Artificial intelligence-based predictive model for relapse in acute myeloid leukemia patients following haploidentical hematopoietic cell transplantation

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ABSTRACT

Background and Objectives: Relapse is one of the most critical causes of transplant failure in patients with acute myeloid leukemia (AML) receiving haploidentical-related donor (HID) hematopoietic stem cell transplantation (HSCT). We aimed to develop an artificial intelligence (AI)-based predictive model for post-transplant relapse in patients with AML receiving HID HSCT. **Methods:** This study included patients with consecutive AML (aged ≥ 12 years) receiving HID HSCT in complete remission (CR). We randomly selected 70% of the entire population (n = 665) as the training cohort for developing the model and nomogram, which were both evaluated using data from the remaining 30% of the patients (validation cohort, n = 286). Furthermore, the model was validated in an independent cohort (n = 213) and in the clinical practice of five experienced clinicians. **Results:** Five variables (AML risk category, number of courses of induction chemotherapy for first CR, disease status, measurable residual disease before HSCT, and blood group disparity) were included in the final model (*i.e.*, PKU-AML model). The concordance index of the nomogram was 0.707. The Hosmer−Lemeshow test showed a good fit for this model (P = 0.205). The calibration curve was close to the ideal diagonal line, and decision curve analysis showed a significantly better net benefit for this model. The reliability of our prediction nomogram was demonstrated in a validation cohort, an independent cohort, and in clinical practice. **Conclusions:** Our PKU-AML model can predict the relapse of patients with AML receiving HID HSCT in CR, providing an effective tool for the early prediction and timely management of post-transplant relapse.

Key words: acute myeloid leukemia, haploidentical, hematopoietic stem cell transplantation, relapse, interferon-α, preemptive

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INTRODUCTION

Acute myeloid leukemia (AML), which is the most common form of acute leukemia in adults, has the shortest survival.[1] Allogeneic hematopoietic stem cell transplantation (HSCT) is the most important curative therapy for AML, which can significantly improve the survival of patients with AML.[2-5] Because a human leukocyte antigen (HLA)-matched sibling donor (MSD) is usually unavailable and the

donor pools of the Unrelated Donor Program are small, haploidentical-related donors (HIDs) are important and even represent the unique option of donors for patients with AML in China.[2,3,6] Since 2019, the proportion of HIDs has increased to > 60% among the allogeneic HSCT recipients and they have become the most frequent donors in China.[6,7] HID HSCT shows superior clinical outcomes compared to chemotherapy as a post-remission treatment of intermediate- and high-risk AML in first complete remission (CR).[8,9] In addition, some multicenter studies have reported that HID HSCT can achieve outcomes similar to[10,11] or even better than[12,13] those of MSD HSCT for patients with AML in CR1, which suggests a stronger graft-versus-leukemia (GVL) effect with HID HSCT than MSD HSCT.[14]

However, the incidence of post-transplant relapse is approximately 20% in patients with AML receiving HID HSCT in CR1,[8-11] suggesting that relapse is still inevitable and is one of the most critical causes of transplant failure.[15,16] Many studies have reported risk factors for relapse after HID HSCT; however, the results are controversial. For example, some authors have reported that the incidence of relapse was as high as 30% in patients with AML with positive measurable residual disease (MRD), which was significantly higher than that in those who were MRD-negative before HID HSCT.[17-19] However, some studies have observed that the incidence of relapse was comparable between patients with AML with or without MRD before HID HSCT.[20-22] In addition, remission status (*e.g.*, beyond CR1 *vs.* CR1) before HID HSCT may be associated with post-transplant relapse,[23] although this has not been supported by other studies.[24] Therefore, single risk factors are insufficient to predict relapse after HID HSCT.

Comprehensive prognostic models have been established to predict clinical outcomes after,[25-30] and some (*e.g.*, disease risk index [DRI],[31] hematopoietic cell transplantation specific comorbidity index [HCT-CI],[32] and disease risk comorbidity index [DRCI][16]) could also predict relapse in HID HSCT recipients. However, these studies included patients with hematological malignancies other than AML. Recently, a prognostic model focusing on patients with AML was established;[33] however, the number of HID HSCT recipients was small. Additionally, most of these studies used survival or non-relapse mortality as the primary endpoint to establish the model. To date, no comprehensive prognostic model has focused on post-transplant relapse in patients with AML receiving HID HSCT. To improve decision-making and determination of candidacy for more intensive relapse prophylaxis, a prediction model for relapse is necessary.

Thus, we aimed to develop an artificial intelligence (AI)-based predictive model (*i.e.*, PKU-AML model) for post-transplant relapse in AML patients receiving HID HSCT in CR.

METHODS

Study design and participants

This study was conducted using the transplant database of Peking University (PKU), Institute of Hematology. The inclusion criteria were as follows: (1) patients with AML; (2) ≥ 12 years of age; (3) received HID HSCT in CR between January 1, 2017, and March 5, 2021; and (4) having complete medical information (Figure 1). The final follow-up was conducted on October 31, 2022. The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Institutional Review Board of Peking University People's Hospital.

Transplant regimen

The protocols of major preconditioning regimen,[10,34] graft-versus-host disease (GVHD) prophylaxis (*i.e.*, antithymocyte globulin [ATG], cyclosporine A, mycophenolate mofetil, and short-term methotrexate), and infection prophylaxis are presented in Supplemental Information.[35-40] MRD before and after HID HSCT was detectable by multiparameter flow cytometry (MFC) and a lower limit of detection (LOD) of 0.01% was targeted (Supplemental information).[21] Patients who showed MRD occurrence after HID HSCT received preemptive immunotherapy including donor lymphocyte infusion (DLI)[41] or interferon-α treatment[42] as previously reported (Supplemental information).

Data collection

The collected data included demographic characteristics of the patients (age, sex, and comorbidities), characteristics of leukemia and treatment before HSCT (white blood cell count and AML risk category at diagnosis, number of courses of induction chemotherapy for first CR, time from diagnosis to HSCT, and disease status before HSCT), characteristics of transplantation (donor/recipient sex-matched, donor/recipient relation, blood group disparity, preconditioning regimen, graft type, and mononuclear cell and $CD34^+$ cell counts in the graft), and MRD status before HSCT (Figure 1, Supplementary Table S1).

Building machine learning models and nomogram

The proposed method consisted of the following three steps: First, feature selection was conducted based on the entire dataset (n = 951). We then randomly selected 70% of the entire population (n = 665) as the training cohort for developing the machine learning model and nomogram, and the remaining 30% (n = 286) were used as the validation cohort.

Therefore, a predictive model was established for the

training cohort. Multivariate logistic regression analysis was used for feature selection. We included variables with coefficients having P values < 0.1 as the input for the machine learning model.

A logistic regression model was selected as the machine learning model to predict relapse. It was developed using data from a training cohort. This model assumes that the probability of relapse (P_{x_i}) can be computed based on Equation (1) using input variables (x_i), where w and b can be trained from the training cohort. We chose w and b to minimize the loss function (with l_2 regularization) represented in Equation (2). When a specific instance of data is entered, the logistic regression model yields a probability (between 0 and 1) of relapse. After obtaining the probability, determining the threshold for producing negative or positive results remains important. We constructed receiver operating characteristic (ROC) curves and calculated the g-means for each threshold. The threshold with the highest g-mean was selected.

$$P_x = \frac{1}{(1 + exp[-(w^T x + b)])} \cdots (1)$$

$$Loss = -\frac{1}{n}\left[\sum_{i=1}^{n} y_i(log(p_{x_i})) + (1 - y_i)log(1 - p_{x_i})\right] + w^T w + b^2 \cdots (2)$$

The accuracy, area under the curve (AUC), sensitivity, and specificity were computed for the training cohort.

A nomogram was developed using the well-trained logistic regression model. We first assigned each variable a point between 0 and 100 based on their estimated coefficients and ranges. We then summed all the points of the variables and used a sigmoid function to map the probabilities.[43] Finally, we drew a horizontal line as a representative of the threshold to facilitate probability assignment. Additionally, we distinguished the nominal variables using dashed axes and applied grids for computational assistance. The workflow is shown in the Supplemental Information.

Validated machine learning models and nomogram

We validated the machine learning models and nomogram in the validation cohort, which was further validated in an independent historical cohort (n = 213).[16] The accuracy, AUC, sensitivity, and specificity were computed for both cohorts. Calibration and decision curves were plotted to determine the usefulness of the nomogram. We also compared the AUCs of our AI-based model with those of other existing predictive models.

Additionally, we validated the discrimination and clinical usefulness[44] of the nomogram by applying it clinically. We developed a questionnaire based on the clinical information and nomogram (Supplemental Information). Five experienced clinicians received the questionnaires and were required to compute the relapse probabilities and binary outcomes (relapse or non-relapse) based on clinical information and nomogram; each clinician was required to evaluate 10 patients. We plotted a calibration figure and confusion matrix to check the agreement between the clinical applications and the real performance of the nomogram.

Definitions

The AML risk category was assessed using the European LeukemiaNet (ELN) genetic risk.[45] The definitions for engraftment, relapse, non-relapse mortality (NRM), event-free survival (EFS), leukemia-free survival (LFS), and overall survival (OS) are shown in Supplemental information.

Statistical analysis

Data were censored at the time of death or last available follow-up. The primary outcome was the relapse rate. Secondary outcomes included MRD, EFS, NRM, LFS, and OS. The minimum sample size was 472 according to calculations carried out in PASS version 11.0.7 (α = 0.05, power[1–β] = 0.9, and R2 = 0.15). In this study, data from 665 patients in the training cohort were used to construct the nomogram. Mann–Whitney U-test was used to compare continuous variables, and χ^2 and Fisher's exact tests was used for categorical variables. The Kaplan–Meier method was used to estimate the probability of survival. We used competing risk analyses to calculate the cumulative incidence of MRD occurrence, NRM, and relapse.[46] Testing was two-sided, with statistical significance set at P < 0.05. Statistical analyses were performed using R software (version 4.2.0) (http://www.r-project.org), Python (version 3.9.12), and SPSS 26.0 software (SPSS, Chicago, IL).

RESULTS

Patient characteristics

Characteristics of the 951 patients are presented in Table 1. Neutrophil engraftment was achieved by 948 (99.6%) patients, and the median time from transplantation to neutrophil engraftment was 13 days (range, 6–33 days). Platelet engraftment was achieved by 900 (94.6%) patients, and the median time from transplantation to platelet engraftment was 16 days (range, 5–184 days). Notably, 516 (54.2%) patients developed acute graft versus host disease (aGVHD) after allo-HSCT. The cumulative incidences of grade I–IV, grade II–IV, and grade III–IV aGVHD 100 days after allo-HSCT were 54.3% (95% CI, 51.1%–57.5%), 23.5% (95% CI, 20.8%–26.2%), and 7.5% (95% CI, 5.8%–9.2%), respectively. Furthermore, 401 (42.1%) patients developed chronic GVHD (cGVHD) after allo-HSCT. The cumulative incidences of moderate to severe and severe

Table 1: Patient characteristics

Characteristics	Adults			Children		
	Training cohort (*n* = 617)	Validation cohort (*n* = 261)	*P* value	Training cohort (*n* = 48)	Validation cohort (*n* = 25)	*P* value
Median age at allo-HSCT, years (range)	35 (18-66)	34 (18-63)	0.301	15 (12-17)	16 (12-17)	0.164
Gender, *n* (%)			0.064			0.451
Male	352 (57.1)	131 (50.2)		27 (56.3)	17 (68.0)	
Female	265 (42.9)	130 (49.8)		21 (43.8)	8 (32.0)	
Number of courses of induction for first CR, median (range)	1 (1-4)	1 (1-5)	0.484	1 (1-5)	1 (1-5)	0.506
Disease status before allo-HSCT, *n* (%)			0.958			0.323
CR1	433 (70.2)	226 (86.6)		35 (72.9)	21 (84.0)	
CR2	146 (23.7)	33 (12.6)		9 (18.8)	4 (16.0)	
≥ CR3	38 (6.2)	2 (0.8)		4 (8.4)	0 (0)	
AML risk category at diagnosis, *n* (%)			0.799			0.861
Favorable	112 (16.8)	50 (19.2)		4 (8.3)	3 (12.0)	
Intermediate	353 (57.2)	152 (58.2)		35 (72.9)	17 (68.0)	
Poor	152 (24.6)	59 (22.6)		9 (18.8)	5 (20.0)	
HCT-CI scores before allo-HSCT, *n* (%)			0.244			0.174
0 (low risk)	460 (74.6)	181 (69.3)		44 (91.7)	19 (76.0)	
1–2 (intermediate risk)	125 (20.3)	66 (25.3)		3 (6.3)	4 (16.0)	
≥ 3 (high risk)	32 (5.2)	14 (5.4)		1 (2.1)	2 (8.0)	
MFC before HSCT, *n* (%)			0.334			0.110
Negative	473 (76.7)	187 (71.6)		36 (75.0)	20 (80.0)	
≥ 0.01%, < 0.1%	22 (3.6)	11 (4.2)		3 (6.3)	0	
≥ 0.1%, < 1% =2	83 (13.5)	47 (18.0)		4 (8.3)	5 (20.0)	
≥ 1% = 3	39 (6.3)	16 (6.1)		5 (10.4)	0	
Conditioning regimen, *n* (%)			0.294			NA
Chemotherapy-based regimen	609 (98.7)	260 (99.6)		48 (100)	25 (100.0)	
TBI-based regimen	8 (1.3)	1 (0.4)		0	0	
Donor/recipient gender matched, *n* (%)			0.290			0.685
Female donor/male recipient combination	500 (81.0)	220 (84.3)		44 (91.7)	22 (88.0)	
Others	117 (19.0)	41 (15.7)		4 (8.3)	3 (12.0)	
Donor/recipient relation, *n* (%)			0.057			0.423
Maternal donor	37 (6.0)	231 (88.5)		5 (10.4)	24 (96.0)	
Collateral donor	14 (2.3)	16 (6.1)		0	1 (4.0)	
Others	566 (91.7)	14 (5.4)		43 (89.6)	0	
Blood group disparity, *n* (%)			0.333			0.758
matched	347 (56.2)	140 (53.6)		23 (47.9)	14 (56.0)	
minor mismatched	126 (20.4)	48 (18.4)		12 (25.0)	6 (24.0)	
major mismatched or minor and major mismatched	144 (23.3)	73 (28.0)		13 (27.1)	5 (20.0)	
MNC counts in graft, median (range, $\times 10^8$/kg)	8.46 (2.18-19.49)	8.59 (2.18-14.9)	0.415	8.90 (6.66-17.27)	8.61 (5.81-15.72)	0.429
$CD34^+$ cell counts in graft, median (range, $\times 10^6$/kg)	2.45 (0.27-34.38)	2.31 (0.33-9.57)	0.342	2.54 (0.24-7.10)	1.96 (0.62-17.86)	0.368
Median follow-up after HSCT, days (range)	941 (24-2190)	1034 (21-2190)	0.056	894.5 (24-2190)	1206 (180-1955)	0.436

Allo-HSCT, allogeneic hematopoietic stem cell transplantation; CR, complete remission; HLA, human leukocyte antigen; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; TBI, total body irradiation; MNC, mononuclear cell.

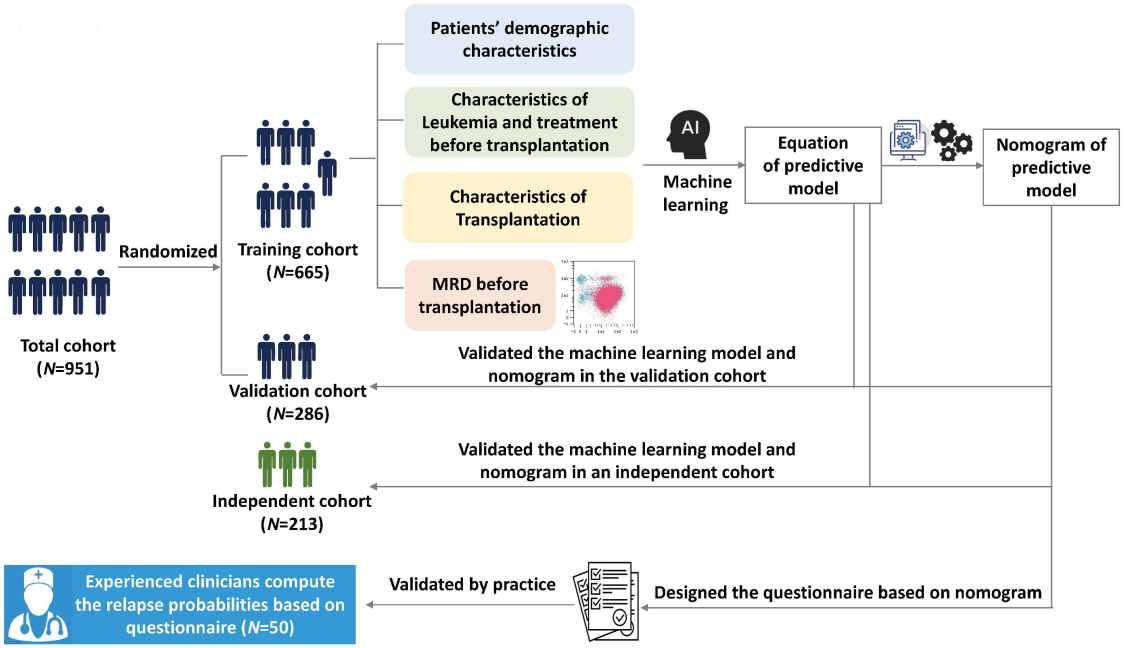


Figure 1: Flow chart of the study and data analysis process.

cGVHD at three years after allo-HSCT was 24.0% (95% CI, 21.2%–26.8%) and 8.2% (95% CI, 6.4–10.0%), respectively. Twenty-six patients (24.7%) with FLT3-ITD mutations simultaneously received sorafenib as a maintenance therapy. The median duration of maintenance therapy was 28 days (range, 11–210 days).

Furthermore, 111 patients experienced relapse, and the median time from HSCT to relapse was 220 days (range, 22–1738 days). Eighty patients died of NRM. The median follow-up duration was 945 days (range, 21–2190) days. The probabilities of relapse, NRM, LFS, and OS at three years after HID HSCT were 12.5% (95% CI, 10.2%–14.7%), 8.7% (95% CI, 6.8%–10.5%), 78.9% (95% CI, 76.2%–81.7%), and 83.2% (95% CI, 80.7%–85.7%), respectively.

Development of machine learning model

Five variables (AML risk category at diagnosis, number of courses of induction chemotherapy for first CR, disease status before HSCT, measurable residual disease before HSCT, and blood group disparity; Supplementary Table S2 and S3, Figure 2A and 2B) were included in the PKU-AML model, and the equation was as follows:

$$\text{Probability (relapse)} = \frac{1}{1 + exp(-Y)}$$

where Y = 0.5677 × (AML risk category at diagnosis) + 0.0690 × (number of courses of induction for first CR) + 0.4583 × (disease status before HSCT) + 0.4061 × (MFC before HSCT) – 0.1623 × (blood group disparity) – 2.9641.

The threshold of probability was set at 0.1106, and the g-mean was 0.668. The force plot (Figure 2C and 2D) illustrates how the features contributed to the prediction of the model for all observations. The sensitivity, specificity, AUC, and accuracy scores of the training cohort are shown in Figure 2E and were 0.7000, 0.6250, 0.7071, and 0.6329, respectively, in the validation cohort (Figure 2F).

Development of prediction nomogram

A nomogram was designed using the training cohort based on the machine learning model (Figure 3A), and the validation cohort showed that the concordance index was 0.707 (95% CI 0.645–0.770). The calibration plots in the training and validation cohorts (Figure 3B and 3C) revealed satisfactory agreement between the nomogram prediction and actual observations for the probability of relapse. Based on the decision curve analysis (Figure 3D and 3E), if the threshold probability was > 0.1, using this nomogram to predict relapse would provide a greater net benefit than either a treat-all-patients scheme or a treat-none scheme. The optimal cutoff value of the total nomogram scores was determined to be 95 (Figure 3F), and the patients were separated into low- and high-risk groups. The Hosmer−Lemeshow test showed that the model had a good fit ($P = 0.205$).

In the training cohort, the three-year cumulative incidence of relapse after HID HSCT were 18.9% (95% CI, 13.8%–24.0%) and 9.2% (95% CI, 6.1%–12.2%) in the high- and low-risk groups, respectively ($P < 0.001$; Figure 3G). In the validation cohort, the three-year cumulative

Table 2: The three-year probability of clinical outcomes after HID HSCT between the low- and high-risk groups.

	High-risk group	Low-risk group	*P* value
	Cumulative incidence (95%CI)	Cumulative incidence (95%CI)	
MRD occurrence	30.8 (26.0–35.6)	23.2 (19.6–26.7)	0.011
EFS	55.8 (50.8–61.2)	65.4 (61.4–69.5)	0.003
NRM	8.0 (4.4–11.6)	9.1 (6.3%–11.9)	0.561
LFS	73.0 (68.5–77.9)	82.7 (79.5–86.0)	<0.001
OS	78.6 (74.4–83.1)	86.1 (83.2–89.2)	0.004

CI, confidence interval; HID haploidentical related donor; HSCT, hematopoietic stem cell transplantation; MRD, measurable residual disease; EFS, event free survival; NRM, non-relapse mortality; LFS, leukemia-free survival; OS, overall survival.

incidence of relapse after HID HSCT were 19.5% (95% CI, 11.9%–27.1%) and 5.9% (95% CI, 2.1%–9.7%) in the high- and low-risk groups, respectively ($P < 0.001$; Figure 3H). We observed that the three-year cumulative incidence of relapse was significantly higher in high-risk patients than in low-risk patients in all subgroups and was as high as 26.8% in high-risk patients who received HID HSCT after CR1 (Supplementary Table S4).

Validation of the PKU-AML model in an independent cohort

A total of consecutive 213 patients with AML were included, and their characteristics are shown in Supplementary Table S5. The AUC and accuracy scores of the PKU-AML model were 0.7074 and 0.8685, respectively (Figure 4A). The concordance index was 0.7074 (95% CI 0.300–1.000). The calibration plots (Figure 4B) revealed a satisfactory agreement between the nomogram prediction and the actual observation of the probability of relapse. Based on decision curve analysis, if the threshold probability was > 0.1, using this nomogram to predict relapse would provide more net benefit than either a treat-all-patient scheme or a treat-none scheme (Figure 4C). The three-year cumulative incidence of relapse after HID HSCT were 16.9% (95% CI, 10.7%–23.0%) and 3.6% (95% CI, 0–8.7%) in the high- and low-risk groups, respectively, ($P = 0.018$; Figure 4D) in this cohort.

Validation of the nomogram in clinical practice

A total of 50 questionnaires were returned. The calibration curve obtained from the questionnaires (Figure 5A) showed that the nomogram-maintained consistency with the predictive probability when applied clinically. It tended to slightly overestimate the probability of relapse when the actual probability was small. The confusion matrix (Figure 5B) illustrated an accuracy of 0.92 for the actual usage. Among the four false-positive instances, three were from one patient predicted by the nomogram with a relapse probability of 0.1006, which was close to the threshold of 0.1106. However, the proportion for patients with nomogram-predicted relapse probability between 0.10 and 0.11 was only 0.031. In this case, false distinguishments rarely occurred.

Comparison of predictive value between our PKU-AML model and other existing models

Five existing models were included: Hematopoietic cell transplantation comorbidity index (HCI-CI) score, HCT-CI/Age score,[47] AML-specific disease risk group,[33] haploidentical European Group for Blood and Marrow Transplantation (EBMT) risk score (haplo-EBMT),[26] and haploidentical DRCI (haplo-DRCI).[16] The ROC and precision-recall curves of our PKU-AML model and these existing models for relapse prediction are shown in Figure 6 and Supplementary Table S6. The AUC and average precision of our PKU-AML model were superior to those of the other existing models for predicting post-transplant relapse after HID HSCT. We compared the PKU-AML model with the MRD before HSCT and ELN genetic risk. The AUC and average precision of our model were superior in predicting post-transplant relapse after HID HSCT (Supplementary Figure S1).

Validation of the prediction nomogram for other outcomes after HID HSCT

As the training cohort was developed based on relapse and not on other outcomes, we combined the training cohort with the validation cohort to analyze secondary outcomes.

Notably, 244 patients developed MRD after HID HSCT. Low-risk patients showed a lower cumulative incidence of MRD occurrence than high-risk patients (Table 2 and S7), and the cumulative incidence of MRD occurrence at three years after HID HSCT were 30.8% (95% CI 26.0%–35.6%) and 23.2% (95% CI 19.6%–26.7%) for the high- and low-risk group, respectively ($P = 0.011$, Supplementary Figure S2). The low-risk group showed a lower probability of EFS than the high-risk group (Tables 2 and S8), and the probability of EFS at three years after HID HSCT were 55.8% (95% CI 50.8%–61.2%) and 65.4%

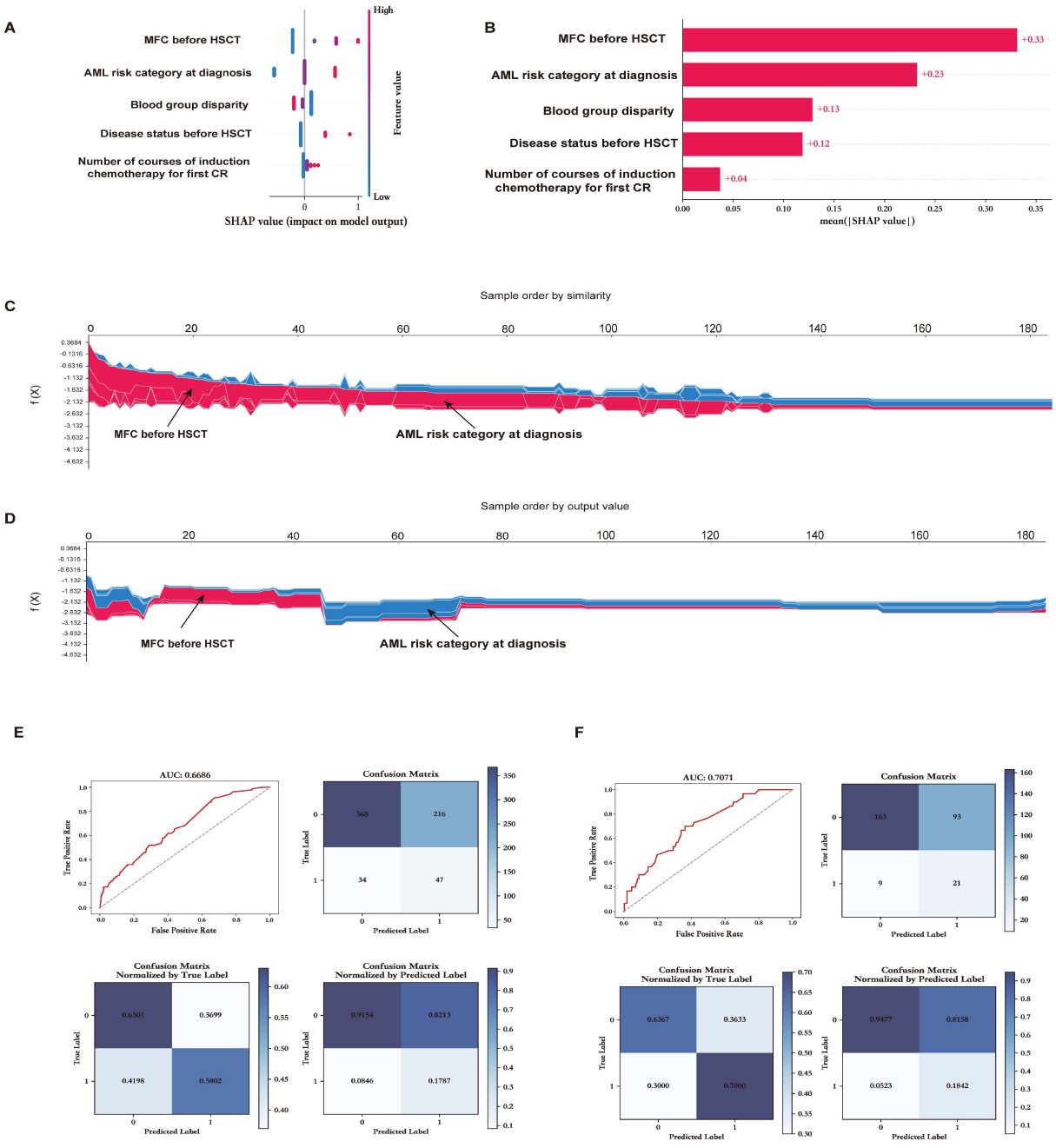
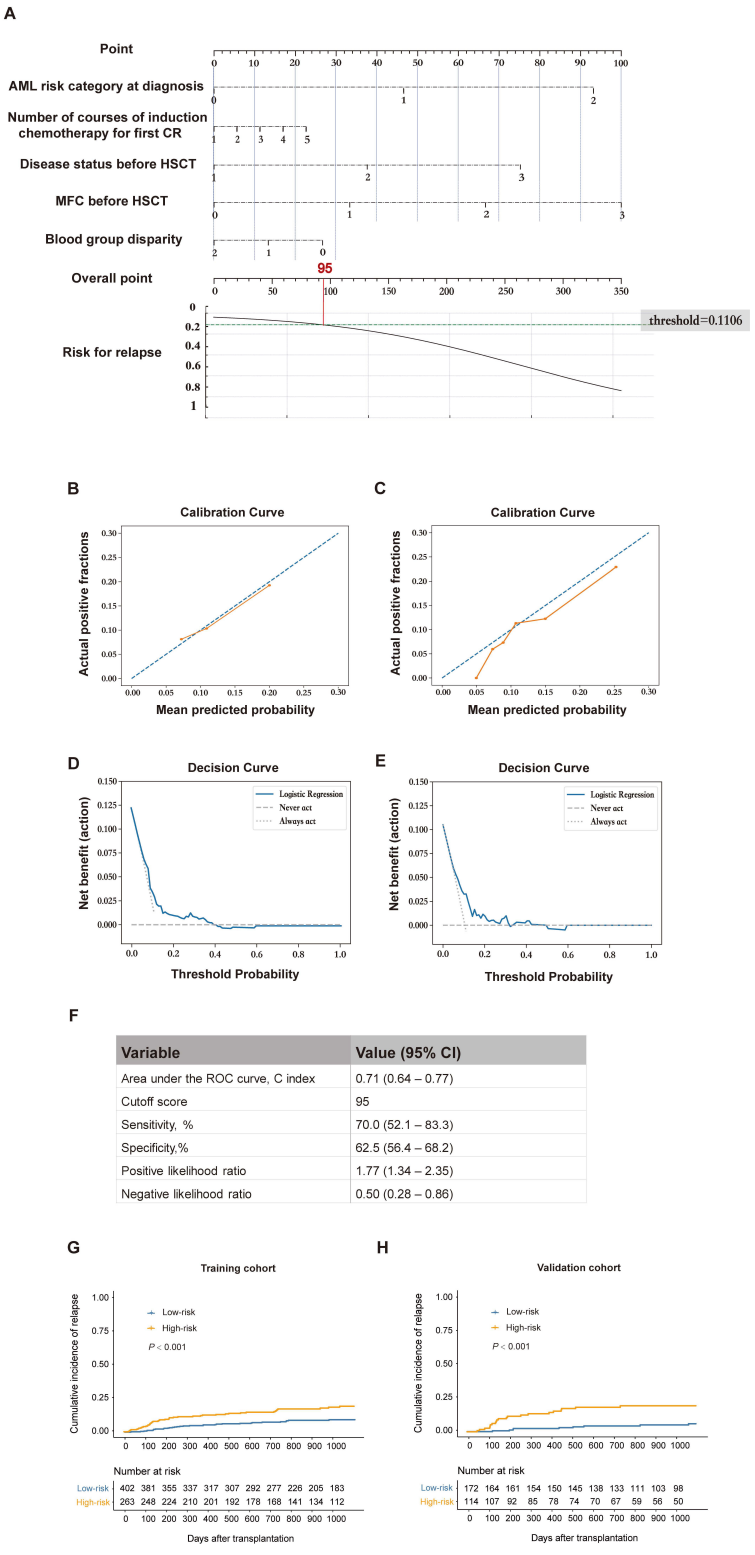


Figure 2: The process of model development. SHAP value summary plot for the logistic regression model. SHAP value (x-axis), feature (y-axis), feature values (color). Explanation: Each point on graph is a feature and corresponding SHAP values of an instance, the position on the y-axis is determined by the feature, the position on the x-axis is determined by the SHAP value, the color represents the feature value from small to large, and the overlapping points are on the y-axis direction, so we can understand the distribution of SHAP values for each feature. (A) SHAP = SHapley Additive exPlanations. The mean absolute SHAP values of the top 5 features (B). The x-axis (instances) values are sorted by (C) similarity, and (D) output values. Values higher on the vertical axis indicate higher likelihood of relapse. Values lower on the vertical axis indicate a lower likelihood of relapse. Values that are red drive the relapse risk up. Values that are blue drive the relapse risk down. Receiver operating characteristic (ROC) curve and confusion matrix for relapse model in the training (E) and validation cohorts (F).

(95% CI 61.4%–69.5%) for the high- and low-risk groups, respectively ($P = 0.003$, Supplementary Figure S2). A total of 210 patients received preemptive immunotherapies, 173 patients received preemptive Interferon (IFN) α treatment, and 37 patients received preemptive DLI. The cumulative incidence of relapse at three years after preemptive immunotherapy were 33.7% (95% CI, 22.5%–44.9%) and 15.9% (95% CI, 9.1%–22.7%) in the high- and low-risk groups, respectively ($P = 0.011$). The probability of LFS at three years after preemptive immunotherapy were 60.6%



Variable	Value (95% CI)
Area under the ROC curve, C index	0.71 (0.64 – 0.77)
Cutoff score	95
Sensitivity, %	70.0 (52.1 – 83.3)
Specificity,%	62.5 (56.4 – 68.2)
Positive likelihood ratio	1.77 (1.34 – 2.35)
Negative likelihood ratio	0.50 (0.28 – 0.86)

Figure 3: Nomogram for estimating the probability of relapse and its predictive performance. Nomogram predicting the probability of relapse for AML patients receiving haploidentical hematopoietic stem cell transplantation in complete remission based on training cohort. AML risk category at diagnosis: favorable = 0, intermediate = 1, adverse = 2; number of courses of induction chemotherapy for first CR: numerical value; disease status before HSCT: CR1 = 1, CR2 = 2, ≥ CR3 = 3; MFC before HSCT: negative = 0, ≥ 0.01% but < 0.1% = 1, ≥ 0.1% but <1% = 2; ≥ 1% = 3; blood group disparity: matched = 0, minor mismatched = 1, major mismatched or minor and major mismatched = 2 (A). Calibration plot of actual probability versus predicted probability of relapse based on training (B) and validation cohort (C). Decision curve analysis demonstrating the net benefit associated with the use of our model for predicting relapse based on training (D) and validation cohort (E). Accuracy of the prediction score of the nomogram for estimating the probability of relapse (F).

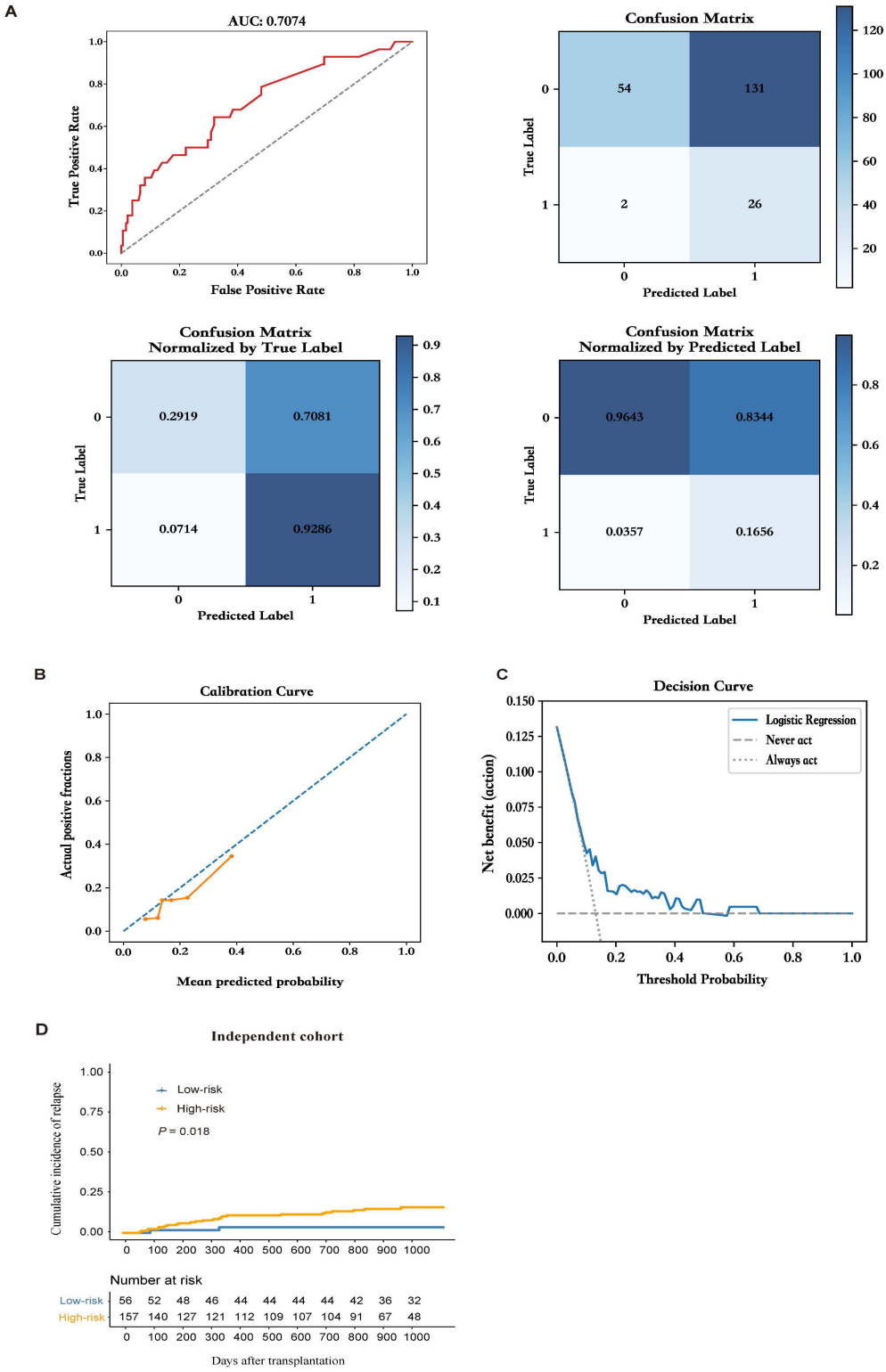


Figure 4: Validation of AI-based model in an independent cohort. Receiver operating characteristic (ROC) curve and confusion matrix for relapse model in the independent cohorts (A). Calibration plot of actual probability versus predicted probability of relapse based on independent cohort (B). Decision curve analysis demonstrating the net benefit associated with the use of our model for predicting relapse based on independent cohort (C). The 3-year cumulative incidence of relapse after transplantation in the low- and high-risk groups in independent cohort (D).

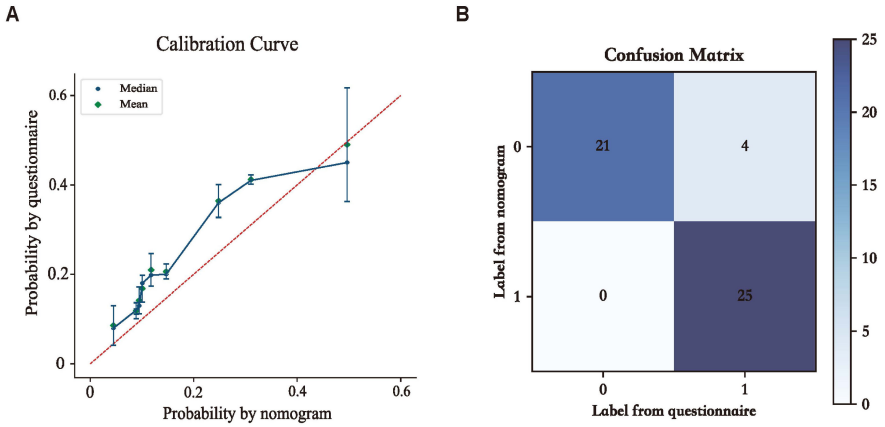


Figure 5: Clinical performance for nomogram. Calibration plot of probability from questionnaire versus actual probability of relapse based on nomogram (A). Confusion matrix of relapse outcome from questionnaire versus actual outcome of relapse based on nomogram (B).

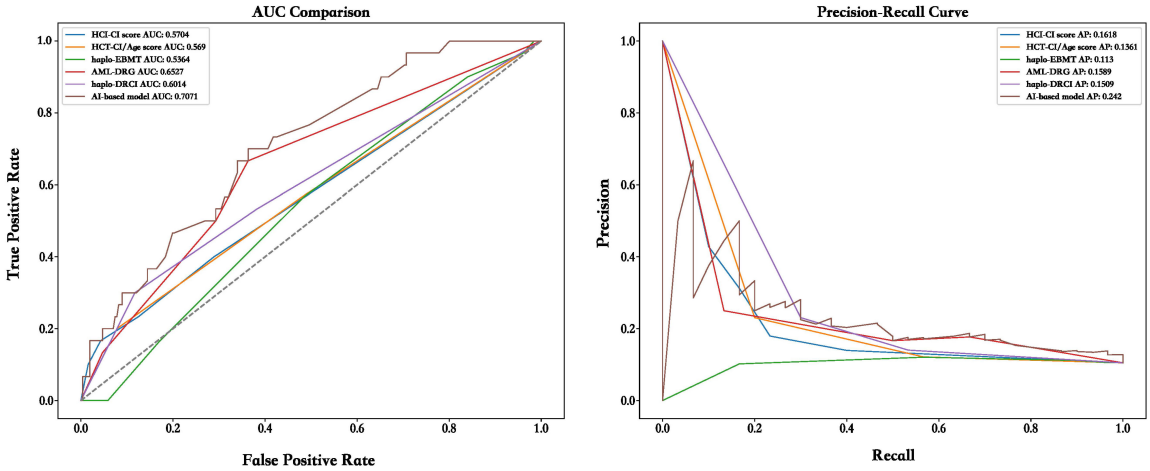


Figure 6: Models performance evaluation and comparisons in validation cohort. Receiver operating characteristic (ROC) curve (A) and precision-recall curves (B) of our AI-based model and other existing models for relapse prediction.

(95% CI, 50.3%–73.1%) and 80.2% (95% CI, 73.1%–88.1%) in the high- and low-risk groups, respectively (P = 0.006). In patients who received preemptive IFN-α therapy, the cumulative incidence of relapse at three years after IFN-α therapy were 23.8% (95% CI, 11.9%–35.6%) and 10.1% (95% CI, 4.1%–16.1%) in the high- and low-risk groups, respectively (P = 0.054). The probability of LFS at three years after IFN-α therapy were 68.8% (95% CI, 57.4%–82.5%) and 85.4% (95% CI, 78.6%–92.8%) in the high- and low-risk groups, respectively (P = 0.023). The high-risk group showed a trend toward a higher incidence of relapse and lower probability of LFS than the low-risk group in patients receiving preemptive DLI.

The probabilities of LFS and OS at three years after HID HSCT for patients in the high-risk group were significantly lower than those for patients in the low-risk group (Table 2). The three-year cumulative incidence of NRM after HID HSCT was comparable between groups (Table 2).

DISCUSSION

Based on a large-sample cohort using relapse as the primary endpoint, we established the PKU-AML model for post-transplant relapse in patients with AML receiving HID HSCT, which was validated in an independent cohort and in clinical practice. It can also predict the occurrence of LFS, OS, and MRD after HID HSCT and the outcomes after preemptive immunotherapies. The AUC of the other existing models ranged from 0.536 to 0.653, and the average precision of these models ranged from 0.113 to 0.162. Therefore, existing models are not sufficient

to predict post-transplant relapse in patients with AML receiving HID HSCT, suggesting that relapse prediction is indeed difficult for these patients. Our PKU-AML model predicted relapse more efficiently than existing models for HID HSCT recipients. To the best of our knowledge, this is the first comprehensive model for relapse prediction in a disease-specific population of patients with AML undergoing HID HSCT for CR.

Current nomogram development methods match the overall points and predictive probabilities through an imbalanced-scale axis, which may lead to misestimation of probabilities. To alleviate this problem, the nomogram developed in this study substituted this matching strategy with risk graph (graph beneath the "Overall Point" axis). In addition, the auxiliary lines among the "Point" axis and other axes of variables (blue dashed vertical lines) also assist the computation of the nomogram. Furthermore, the graphic design for the axes of the variables was improved. Different styles of axes represent different variable types; for instance, dashed lines represent nominal variables and solid lines represent continuous variables. These assistant designs significantly improved the speed and accuracy of the calculations. Assuming that n variables are included in the logistic regression model, the computational complexity of computing the logistic regression by hand is at least O (n^2). In contrast, the complexity of computation using the nomogram is O(n), which drastically reduces the difficulty of applying the logistic regression model. The calibration curve and confusion matrix showed excellent performance for clinical use.

Posttransplant relapse is simultaneously influenced by several risk factors. For example, Jentzsch *et al.*[48] reported that ELN intermediate-risk patients who were MRD-positive during second remission and underwent HSCT showed the highest incidence of relapse, even higher than that in ELN high-risk patients who were MRD-negative during second remission and underwent HSCT. This suggests that combining multiple risk factors can predict post-transplant relapse more effectively and establishing a comprehensive prognostic model.

MRD can significantly increase the risk of post-transplant relapse.[49-51] In a study by Liu *et al.*,[52] patients with AML with increasing MRD after HID HSCT showed the highest incidence of relapse (100%) than those with decreasing MRD (19.2%) or MRD-negative (9.6%) peri-HSCT. Our nomogram predicted the occurrence of MRD after HID HSCT, which might explain why it can effectively predict post-transplant relapse.

Considering the fact that our nomogram could predict relapse after HID HSCT, which methods could further decrease the risk of relapse is important to improve the outcomes of high-risk patients. Some intensified conditioning regimens (*e.g.*, cladribine-based[53] or decitabine-based[54] regimen) have been used in patients with advanced-stage acute leukemia. Therefore, high-risk patients with AML identified by our prediction nomogram may also benefit from these intensified conditioning regimens; however, their safety should be further confirmed in HID HSCT recipients.

Prophylactic DLI has been reported to decrease relapse in patients with refractory/relapsed acute leukemia.[55,56] Based on this, Yan *et al.*[57] developed a total therapy strategy (*i.e.*, prophylactic DLI with multiple DLIs subsequently administered based on MRD and GVHD status) that could decrease relapse and improve long-term LFS in refractory/relapsed patients with AML. Maintenance therapy, including additional agents targeting specific molecular aberrations (*e.g.*, FLT3 inhibitors[53]), hypomethylating agents, and certain new drugs (*e.g.*, venetoclax), may help decrease relapse and improve the survival of patients with advanced-stage AML.[58,59] Therefore, the efficacy and safety of these maintenance therapy strategies require further studies in high-risk HID HSCT recipients identified by our prediction nomogram.

Although preemptive immunotherapy can decrease the risk of relapse and improve the survival of patients with MRD,[49] we observed that nearly one-third of the high-risk patients who showed MFC positivity after allo-HSCT experienced relapse even after receiving preemptive immunotherapy. This suggests that preemptive immunotherapies may not overcome the poor prognostic significance of MRD positivity in patients with AML categorized into high-risk groups by PKU-AML model. Considering that patients with a low disease burden are more likely to benefit from a second HSCT,[60] using it for the upfront management of high-risk patients identified by our PKU-AML model may be reasonable when they experience MRD after HID HSCT. In addition, other protocols (*e.g.*, venetoclax, PD-1 inhibitors, daratumumab, and selinexor) should be identified.

We chose the final follow-up date as the time point for assessing relapse to determine whether relapse occurred within an observable timeframe. We chose this time point to explore whether relapse occurred during the foreseeable time period. In the study of Ji *et al.*[61], the median follow-up period was 56.0 months (interquartile range [IQR], 39.0–74.4) for the training set, 41.6 months (IQR, 33.5–53.1) for the internal validation set, and 59.5 months (IQR, 37.0–79.8) for the external validation set. Chu *et al.*[62] retrospective reviewed patients treated over a 19-year period between October 1, 2000, and October 1,

2019. Therefore, we selected a final follow-up period for our model.

This study had some limitations. Although this PKU-AML model was established based on a large cohort, this was a single-center study, and the efficacy of this model should be further validated in other independent cohorts. Additionally, MRD monitoring and preemptive interventions were commonly used in our cohort, which may have prevented relapse in some patients. This may artificially decrease the incidence of posttransplant relapse. However, considering the higher incidence of MRD and the poorer efficacy of preemptive immunotherapy in high-risk patients, we speculate that the difference in relapse between high- and low-risk patients may be more significant in cohorts without preemptive interventions. In addition, we did not include any additional mutations. We believe that the more variables included in the model, the worse it will be generalized in the clinic. Additionally, the size of the training set was not sufficiently large. If we include all mutation statuses in the model, we may require a larger dataset. If a larger dataset is available, our model and nomogram can be validated. Finally, ATG was administered to prevent GVHD in this study. Therefore, the predictive value of our model should be further confirmed in patients receiving HID HSCT with post-transplantation cyclophosphamide, and in those receiving MSD or unrelated donor HSCT.

In summary, we established the PKU-AML model to predict post-transplant relapse in patients with AML receiving HID HSCT in CR, which was further confirmed using an independent cohort and in clinical practice. This model can be popularized easily, helps provide risk stratification-directed prophylaxis, and may help decrease the risk of relapse. Future prospective multicenter studies should further confirm the efficacy of our PKU-AML model.

Supplementary Information

Supplementary information of this article can be found online at www.intern-med.com.

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Author Contributions

Mo XD and Huang JH designed the protocol; Fan S, Wen Q and Mo DM wrote the manuscript. Fan S, Hong H and Hong S performed the analysis; all authors contributed patients and provided clinical and laboratory data; all authors revised, corrected, and approved the manuscript. Fan S, Hong H, and Wen Q contributed equally to this manuscript.

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Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of Peking University People's Hospital.

Informed Consent

We have obtained consent to publish from the participant to report individual patient data.

Conflict of Interest

The authors declare no competing interests.

Use of Large Language Models, AI and Machine Learning Tools

None declared.

Data Availability Statement

The datasets generated during the analysis of the current study are available from the corresponding author on reasonable request. The codes for developing nomogram can be found through http://github.com/Hhy096/nomogram.

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