in the peripheral blood at transplantation. We excluded patients who underwent HCT within 90 days of the last HCT and those who had missing data for potential predictors. We retrieved the data for HCT outcomes from patients at the Transplant Registry Unified Management Program (TRUMP)13-15 across >300 transplant centers in Japan. The data of patients who underwent allo-HCT between 2000 and 2014 were used to develop the prognostic models; the data of patients who underwent haploidentical transplantation were excluded. To validate the constructed models, we analyzed the data of patients who underwent allo-HCT between 2015 and 2016. Figure 1 shows the design of our study.

2.2 | Variables of interest

Data on clinical outcomes and patient characteristics were retrieved from the registry database. Based on previous reports, we selected the following potential predictors (Tables 1-3): age of the recipient at transplantation,1,10,16-20 sex,10,16-20
Eastern Cooperative Oncology Group (ECOG) performance status (PS) at transplantation, hematopoietic cell transplantation-comorbidity index (HCT-CI), percentage of blasts in the peripheral blood, French–American–British (FAB) classification, cytogenetics, response to chemotherapy, disease status, year of transplantation, number of transplantations, donor type, human leukocyte antigen (HLA) compatibility, total number of nucleated cells in the cord blood (only for CBT), conditioning regimen, prophylaxis for graft versus host disease, and use of anti-thymocyte globulin.

Recently, several studies, including prospective randomized studies or a meta-analysis, have compared reduced-intensity conditioning (RIC) and myeloablative conditioning (MAC). However, these studies did not show a statistically significant difference between RIC and MAC in terms of OS. On the other hand, an excellent survival benefit was reported in individual conditioning regimens. Therefore, we stratified conditioning regimens before HCT into six categories based on the combination of chemotherapy drugs and total body irradiation (TBI) of ≥8 Gy, rather than categorizing them based on intensity. AML was categorized according to the FAB classification. Donor-recipient HLA-A, HLA-B, and HLA-DR compatibilities were determined. Patients with a 6/6 match at HLA-A, -B and -DR were placed in the matched group and those with ≥1 mismatch were placed in the mismatched group. We classified cytogenetic risk according to the National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2016 as favorable risk \([t(8;21), t(15;17), \text{inv}(16), t(16;16)]\), poor risk \([-5/\text{del}(5q),\text{−7/}\text{del}(7q)\text{−6/}\text{del}(6q)\text{−5/}\text{del}(5q)\text{−17p}−\text{19p}]\).
Table 1  Characteristics of patients who underwent cord blood transplantation

| Characteristic                                      | Development cohort  | Validation cohort | p     |
|-----------------------------------------------------|---------------------|-------------------|-------|
|                                                     | (n = 1077); n (%) or median [IQR] | (n = 434); n (%) or median [IQR] |       |
| Age (years)\(a\)                                    | 56 [44, 64]         | 57 [45, 65]       | 0.112 |
| Sex                                                 |                     |                   | 0.415 |
| Female                                              | 427 (39.6)          | 162 (37.3)        |       |
| Male                                                | 650 (60.4)          | 272 (62.7)        |       |
| ECOG performance status                             |                     |                   | <0.001|
| 0                                                   | 246 (22.8)          | 116 (26.7)        |       |
| 1                                                   | 520 (48.3)          | 243 (56.0)        |       |
| 2                                                   | 205 (19.0)          | 55 (12.7)         |       |
| 3                                                   | 81 (7.5)            | 17 (3.9)          |       |
| 4                                                   | 25 (2.3)            | 3 (0.7)           |       |
| HCT-CI                                              |                     |                   | 0.528 |
| 0                                                   | 461 (42.8)          | 189 (43.5)        |       |
| 1–3                                                 | 470 (43.6)          | 179 (41.2)        |       |
| 4–6                                                 | 129 (12.0)          | 55 (12.7)         |       |
| ≥7                                                  | 17 (1.6)            | 11 (2.5)          |       |
| Peripheral blasts (%)\(a\)                         | 12.0 [140, 46.0]    | 13.0 [200, 50.0]  | 0.669 |
| FAB classification                                   |                     |                   | 0.59  |
| M0                                                  | 88 (8.2)            | 27 (6.2)          |       |
| M1–2                                                | 528 (49.0)          | 209 (48.2)        |       |
| M4–5                                                | 174 (16.2)          | 73 (16.8)         |       |
| M6                                                  | 67 (6.2)            | 36 (8.3)          |       |
| M7                                                  | 15 (1.4)            | 5 (1.2)           |       |
| Other                                               | 205 (19.0)          | 84 (19.4)         |       |
| Cytogenetic risk\(b\)                              |                     |                   | 0.025 |
| Favorable                                           | 618 (57.4)          | 226 (52.1)        |       |
| Intermediate                                         | 324 (30.1)          | 131 (30.2)        |       |
| Poor                                                | 135 (12.5)          | 77 (17.7)         |       |
| Response to chemotherapy                            |                     |                   | <0.001|
| Primary induction failure                            | 438 (40.7)          | 187 (43.1)        |       |
| Duration of first CR, <6 month                       | 205 (19.0)          | 124 (28.6)        |       |
| Duration of first CR, ≥6 month                       | 275 (25.5)          | 50 (11.5)         |       |
| No treatment before transplantation                  | 159 (14.8)          | 73 (16.8)         |       |
| Disease status                                       |                     |                   | 0.856 |
| De novo AML                                         | 959 (89.0)          | 385 (88.7)        |       |
| Secondary AML                                       | 118 (11.0)          | 49 (11.3)         |       |
| Year of transplantation                              |                     |                   | <0.001|
| 2000–2010                                           | 422 (39.2)          | 0 (0.0)           |       |
| 2011–2012                                           | 313 (29.1)          | 0 (0.0)           |       |
| 2013–2014                                           | 342 (31.8)          | 0 (0.0)           |       |
| 2015–2016                                           | 0 (0.0)             | 434 (100.0)       |       |
| Number of transplantations                           | 1                   |                   |       |
| 1                                                   | 828 (76.9)          | 334 (77.0)        |       |

(Continues)
−7/del(7q), inv(3), t(3;3), 11q23 other than t(9;11), t(6;9), t(9;22), complex karyotype (CK), monosomal karyotype], or intermediate risk [normal, +8 alone, t(9;11), other non-defined]. However, patients with favorable risk did not have a better prognosis than those with intermediate risk in that situation. We then revised the classification of cytogenetic risk based on the findings of univariable analysis (see Results).

2.3 | Statistical analyses

OS was defined as the time from HCT to last contact or death from any cause. The OS rates were determined using the Kaplan–Meier method and analyzed using the log-rank test. We used a Cox proportional hazards model for multivariate analysis; the prognostic factors from potential predictors were identified by applying backward stepwise selection.
TABLE 2  Characteristics of patients who underwent bone marrow transplantation

|                                | Development cohort | Validation cohort | p       |
|--------------------------------|--------------------|------------------|---------|
|                                | (n = 786); n (%) or median [IQR] | (n = 193); n (%) or median [IQR] |         |
| Age (years)a                   | 53 [42, 60]        | 56 [45, 63]      | 0.016   |
| Sex                            |                    |                  | 0.508   |
| Female                         | 292 (37.2)         | 77 (39.9)        |         |
| Male                           | 494 (62.8)         | 116 (60.1)       |         |
| ECOG performance status        |                    |                  | 0.274   |
| 0                              | 278 (35.4)         | 84 (43.5)        |         |
| 1                              | 354 (45.0)         | 79 (40.9)        |         |
| 2                              | 108 (13.7)         | 20 (10.4)        |         |
| 3                              | 36 (4.6)           | 7 (3.6)          |         |
| 4                              | 10 (1.3)           | 3 (1.6)          |         |
| HCT-CI                          |                    |                  | 0.37    |
| 0                              | 389 (49.5)         | 85 (44.0)        |         |
| 1–3                            | 321 (40.8)         | 86 (44.6)        |         |
| 4–6                            | 66 (8.4)           | 21 (10.9)        |         |
| ≥7                             | 10 (1.3)           | 1 (0.5)          |         |
| Peripheral blasts (%)a         | 6.05 [0.50, 30.0]  | 3.00 [0.00, 20.0] | 0.019   |
| FAB classification             |                    |                  | 0.016   |
| M0                             | 74 (9.4)           | 15 (7.8)         |         |
| M1-2                           | 386 (49.1)         | 83 (43.0)        |         |
| M4-5                           | 156 (19.8)         | 29 (15.0)        |         |
| M6                             | 63 (8.0)           | 26 (13.5)        |         |
| M7                             | 18 (2.3)           | 8 (4.1)          |         |
| Other                          | 89 (11.3)          | 32 (16.6)        |         |
| Cytogenetic riskb              |                    |                  | 0.142   |
| Favorable                      | 440 (56.0)         | 100 (51.8)       |         |
| Intermediate                   | 247 (31.4)         | 58 (30.1)        |         |
| Poor                           | 99 (12.6)          | 35 (18.1)        |         |
| Response to chemotherapy       |                    |                  | < 0.001 |
| Primary induction failure      | 362 (46.1)         | 90 (46.6)        |         |
| Duration of first CR, <6 month | 167 (21.2)         | 64 (33.2)        |         |
| Duration of first CR, ≥6 month | 169 (21.5)         | 19 (9.8)         |         |
| No treatment before transplantation | 88 (11.2)        | 20 (10.4)        |         |
| Disease status                 |                    |                  | 0.074   |
| De novo AML                    | 691 (87.9)         | 160 (82.9)       |         |
| Secondary AML                  | 95 (12.1)          | 33 (17.1)        |         |
| Year of transplantation        |                    |                  | <0.001  |
| 2000–2010                      | 352 (44.8)         | 0 (0.0)          |         |
| 2011–2012                      | 216 (27.5)         | 0 (0.0)          |         |
| 2013–2014                      | 218 (27.7)         | 0 (0.0)          |         |
| 2015–2016                      | 0 (0.0)            | 193 (100.0)      |         |
| Number of transplantations     |                    |                  | 0.16    |
| 1                              | 672 (85.5)         | 173 (89.6)       |         |

(Continues)
and retaining the variables with \( p \) values <0.05. Nomograms and a web application were developed based on the results of the multivariate analyses. The accuracy of the prognostic models was validated through calibration (assessed by plotting the predicted vs. observed OS rates), discrimination (assessed by concordance probability estimate; \( c \)-index\(^{34} \)), and survival curves. A \( c \)-index of 1 indicated perfect discrimination, while a \( c \)-index of 0.5 indicated no discrimination. Internal validation of each prognostic model was performed using the bootstrap method with 1000 resamples for calibration and discrimination using the respective development cohorts. To validate each prognostic model, we used the respective validation cohort. Moreover, we applied a previously reported scoring system for patients with AML relapse or primary induction failure who underwent BMT and PBSCT\(^{18} \) to our validation cohort (cases with missing values were excluded). Briefly, the scoring system was based on the response to chemotherapy, cytogenetics, HLA-match, circulating blasts, and Karnofsky score. Subsequently, the patients were categorized into four groups (scores of 0, 1, 2, and \( \geq 3 \)). Analyses were performed using SAS (version 9.4, SAS Institute), SPSS (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.), EZR,\(^{35} \) and R 3.2.3 software (https://www.r-proje

| TABLE 2 (Continued) | Development cohort \((n = 786); n (%) or median [IQR]\) | Validation cohort \((n = 193); n (%) or median [IQR]\) | \( p \) |
|----------------------|-------------------------------------------------|-------------------------------------------------|------|
| \( \geq 2 \) | 114 (14.5) | 20 (10.4) | 0.153 |
| Donor type | 0.153 | 0.12 | 0.001 |
| Related | 109 (13.9) | 19 (9.8) | 677 (86.1) | 174 (90.2) |
| Unrelated | 0.12 | 0.001 | 0.005 | 0.035 |
| HLA compatibility | 0.001 | 0.005 | 0.035 |
| Match | 623 (79.3) | 143 (74.1) | 163 (20.7) | 50 (25.9) |
| Mismatch | 0.79 | 0.58 | 0.6 \(| 0.5 \) | 0.009 | 0.005 | 0.035 |
| Conditioning regimen | 0.009 | 0.005 | 0.035 |
| CY+TBI | 102 (13.0) | 25 (13.0) | 61 (7.8) | 11 (5.7) |
| BU+CY | 122 (15.5) | 21 (10.9) | 373 (47.5) | 89 (46.1) |
| CA+CY+TBI | 0.009 | 0.005 | 0.035 |
| FLU+(BU or MEL) | 66 (8.4) | 37 (19.2) | 0.009 | 0.005 | 0.035 |
| FLU+(BU or MEL)+(BU or MEL or CA or CY) | 0.009 | 0.005 | 0.035 |
| Other regimen | 62 (7.9) | 10 (5.2) | 0.009 | 0.005 | 0.035 |
| GVHD prophylaxis | 0.009 | 0.005 | 0.035 |
| CSA+MTX | 182 (23.2) | 22 (11.4) | 12 (1.5) | 5 (2.6) |
| TAC+MMF | 0.009 | 0.005 | 0.035 |
| TAC+MTX | 541 (68.8) | 159 (82.4) | 5 (0.6) | 0 (0.0) |
| CSA+MMF | 46 (5.9) | 7 (3.6) | 0.009 | 0.005 | 0.035 |
| Other | 0.009 | 0.005 | 0.035 |
| Use of ATG | 0.009 | 0.005 | 0.035 |
| No | 750 (95.4) | 173 (89.6) | 36 (4.6) | 20 (10.4) |
| Yes | 0.009 | 0.005 | 0.035 |
| Treatment for AML after transplantation | 0.009 | 0.005 | 0.035 |
| No | 613 (78.0) | 135 (69.9) | 0.009 | 0.005 | 0.035 |
| Yes | 170 (21.6) | 58 (30.1) | 0.009 | 0.005 | 0.035 |
| Missing | 3 (0.4) | 0 (0.0) | 0.009 | 0.005 | 0.035 |

Note: \( p \)-values were calculated by Fisher’s exact test or Wilcoxon Mann–Whitney test based on categorical or continuous variables.

Abbreviations: AML, acute myeloid leukemia; ATG, anti-thymocyte globulin; BU, busulfan; CA, cytarabine; CR, complete remission; CSA, cyclosporine; CY, cyclophosphamide; FAB, French-American-British; FLU, fludarabine; GVHD, graft versus host disease; HCT-CI, hematopoietic cell transplantation-comorbidity index; IQR, interquartile range; MEL, melphalan; MMF, mycophenolate mofetil; MTX, methotrexate; TAC, tacrolimus; TBI, total body irradiation.

\(^{a}\)Continuous variable.

\(^{b}\)Cytogenetic risk determined by this study.
### TABLE 3  Characteristics of patients who underwent peripheral blood stem cell transplantation

| Characteristic                                    | Development cohort | Validation cohort | p   |
|-------------------------------------------------|--------------------|-------------------|-----|
| **Age (years)**                                 | 50 [37, 59]        | 48 [37.5, 58]     | 0.762 |
| **Sex**                                         |                    |                   | 0.612 |
| Female                                          | 167 (39.1)         | 49 (36.3)         |     |
| Male                                            | 260 (60.9)         | 86 (63.7)         |     |
| **ECOG performance status**                     |                    |                   | 0.115 |
| 0                                               | 118 (27.6)         | 50 (37.0)         |     |
| 1                                               | 208 (48.7)         | 54 (40.0)         |     |
| 2                                               | 69 (16.2)          | 17 (12.6)         |     |
| 3                                               | 24 (5.6)           | 12 (8.9)          |     |
| 4                                               | 8 (1.9)            | 2 (1.5)           |     |
| **HCT-CI**                                      |                    |                   | 0.097 |
| 0                                               | 235 (55.0)         | 59 (43.7)         |     |
| 1–3                                            | 154 (36.1)         | 64 (47.4)         |     |
| 4–6                                            | 34 (8.0)           | 11 (8.1)          |     |
| ≥7                                             | 4 (0.9)            | 1 (0.7)           |     |
| **Peripheral blasts (%)**                       | 6.00 [0.00, 30.0]  | 5.00 [0.00, 30.5] | 0.847 |
| **FAB classification**                          |                    |                   | 0.29  |
| M0                                             | 33 (7.7)           | 12 (8.9)          |     |
| M1–2                                           | 223 (52.2)         | 79 (58.5)         |     |
| M4–5                                           | 84 (19.7)          | 24 (17.8)         |     |
| M6                                             | 22 (5.2)           | 9 (6.7)           |     |
| M7                                             | 11 (2.6)           | 3 (2.2)           |     |
| Other                                           | 54 (12.6)          | 8 (5.9)           |     |
| **Cytogenetic risk**                            |                    |                   | 0.633 |
| Favorable                                       | 243 (56.9)         | 79 (58.5)         |     |
| Intermediate                                    | 142 (33.3)         | 40 (29.6)         |     |
| Poor                                            | 42 (9.8)           | 16 (11.9)         |     |
| **Response to chemotherapy**                    |                    |                   | 0.003 |
| Primary induction failure                       | 194 (45.4)         | 68 (50.4)         |     |
| Duration of first CR, <6 month                  | 75 (17.6)          | 37 (27.4)         |     |
| Duration of first CR, ≥6 month                  | 103 (24.1)         | 16 (11.9)         |     |
| No treatment before transplantation             | 55 (12.9)          | 14 (10.4)         |     |
| **Disease status**                              |                    |                   | 1    |
| De novo AML                                     | 383 (89.7)         | 122 (90.4)        |     |
| Secondary AML                                   | 44 (10.3)          | 13 (9.6)          |     |
| **Year of transplantation**                     |                    |                   | <0.001 |
| 2000–2010                                       | 157 (36.8)         | 0 (0.0)           |     |
| 2011–2012                                       | 136 (31.9)         | 0 (0.0)           |     |
| 2013–2014                                       | 134 (31.4)         | 0 (0.0)           |     |
| 2015–2016                                       | 0 (0.0)            | 135 (100.0)       |     |
| **Number of transplantations**                  |                    |                   | 0.447 |
| 1                                               | 351 (82.2)         | 107 (79.3)        |     |
| ≥2                                              | 76 (17.8)          | 28 (20.7)         |     |

(Continues)
The web application was developed using R 3.2.3 software with shiny version 1.0.5 (https://shiny.rstudio.com).

3 | RESULTS

3.1 | Characteristics and survival of patients

The characteristics of the patients in the development (CBT, n = 1077; BMT, n = 786; and PBSCT, n = 427) and validation cohorts (CBT, n = 434; BMT, n = 193; and PBSCT, n = 135) are listed in Tables 1–3. In the cohort, CBT was performed with a single unit, most bone marrow grafts were unrelated, and most peripheral blood grafts were related. The 1- and 5-year OS rates in the development cohort were 31.1% (95% confidence interval [CI], 28.3%–34.0%) and 20.3% (95% CI, 17.5%–23.2%), respectively, after CBT; 37.2% (95% CI, 33.7%–40.6%) and 23.1% (95% CI, 19.7%–26.6%), respectively, after BMT; and 38.1% (95% CI, 33.3%–42.8%) and 18.9% (95% CI, 14.6%–23.6%), respectively, after PBSCT. The 1-year OS rates in the validation cohort was 39.4% (95% CI, 34.5%–44.3%).
after CBT, 33.8% (95% CI, 26.6%–41.2%) after BMT, and 37.4% (95% CI, 28.4%–46.4%) after PBSCT.

### 3.2 | Identification of cytogenetic risk for allogenic hematopoietic stem cell transplantation in acute myeloid leukemia in non-complete remission

The Kaplan–Meier curve was plotted based on the cytogenetic risk classified by the NCCN Guidelines (Figure S1A). However, patients with favorable risk did not have a better prognosis than those with intermediate risk. To identify the cytogenetic risk for allo-HCT in non-CR AML, we performed univariable analysis. Based on these results, the cytogenetic risk was classified as poor [−5/del(5q), −17, t(6;9), not evaluable], intermediate [CK, −7/del(7q), inv(3), t(3;3), 11q23 other than t(9;11), t(8;21)], or favorable [normal, inv(16), +8 alone, t(9;11), other non-defined] (Table S1). If cytogenetic risk was categorized into two groups, the worse risk classification was adopted. This grouping successfully stratified patients with non-CR AML who underwent allo-HCT (Figure S1B).

### 3.3 | Conditioning regimen of ≥3 drugs including fludarabine in cord blood transplantation was associated with favorable overall survival and leukemia-free survival

Using the backward stepwise selection method in the Cox proportional hazards model, we identified the following significant prognostic factors for OS in patients in the development cohort who underwent CBT: age of the recipient at transplantation, sex, ECOG PS, HCT-CI, percentage of peripheral blasts, cytogenetic risk classification, response to chemotherapy, number of transplantations, and conditioning regimen (Table 4). Interestingly, compared with cyclophosphamide/TBI (conditioning regimen), the use of ≥3 drugs (including fludarabine) with CBT showed the lowest hazard ratio for mortality (0.384; 95% CI, 0.266–0.554; \( p < 0.0001 \)). Among all conditioning regimens, the use of ≥3 drugs (including fludarabine) with CBT showed the best leukemia-free survival (LFS) and favorable OS (Figure 2), whereas the regimen with BMT or PBSCT did not show the best prognosis (Figure S2). Table S2 lists the details of the ≥3 drug regimen, including fludarabine, administered with CBT. A combination of fludarabine, melphalan, and busulfan (FLU/BU/MEL) was most frequently used (34.9%). Similar to those in patients undergoing CBT, the age of the recipient at transplantation, ECOG PS, HCT-CI, percentage of peripheral blasts, FAB classification, cytogenetic risk classification, response to chemotherapy, and number of transplantations

| Table 4 Results of the multivariate analysis of the overall survival of patients who underwent cord blood transplantation |
|-----------------|--------|-----------------|
| Age (per year)\(^a\) | 1.014 | 1.008–1.02 <0.0001 |
| Sex | | |
| Female | 1.000 | |
| Male | 1.404 | 1.210–1.628 <0.0001 |
| ECOG performance status | | |
| 0 | 1.000 | |
| 1 | 1.310 | 1.080–1.588 0.0061 |
| 2 | 1.801 | 1.429–2.269 <0.0001 |
| 3 | 3.386 | 2.538–4.519 <0.0001 |
| 4 | 7.703 | 4.898–12.116 <0.0001 |
| HCT-CI | | |
| 0 | 1.000 | |
| 1–3 | 1.133 | 0.967–1.328 0.1211 |
| 4–6 | 1.215 | 0.958–1.543 0.1089 |
| ≥7 | 2.060 | 1.221–3.475 0.0068 |
| Peripheral blasts (per percentage)\(^a\) | | |
| Favorable | 1.005 | 1.003–1.007 <0.0001 |
| Intermediate | 1.316 | 1.124–1.54 0.0006 |
| Poor | 1.596 | 1.286–1.98 <0.0001 |
| Response to chemotherapy | | |
| Primary induction failure | 1.000 | |
| Duration of first CR, <6 month | 1.328 | 1.087–1.622 0.0056 |
| Duration of first CR, ≥6 month | 0.971 | 0.799–1.18 0.7666 |
| No treatment before transplantation | 0.713 | 0.566–0.899 0.0042 |
| Number of transplantations | | |
| 1 | 1.000 | |
| ≥2 | 1.589 | 1.312–1.924 <0.0001 |
| Conditioning regimen | | |
| CY+TBI | 1.000 | |
| BU+CY | 0.605 | 0.343–1.067 0.0828 |
| CA+CY+TBI | 0.501 | 0.340–0.737 0.0005 |
| FLU+(BU or MEL) | 0.554 | 0.387–0.792 0.0012 |
| FLU+(BU or MEL)+(BU, MEL, CA, or CY) | 0.384 | 0.266–0.554 <0.0001 |
| Other regimen | 0.624 | 0.416–0.936 0.0227 |

Abbreviations: BU, busulfan; CA, cytarabine; CR, complete remission; CY, cyclophosphamide; FLU, fludarabine; HCT-CI, hematopoietic cell transplantation-comorbidity index; HR, hazard ratio; MEL, melphalan; TBI, total body irradiation.

\(^a\)Continuous variable.

\(^b\)Cytogenetic risk determined by this study.
were identified as significant prognostic factors for OS in patients who underwent BMT (Table 5); age of the recipient at transplantation, sex, ECOG PS, percentage of peripheral blasts, cytogenetic risk classification, response to chemotherapy, and number of transplantations. The hazard ratio for the overall survival of patients in the FLU+(BU or MEL) group versus those in the FLU+(BU or MEL)+(BU, MEL, CA, or CY) group was 1.442 (95% confidence interval [CI], 1.211–1.718; p = 0.0027). The hazard ratio for the leukemia-free survival of patients in the FLU+(BU or MEL) group versus those in the FLU+(BU or MEL)+(BU, MEL, CA, or CY) group was 1.533 (95% CI, 1.282–1.817; p < 0.0001); in the CA +CY + TBI group versus those in the FLU+(BU or MEL) group was 1.320 (95% CI, 1.013–1.719; p = 0.0395); in the BU +CY group versus those in the FLU+(BU or MEL)+(BU, MEL, CA, or CY) group was 2.045 (95% CI, 1.013–1.719; p = 0.0395); in the BU +CY group versus those in the FLU+(BU or MEL)+(BU, MEL, CA, or CY) group was 1.303 (95% CI, 0.992–1.712; p = 0.0574); in the BU +CY group versus those in the FLU+(BU or MEL)+(BU, MEL, CA, or CY) group was 1.576 (95% CI, 0.966–2.571; p = 0.0685). The hazard ratio for the leukemia-free survival of patients in the FLU+(BU or MEL)+(BU, MEL, CA, or CY) group was 1.576 (95% CI, 0.966–2.571; p = 0.0685).

### 3.4 Development and Validation of Nomograms

Based on the results of the multivariate analyses, we constructed nomograms to predict the 1-, 3-, and 5-year OS of patients after CBT, BMT, and PBSCT (Figures 3–5). The point of each characteristic was determined by drawing an upward vertical line from the covariate to the points axis. The total points score was obtained by summing each point. The 1-, 3-, and 5-year overall survival probabilities were determined by drawing a downward vertical line from the total points score.

Next, we validated the performance of the prognostic models. Figures 6A and B, 7A and B, and 8A and B show the calibration plots of the 1- and 5-year OS for CBT, BMT, and PBSCT in the development cohort using the bootstrap method, and Figures 6C, 7C, and 8C show the calibration plot of 1-year OS in the validation cohort. Sample points lie on the diagonal line when the predicted OS is equal to the observed OS. The calibration plots correlated well with the predicted and observed OS, indicating the accuracy of the prognostic models. Furthermore, we confirmed that the actual Kaplan–Meier curves in the validation cohort were successfully stratified by our nomograms (Figures 6D, 7D, and 8D). In the internal validation, the bootstrap-corrected c-indices of the nomograms for CBT, BMT, and PBSCT were 0.671 (95% CI, 0.652–0.690), 0.675 (95% CI, 0.652–0.699), and 0.654 (95% CI, 0.621–0.688), respectively. In the validation cohort, the c-indices of the nomograms for CBT, BMT, and PBSCT were 0.648 (95% CI, 0.613–0.682), 0.600 (95% CI, 0.542–0.658), and 0.658 (95% CI, 0.596–0.720), respectively. Using a previous scoring system, the c-indices for BMT and PBSCT were 0.587 (95% CI, 0.529–0.645) and 0.570 (95% CI, 0.491–0.650), respectively. The distribution of scores in the validation cohort
is given in Table S3. These data indicate that our nomograms were at least as accurate as the previous scoring system. We also developed a web application (https://JSHCT-AMLWG.shinyapps.io/Predict-OS-non-CR-AML-post-HCT/) based on these prognostic models. This enabled us to simultaneously estimate the prognosis and construct survival curves after CBT, BMT, and PBSCT with ease (Figure 9).

**4 | DISCUSSION**

We developed three nomograms and a web application to predict the 1-, 3-, and 5-year OS of patients with AML in non-CR after CBT, BMT, and PBSCT. We validated the nomograms showing adequate calibration and discrimination despite the diversity in patient characteristics, leukemia subtype, and treatments.

In this study, we revealed the common significant prognostic factors for the three types of HCTs. These factors...
were attributed to patient characteristics and tumor characteristics and not to treatment. Intriguingly, the conditioning regimen that physicians selected was a significant prognostic factor only in CBT. A previous single-arm study showed excellent survival outcomes (2-year OS rate = 54.9%; 2-year progression-free survival rate = 54.9%) of patients with myeloid malignancies in non-CR who underwent CBT and were treated with FLU/BU/MEL. Notably, we demonstrated that the use of a ≥3 drug regimen, including fludarabine, such as the combination FLU/BU/MEL, resulted in a favorable prognosis, but the conditioning regimen was not a significant prognostic factor for the OS of patients undergoing BMT or PBSCT. It was reported that cyclophosphamide/TBI supplemented with high-dose cytarabine was effective for patients undergoing CBT but not for those undergoing BMT or PBSCT. Which is in accordance with the findings of our study. The distinct difference may be due to differences in the composition and properties of cord blood and bone marrow or peripheral blood. Our data suggests the importance of selecting appropriate conditioning regimens for each donor source.

The ≥3 drug regimen such as FLU/BU/MEL had a positive impact on prognosis. This is because the respective chemotherapy drugs may have different anti-tumor mechanisms. For example, fludarabine inhibits DNA/RNA synthesis by incorporating the drug into DNA or RNA. Melphalan and busulfan are alkylating agents, but melphalan is classified as nitrogen mustards and busulfan as alkyl alkane sulfonates. Melphalan reacts with N7-guanine, N3-adenine, and O6-guanine in DNA to form covalent alkyl lesions. Whereas, busulfan reacts with not only N7-guanine and N3-adenine, but also with proteins. Furthermore, busulfan does not elicit toxicity via alkylation of O6-guanine. Thus, the combination of drugs with different mechanisms may be useful in enhancing the anti-tumor effect and eradicating leukemia cells. Actually, a previous study showed that fludarabine and double alkylating agents (busulfan and thiotepa) could enhance the anti-tumor effect compared with fludarabine and a single-alkylating agent (busulfan). It was previously reported that circulating blasts, cytogenetic risk, duration of first CR, and Karnofsky or Lansky score significantly affected the OS of patients with relapsed AML or failure in primary induction who underwent BMT or PBSCT. In our study, they were also selected as prognostic factors for CBT as well as for BMT and PBSCT. Moreover, we found that an increase in the number of transplantations

![Nomogram to predict the overall survival after cord blood transplantation. This nomogram predicts the 1-, 3-, and 5-year overall survival probabilities of patients with acute myeloid leukemia undergoing cord blood transplantation in non-complete remission. BU, busulfan; CA, cytarabine; CBT, cord blood transplantation; CY, cyclophosphamide; FLU, fludarabine; HCT-CI, hematopoietic cell transplantation comorbidity index; MEL, melphalan; PIF, primary induction failure; Relapse ≥6 months, the duration of the first complete remission was ≥6 months; Relapse <6 months, the duration of the first complete remission was <6 months; TBI, total body irradiation.](image-url)
**FIGURE 4** Nomogram to predict overall survival after bone marrow transplantation. This nomogram predicts the 1-, 3-, and 5-year overall survival probabilities of patients with acute myeloid leukemia undergoing bone marrow transplantation in non-complete remission. BMT, bone marrow transplantation; FAB, French-American-British; HCT-CI, hematopoietic cell transplantation comorbidity index; PIF, primary induction failure; Relapse ≥6 months, the duration of the first complete remission was ≥6 months; Relapse <6 months, the duration of the first complete remission was <6 months

**FIGURE 5** Nomogram to predict overall survival after peripheral blood stem cell transplantation. This nomogram predicts the 1-, 3-, and 5-year overall survival probabilities of patients with acute myeloid leukemia undergoing peripheral blood stem cell transplantation in non-complete remission. PB SCT, peripheral blood stem cell transplantation; PIF, primary induction failure; Relapse ≥6 months, the duration of the first complete remission was ≥6 months; Relapse <6 months, the duration of the first complete remission was <6 months
FIGURE 6 Validation of the overall survival nomogram for cord blood transplantation. In the upper panels, the calibration plots show the bootstrap internal validation for the 1- (A) and 5-year (B) overall survival. The lower left panel shows the calibration plot of 1-year overall survival in the validation cohort (C). The x-axis represents the overall survival rate predicted by the nomogram. The y-axis represents the observed overall survival rate estimated using the Kaplan–Meier method. Patients were divided into four groups of equal size based on the predicted overall survival rate. The dashed line shows the ideal line, which indicates that the predicted overall survival rate is the same as the observed overall survival rate. The dots show the median values and error bars show 95% CIs. Kaplan–Meier curves according to nomogram predictions are shown (D). CBT indicates cord blood transplantation; 1-yr, 1-year; OS, overall survival

FIGURE 7 Validation of the overall survival nomogram for bone marrow transplantation. In upper panels, the calibration plots show the bootstrap internal validation for the 1- (A) and 5-year (B) overall survival. The lower left panel shows the calibration plot of 1-year overall survival in the validation cohort (C). The x-axis represents the overall survival rate predicted by the nomogram. The y-axis represents the observed overall survival rate estimated by the Kaplan–Meier method. Patients were divided into four groups of equal size based on the predicted overall survival rate. The dashed line shows the ideal line, which represents that the predicted overall survival rate is the same as the observed overall survival rate. The dots show the median values and error bars show 95% CIs. The Kaplan–Meier curves according to prediction by the nomogram are shown (D). BMT indicates bone marrow transplantation; 1-yr, 1-year; OS, overall survival
was associated with a poor prognosis for any stem cell source. This might be attributed to the condition of patients with AML and an increase in leukemic stem cell frequency and heterogeneity after unsuccessful treatment.\(^\text{24,25}\)

Commonly used risk scores to predict the OS of patients with AML in relapse or with primary induction failure undergoing BMT and PBSCT have been developed using a large cohort.\(^\text{18}\) In the commonly used risk scores, each prognostic factor has an equal prognostic weight in the outcome despite having a different hazard ratio, which results in a reduction of the predictive accuracy of the prognostic model.\(^\text{43}\) However, each hazard ratio in this study was accurately represented in the prognostic model. Various studies have documented the superiority of the method used in this study over risk categorization.\(^\text{43,44}\) We selected candidate predictors that they have not been previously included, such as HCT-CI, FAB classification, and number of transplantations. Moreover, the model included data from pediatric AML patients; however, recent studies have indicated a distinct difference in biological and molecular profiling between pediatric and adult AML.\(^\text{45,46}\) Therefore, to develop a prognostic model suitable for adult AML patients, we focused only on data from adult patients. These reasons could have resulted in the improved performance of our prognostic models compared with that of the previous scoring system.\(^\text{18}\) Furthermore, our prognostic models can compare the prognosis of different types of transplantations. They can be useful because there have been no randomized trials to determine appropriate donor sources.\(^\text{47}\)

Recently, the use of haploidentical transplantation has been increasing for refractory AML. However, there are a few retrospective studies comparing haploidentical transplantation with other transplants for refractory AML, and there are no published randomized clinical trials. Suitable situations for haploidentical transplantation are not yet fully

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**FIGURE 8** Validation of the overall survival nomogram for peripheral blood stem cell transplantation. In upper panels, the calibration plots show the bootstrap internal validation for the 1- (A) and 5-year (B) overall survival. The lower left panel shows the calibration plot of 1-year overall survival in the validation cohort (C). The x-axis represents the overall survival rate predicted by the nomogram. The y-axis represents the observed overall survival rate estimated by the Kaplan–Meier method. Patients were divided into four groups of equal size based on the predicted overall survival rate. The dashed line shows the ideal line, which represents that the predicted overall survival rate is the same as the observed overall survival rate. The dots show the median values and error bars show 95% CIs. The Kaplan–Meier curves according to prediction by the nomogram are shown (D). PBSCT, peripheral blood stem cell transplantation; 1-yr, 1-year; OS, overall survival
understood. It was reported that haploidentical transplantation for refractory/relapsed AML was associated with shorter GVHD-free relapse-free survival, inferior LFS, and shorter OS than transplantation from an HLA-identical sibling, mainly due to infections, whereas another report showed no differences in GVHD-free relapse-free survival, LFS, or OS between haploidentical transplants and transplants from HLA-identical siblings for AML in first CR with high-risk cytogenetics. As our data could be used to estimate OS adjusted for the characteristics of patients after allo-HCTs, except for haploidentical transplantation, it may be useful for a reference when haploidentical results are evaluated.

It is important to note the limitations of this study. First, the regimens for haploidentical transplantation were heterogeneous in our cohort because of limited previous evidence, and the number of transplantations was insufficient to build an accurate prognostic model. Therefore, haploidentical transplantation was excluded. Second, in this study, we used a Japanese cohort, which differs from other populations in some aspects. For example, in the US, most CBTs in adults are performed with a single unit. Moreover, for unrelated transplantations, in the US, most grafts are derived from peripheral blood, whereas in Japan, most grafts are derived from bone marrow. Such differences may limit the generalizability of the findings and prognostic models. Therefore, our findings must be validated using data from other countries. Third, comprehensive genomic studies on AML using next-generation sequencing have recently revealed the relevance of clinical outcomes. However, data on somatic mutations were not available. Thus, in future studies, genomic information should be incorporated for developing effective prognostic models.

In conclusion, we designed and validated novel nomograms and a web application to predict the OS of patients with AML undergoing allo-HCTs in non-CR, indicating that the performance of our models was at least as favorable as that of the previous scoring system. These prognostic models can be helpful in estimating the benefits and risks of a patient and can provide clues as to whether to conduct transplantation when encountering a patient with AML in non-CR. Furthermore, the web application enables us to easily compare the OS in Japan. CBTs in adults are performed with a single unit.
a variety of settings; therefore, the study can be useful for designing prospective clinical trials. Moreover, our study revealed that the use of multiple chemotherapeutic drugs in CBT greatly contributed to the prognosis of patients with non-CR AML.

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CONFLICT OF INTEREST
The authors have no conflict of interest associated with this work.

ETHICAL STATEMENT
This study complied with the ethical principles of the Declaration of Helsinki and was approved by the data management committees of TRUMP and the Ethics Committee of Kyoto University, where this study was conducted. Written informed consent was obtained from all patients.

DATA AVAILABILITY STATEMENT
The data were obtained from the TRUMP database and are not publicly available.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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