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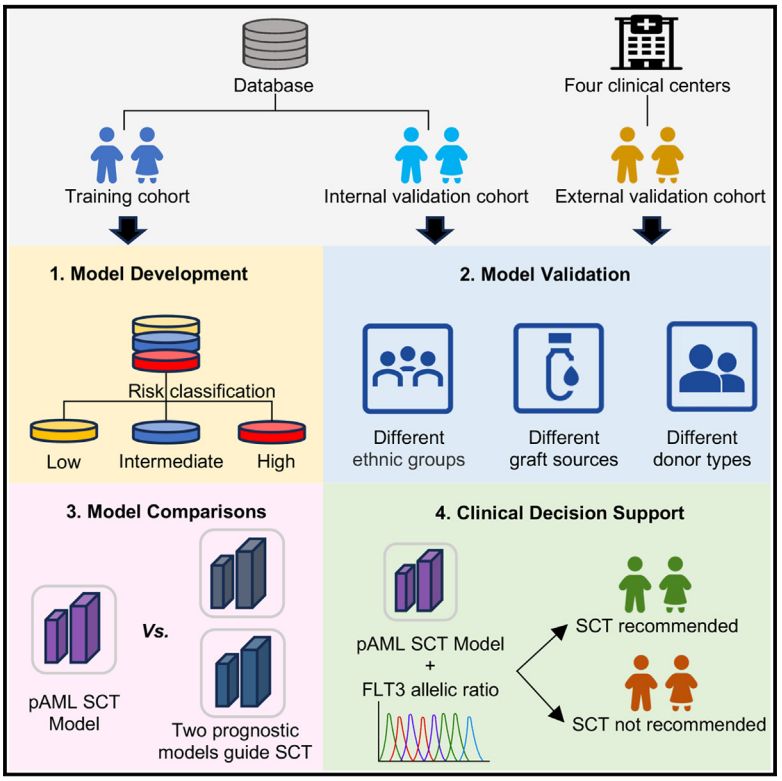
A simplified and robust risk stratification model for stem cell transplantation in pediatric acute myeloid leukemia

Graphical abstract



Highlights

- A simplified and robust prognostic model is developed for SCT in pAML patients at CR1
- The model, independent of cytomolecular risk, offers good predictive accuracy
- The model shows reliable accuracy across graft sources and donor types
- With the FLT3/ITD AR, the model precisely identifies SCT candidates likely to benefit

Authors

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In brief

Hua et al. develop a simplified and robust risk stratification model for SCT in pAML patients at CR1 stage. Independent of cytomolecular risk stratification, the model provides reliable predictions across diverse populations, graft sources, and donor types. Incorporating the FLT3/ITD allelic ratio enhances its ability to select suitable candidates.

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A simplified and robust risk stratification model for stem cell transplantation in pediatric acute myeloid leukemia

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SUMMARY

The efficacy of stem cell transplantation (SCT) in pediatric acute myeloid leukemia (pAML) remains unsatisfactory due to the limitations of existing prognostic models in predicting efficacy and selecting suitable candidates. This study aims to develop a cytomolecular risk stratification-independent prognostic model for SCT in pAML patients at CR1 stage. The pAML SCT model, based on age, KMT2A rearrangement (KMT2A-r), and minimal residual disease at end of course 1 (MRD1), effectively classifies patients into low-, intermediate-, and high-risk groups. We validate the effectiveness in an internal validation cohort and in four external validation cohorts, consisting of different graft sources and donors. Moreover, by incorporating the FMS-like tyrosine kinase 3/internal tandem duplication (FLT3/ITD) allelic ratio, the pAML SCT model is refined, enhancing its ability to effectively select suitable candidates. We develop a simple and robust risk stratification model for pAML patients undergoing SCT, to aid in risk stratification and inform pretransplant decision-making at CR1 stage.

INTRODUCTION

Acute myeloid leukemia (AML) is the second most common blood cancer in children, yet it accounts for half of all childhood leukemia deaths.[1–4] Pediatric consortia worldwide focus on developing specialized risk classifications for children to help tailor treatment plans effectively. Prominent consortia such as the Children's Oncology Group (COG),[5,6] International Berlin-Frankfurt-Münster Study Group (I-BFM-SG),[7] Medical Research Council (MRC),[8] and Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG)[9] are currently performing risk stratification based on cytogenetic and molecular (cytomolecular) risks.[7] For example, in the COG, the tool used to determine the risk stratification of pediatric AML (pAML) patients is the study-defined risk group.[10] Besides, high risk is defined by the patient's response to induction therapy, which can be measured using minimal residual disease (MRD) tested in bone marrow.[11–13]

Stem cell transplantation (SCT) was recommended for pAML patients in high-risk AML patients with first complete remission (CR1).[10,14] Although SCT in CR1 may improve survival for a subset of patients, the benefit for the majority of patients remains unclear.[7,15] Studies indicate that approximately 40% of pediatric AML patients relapse and die after intensive therapy and SCT.[16] It is worth noting that the FMS-like tyrosine kinase 3/internal tandem duplication (FLT3/ITD) mutation is identified as a significant adverse prognostic factor, with patients exhibiting this

mutation also classified as high risk and recommended for SCT.[17,18] Although SCT may improve outcomes for patients exhibiting FLT3/ITD mutations, the relapse rate remains significantly higher in comparison to those without these mutations.[17] These emphasize the importance of establishing a robust prognostic model that accurately predicts outcomes and potentially aids in the accurate screening of SCT candidates.

Currently, very little attention has been paid to develop a specialized prognostic prediction model for pAML patients receiving SCT. The allogeneic hematopoietic cell transplantation (HCT) risk model remains the only prognostic model for pAML patients undergoing SCT and initially provides an effective means to assess their prognosis.[19] However, several clinical issues remain to be addressed. Firstly, the allogeneic HCT risk model, which incorporates results from the second complete remission (CR2), is limited in its ability to provide prognostic assessments for pAML patients undergoing SCT during CR1. Given the significance of CR1 phase in assessing SCT suitability, timing, and strategy for pAML patients, there is an urgent need for an SCT prognostic model that provides insights during CR1.[20] Secondly, the allogeneic HCT risk model incorporates a cytomolecular risk stratification system, which requires an updated model accordingly to adapt to its continuously cytomolecular evolvement.[19,21] Moreover, in the allogeneic HCT risk model, patients who are suitable for transplantation were not identified.[7]

Therefore, we aim for developing a simplified and robust risk stratification model that is independent of cytomolecular risk stratification, which will be used for early-stage prognosis assessment and transplant suitability determination in pAML patients undergoing SCT in CR1 stage. A risk stratification model was developed by combining age at diagnosis, KMT2A rearrangement (KMT2A-r), and minimal residual disease at end of course 1 (MRD1). Additionally, the model was improved by including the FLT3/ITD allelic ratio (AR), enabling the accurate identification of transplant candidates. To our knowledge, this is the first cytomolecular risk stratification-independent prognostic model for SCT specifically designed for pAML patients at CR1 stage.

RESULTS

Patient characteristics

Figure 1 illustrates the workflow of this study, which consists of four stages: model development (Figure 1A), model validation (Figure 1B), model comparison (Figure 1C), and clinical decision support (Figure 1D). First, the pAML SCT model, a specialized model for risk stratification of pAML patients undergoing SCT, is developed (Figure 1A). Second, the model undergoes internal and external validation. Internal validation focuses on verifying the model's risk stratification ability, discrimination, calibration, and robustness. External validation re-examines the model's risk stratification ability, discrimination, and generalizability in different cohorts and subgroups (Figure 1B). Subsequently, the pAML SCT model is compared with the study-defined risk group and the allogeneic HCT risk model in terms of risk stratification ability, discrimination, and clinical utility (Figure 1C). Finally, the pAML SCT model, combined with the FLT3 allelic ratio, is used to precisely screen the most suitable candidates for SCT (Figure 1D).

The average follow-up time for the Treatment Applicability Research Generating Effective Treatments (TARGET) 308 cohort was 3.50 ± 2.12 years. Figure S1 outlines the inclusion and exclusion criteria for the training, internal validation, and external validation cohorts. Clinical characteristics of the pAML patients in the training and internal validation cohort were shown in Figure S2. There was no significant effect of the different treatment regimens on the overall survival (OS) of the TARGET 308 patients ($p = 0.085$, Figure S3). No significant differences in patient clinical characteristics were observed between the training and internal validation cohorts (Table S1). This consistency establishes a robust foundation for the subsequent analysis of model development and performance.

Model development and performance in the training cohort

To develop the risk stratification model, univariate and multivariate Cox analyses were performed to identify the potential predictors affecting OS (Table 1). The cutoff point for age at diagnosis is 5 years by using the Youden index. In the univariate analysis, only age at diagnosis, KMT2A-r status, and MRD1 status demonstrated a significant association with a $p < 0.05$. Subsequently, these three factors were included in the multivariable analysis and were all found to have a significant association with $p < 0.05$ (Figure 2A). A three-factor risk score (pAML SCT model) was then established by integrating the coefficients derived from multivariable Cox regression analyses (Figure S4), and the formula was displayed as follows:

$$\text{Risk Score} = (0.612 \times \text{KMT2A} - \text{r}) + (0.643 \times \text{MRD1}) - (0.682 \times \text{Age at diagnosed} < 5)$$

Based on the risk score quartiles (25% and 75%), the training cohort was categorized into three risk groups: low, intermediate, and high risk. Patients with a risk score of -0.682 or lower were classified as low risk, while those with a risk score greater than 0.574 were considered as high risk. Patients with risk scores between -0.681 and 0.573 fell into the intermediate-risk category. This classification resulted in 57, 96, and 35 cases in the low-, intermediate-, and high-risk groups, respectively. The respective 5-year OS rates were 76%, 65%, and 35% ($p < 0.0001$, Figure 2B), and 5-year event-free survival (EFS) rates were 65%, 56%, and 32% for the low-risk, intermediate-risk, and the high-risk groups ($p = 0.00045$, Figure 2C), respectively. The 1-, 3-, and 5-year OS and EFS rates for each risk group in the training cohort are illustrated in Tables S2 and S3. Assessment of variance inflation factor showed no multicollinearity (all variance inflation factors < 1.2, Figure 2D).

Performance evaluation of the pAML SCT model in the internal validation cohort

We next assess the model's performance in the internal validation cohort to examine its discrimination, calibration, and robustness. There were 27, 42 and 13 cases identified in the low-, intermediate- and high-risk groups in the validation cohort. The pAML SCT model exhibited satisfactory risk stratification ability. Patients with higher risk levels had significantly reduced OS

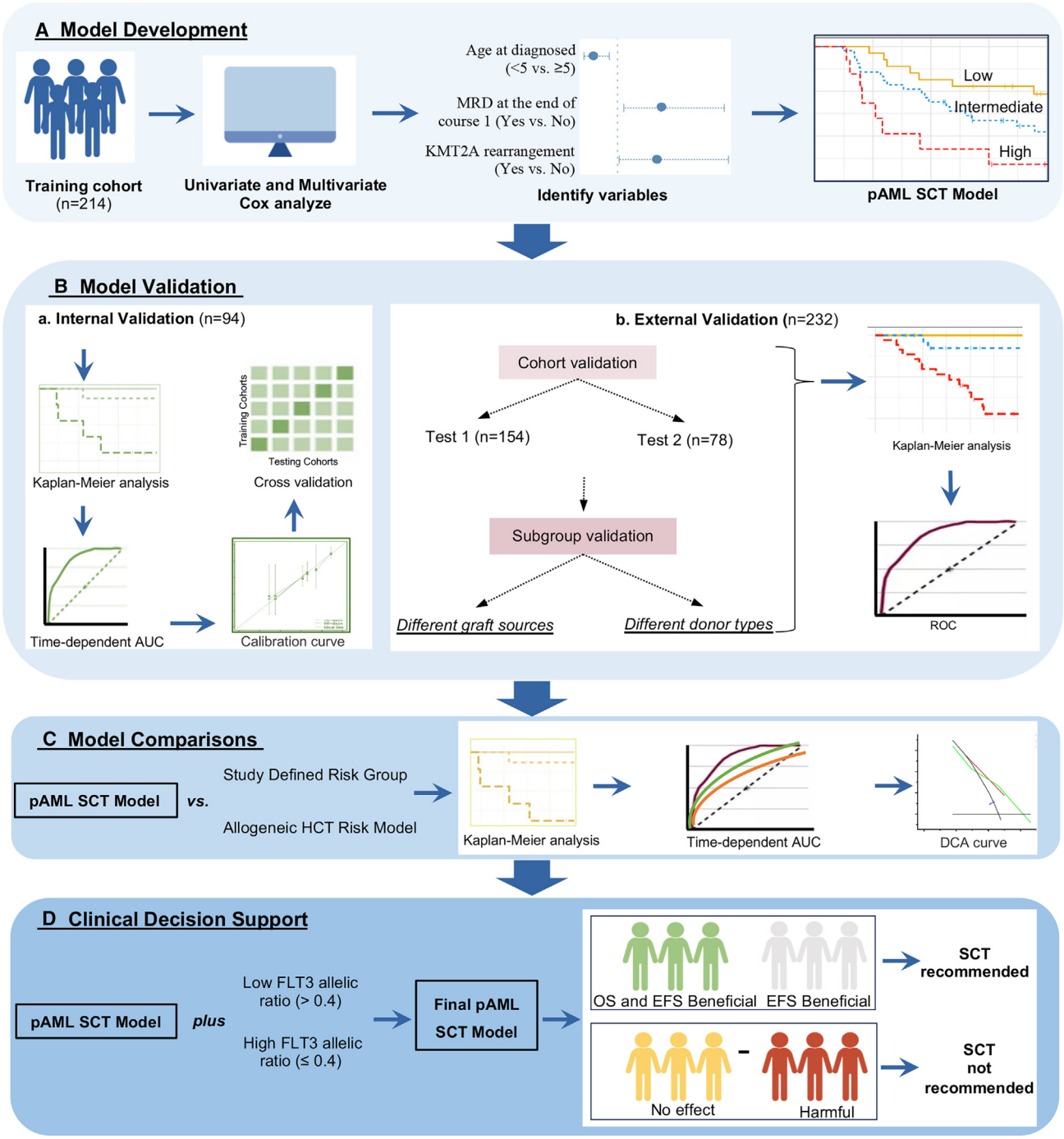


Figure 1. Flowchart of the study design

(A) The process of the pAML SCT model development.

(B) Validation of the prognostic performance of the pAML SCT model by internal cohort and external cohorts.

(C) The process of comparing the pAML SCT model with two other prognostic models used to guide SCT.

(D) In combination with FLT3 allelic ratio to build the final pAML SCT model and utilized to aid in the screening of suitable candidates for SCT. AUC, area under the curve; MRD, minimal residual disease; SCT, stem cell transplantation.

(p = 0.024, Figure 3A) and EFS (p = 0.00071, Figure 3B). For the low-, intermediate-, and high-risk groups, the 5-year OS rates were 73%, 52%, and 34%, while the 5-year EFS rates were 74%, 50%, and 23%. The 1-, 3-, and 5-year OS and EFS for the three risk groups in the internal validation cohort are summarized in Tables S4 and S5, respectively.

Table 1. Univariate and multivariate Cox analyses of overall survival of patients in the training cohort

	Univariate analyses				Multivariate analyses			
Characteristic	N	HR	95% CI	*p* value	B	HR	95% CI	*p* value
Age at diagnosis	214	–	–	–	−0.682	0.506	0.308, 0.830	0.007*
<5	58	–	–	–	–	–	–	–
>5	156	0.607	0.377, 0.978	0.040*	–	–	–	–
Gender	214	–	–	–	–	–	–	–
Female	85	–	–	–	–	–	–	–
Male	129	1.032	0.648, 1.642	0.895	–	–	–	–
CNS disease (yes vs. no)	213	1.142	0.715, 1.824	0.578	–	–	–	–
Chloroma (yes vs. no)	151	1.445	0.617, 3.384	0.397	–	–	–	–
FAB category	75	–	–	–	–	–	–	–
M0 undifferentiated	1	–	–	–	–	–	–	–
M1	15	0.143	0.015, 1.402	0.095	–	–	–	–
M2	8	0.173	0.015, 1.941	0.155	–	–	–	–
M4	18	0.328	0.040, 2.714	0.301	–	–	–	–
M5	25	0.344	0.043, 2.731	0.313	–	–	–	–
M6	0	–	–	–	–	–	–	–
M7	3	0.222	0.014, 3.605	0.290	–	–	–	–
Not classified	5	0.510	0.052, 4.976	0.562	–	–	–	–
inv 16 (yes vs. no)	210	0.000	0.000, Inf	0.996	–	–	–	–
del5q (yes vs. no)	210	0.624	0.087, 4.493	0.640	–	–	–	–
del7q (yes vs. no)	210	1.226	0.386, 3.898	0.729	–	–	–	–
monosomy 7 (yes vs. no)	210	1.487	0.644, 3.432	0.352	–	–	–	–
KMT2A (yes vs. no)	210	1.949	1.118, 3.399	0.019*	0.612	1.845	1.035, 3.073	0.038*
FLT3/ITD positive (yes vs. no)	214	0.856	0.534, 1.372	0.518	–	–	–	–
FLT3/ITD allelic ratio	83	1.006	0.858, 1.180	0.937	–	–	–	–
Group of FLT3/ITD allelic ratio	83	–	–	–	–	–	–	–
≤ 0.4	22	–	–	–	–	–	–	–
> 0.4	61	0.488	0.226, 1.054	0.068	–	–	–	–
NPM mutation (yes vs. no)	213	0.761	0.379, 1.528	0.443	–	–	–	–
CEBPA mutation (yes vs. no)	212	0.236	0.033, 1.695	0.151	–	–	–	–
MRD at the end of the first treatment course (yes vs. no)	192	1.920	1.156, 3.186	0.012*	0.643	1.901	1.130, 3.200	0.016*
MRD at the end of the second treatment course (yes vs. no)	159	0.800	0.401, 1.594	0.526	–	–	–	–
CR status at the end of course 1	214	–	–	–	–	–	–	–
CR	153	–	–	–	–	–	–	–
Not in CR	55	1.395	0.849, 2.294	0.189	–	–	–	–
Unevaluable	6	2.741	0.986, 7.619	0.053	–	–	–	–
Gemtuzumab ozogamicin treatment (yes vs. no)	214	1.442	0.818, 2.541	0.205	–	–	–	–
WBC	214	–	–	–	–	–	–	–
<100	165	–	–	–	–	–	–	–
≥100	49	0.731	0.409, 1.307	0.291	–	–	–	–
Study-defined risk group	212	–	–	–	–	–	–	–
High	78	–	–	–	–	–	–	–
Low	19	0.522	0.178, 1.529	0.236	–	–	–	–
Standard	115	0.518	0.276, 0.970	0.040	–	–	–	–
Final risk group	93	–	–	–	–	–	–	–
High	77	–	–	–	–	–	–	–

(*Continued on next page*)

Table 1. *Continued*

Characteristic	Univariate analyses				Multivariate analyses			
	N	HR	95% CI	*p* value	B	HR	95% CI	*p* value
Low	16	0.589	0.230, 1.506	0.269	–	–	–	–
Cytogenetic fusion molecular risk	93	–	–	–	–	–	–	–
High	56	–	–	–	–	–	–	–
Low	13	0.664	0.229, 1.926	0.451	–	–	–	–
Standard	121	1.405	0.707, 2.791	0.332	–	–	–	–
LncScore	93	–	–	–	–	–	–	–
Negative	35	–	–	–	–	–	–	–
Positive	58	1.390	0.704, 2.746	0.342	–	–	–	–

HR, hazard ratio; CI, confidence interval; WBC, the absolute peripheral white blood cell count; CNS, central nervous system disease at diagnosis present; Chloroma, chloroma disease at diagnosis present; FAB, Leukemia French American British Morphology Code; Protocol, Children's Oncology Group clinical study protocol; MRD, minimal residual disease; CR, the remission status determined by morphologic evaluation of marrow; <5% blast, CR; inv(16), cytogenetic abnormality chromosomal inversion chromosome 16 present; del5q, cytogenetic abnormality deletion mutation 5q present; del7q, cytogenetic abnormality deletion mutation 7q present; monosomy 7, cytogenetic abnormality monosomy 7 present; KMT2A, rearrangement of the *KMT2A* gene present; FLT3_ITD, FLT3 internal tandem duplication present; NPM, mutation of the NPM gene present; CEBPA, mutation of the CEBPA gene present. Asterisk (*) indicates values that are statistically significant ($p < 0.05$).

The calibration of the model was evaluated through calibration curves for 1, 3, and 5 year. The calibration curve, represented by the green line, demonstrated a good agreement between the real observed OS and the ideal nomogram-predicted OS in 5-year survival (Figure 3C). Similarly, the model's calibration curve for EFS, also depicted by the green line, demonstrated good calibration (Figure 3D). In terms of discrimination, the 1-, 3-, and 5-year area under the receiver operating characteristic curves (AUCs) for OS was 0.70, 0.66, and 0.71 and for EFS was 0.71, 0.69, and 0.77, respectively (Figure S5A). Besides, the robustness has been tested in the TARGET 308 cohort. The 5-fold cross-validation demonstrated concordance for both OS and EFS (Table S6). These combined results indicate that our model exhibits strong discrimination, calibration, and robustness.

Further validation of the performance of the pAML SCT model in external validation cohorts

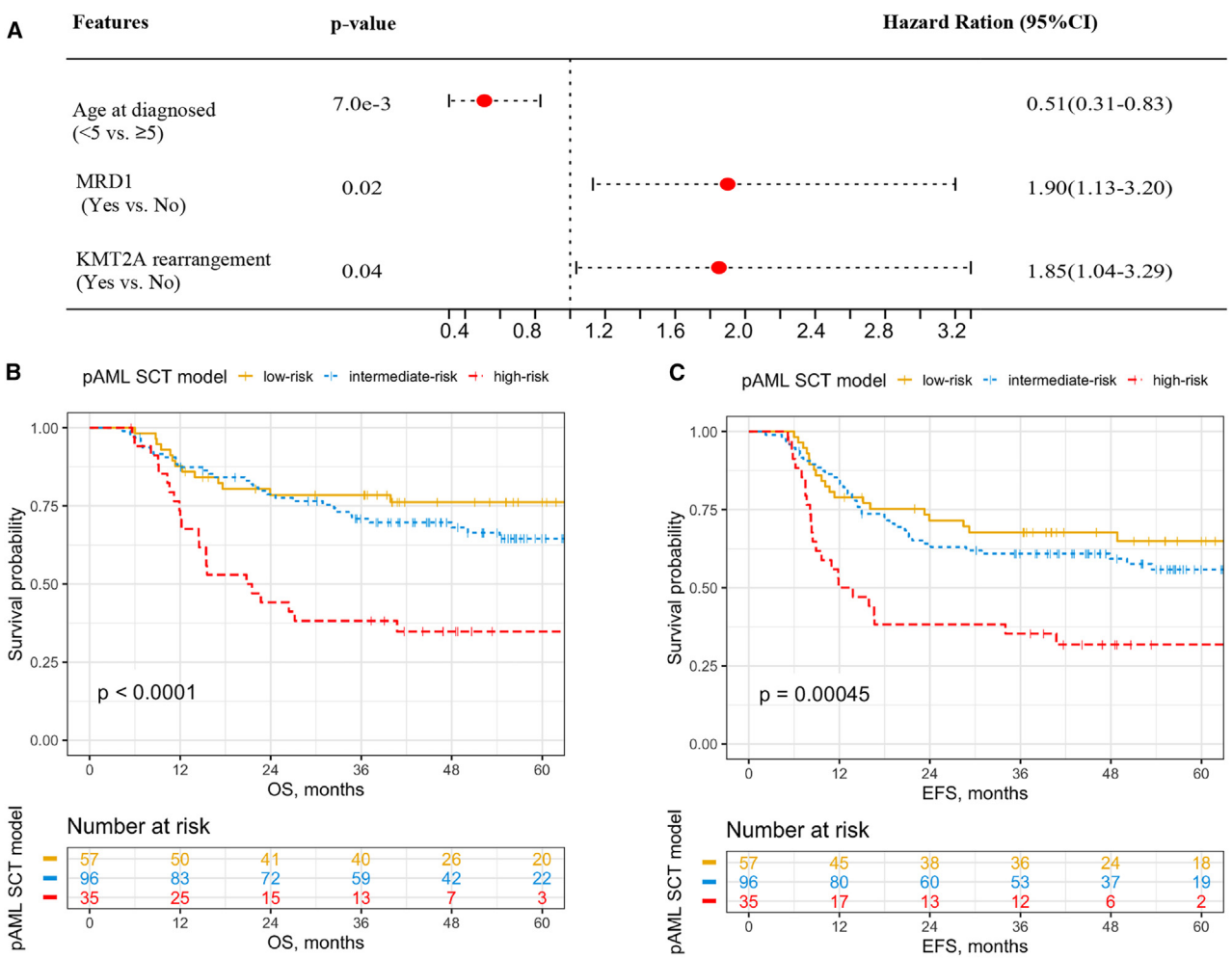
We then evaluate the risk stratification ability, discrimination, and generalizability in diverse external validation cohorts. After applying the same inclusion and exclusion criteria as those of the TARGET 308 cohort, the overall external validation cohort consisted of 232 patients with pAML from four centers, with 154, 36, 26, and 16 patients, respectively. No statistically significant differences were observed in the baseline clinical characteristics of the training, internal validation, and external validation cohorts in Table S7. Of the overall external validation cohort, 26.7% underwent bone marrow transplantation, 66.4% received umbilical cord blood transplants, and 6.9% had peripheral blood stem cell transplants. Regarding donor relationships, 28.4% were from related donors (parents, siblings) and 71.6% were from unrelated donors. Clinical characteristics of the two validation cohort are summarized in the Table S8.

In the test 1 cohort, the Kaplan-Meier analysis demonstrated that the pAML SCT model effectively differentiated between three risk groups for both OS ($p = 0.038$, Figure 4A) and EFS ($p = 0.026$, Figure S6A). Likewise, in the test 2 cohort, the Kaplan-Meier analysis also showed that the pAML SCT model effectively differentiated between three risk groups for both OS ($p = 0.0051$, Figure 4B) and EFS ($p < 0.0001$, Figure S6B).

Next, the two external validation cohorts were combined, and the generalizability of the pAML SCT model was evaluated through subgroup analysis. The pAML SCT model was preliminarily validated in cohorts with different graft sources. Due to the limited number of patients using peripheral blood as the graft source ($n = 16$), they were excluded from the analysis. Significant differences in Kaplan-Meier OS analysis were observed in both the bone marrow ($p = 0.03$, Figure 4C) and cord blood cohorts ($p = 0.019$, Figure 4D). Similarly, Kaplan-Meier EFS analysis also observed significant differences in prognosis among the three risk groups in both the bone marrow ($p = 0.0028$, Figure S6C) and cord blood cohorts ($p = 0.013$, Figure S6D). With regard to the subgroup analysis based on donor types, it was observed that there were statistically significant differences in OS among the three risk groups defined by the pAML SCT model in both the related ($p = 0.015$, Figure 4E) and unrelated ($p = 0.027$, Figure 4F) cohorts. Similarly, the same prognostic trends were observed in EFS. Significant differences were observed in the unrelated cohort ($p = 0.011$, Figure S6F), while the related cohort did not show statistically significant differences ($p = 0.27$, Figure S6E). This was likely due to overlap between the intermediate- and high-risk groups in the early stages of the related cohort. Except for the EFS results of the related cohort, the other external validation cohorts achieved similar AUC for both OS and EFS (Table S9).

Comparison with existing pAML prognostic models guiding SCT

Following internal and external validation of the model, we sought to compare its performance with existing mainstream AML prognostic models that guide SCT. These include the study-defined risk group for risk stratification of patients with pAML and recommendation of SCT for high-risk patients,[10] and the allogeneic HCT risk model,[19] the only SCT prognostic model specifically designed for pediatric AML.



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Variable	Type	Variance Inflation Factor
Age at diagnosed	Categorical	
≥5 vs. <5		1.1413
KMT2A rearrangement	Categorical	
Yes vs. No		1.1666
MRD1	Categorical	
Yes vs. No		1.0358

Figure 2. Model development and performance in the training cohort

(A) Forest plot of age at diagnosis, KMT2A-r status, and MRD1 status in the training cohort.

(B) OS of patients in high-, intermediate-, and low-risk groups decreased sequentially ($p < 0.001$).

(C) The EFS of patients in the high-, intermediate-, and low-risk groups decreases sequentially ($p = 0.00045$).

(D) Variance inflation factor results for the three variables in the pAML SCT model. MRD1, minimal residual disease at the end of the first treatment course; OS, overall survival; EFS, event-free survival.

Firstly, we compared the pAML SCT model with the study-defined risk group. Both the internal and external validation cohorts of the pAML SCT model showed higher AUC (Figure S7) compared to the study-defined risk group, indicating that the pAML SCT model has better discrimination ability. Subsequently, in comparison with the allogeneic HCT risk model, although the pAML SCT model and the allogeneic HCT risk model had similar AUC (Figure S7), we found that the discrimination in the high-risk group of the allogeneic HCT risk model was not ideal. In the training cohort of the allogeneic HCT risk model,

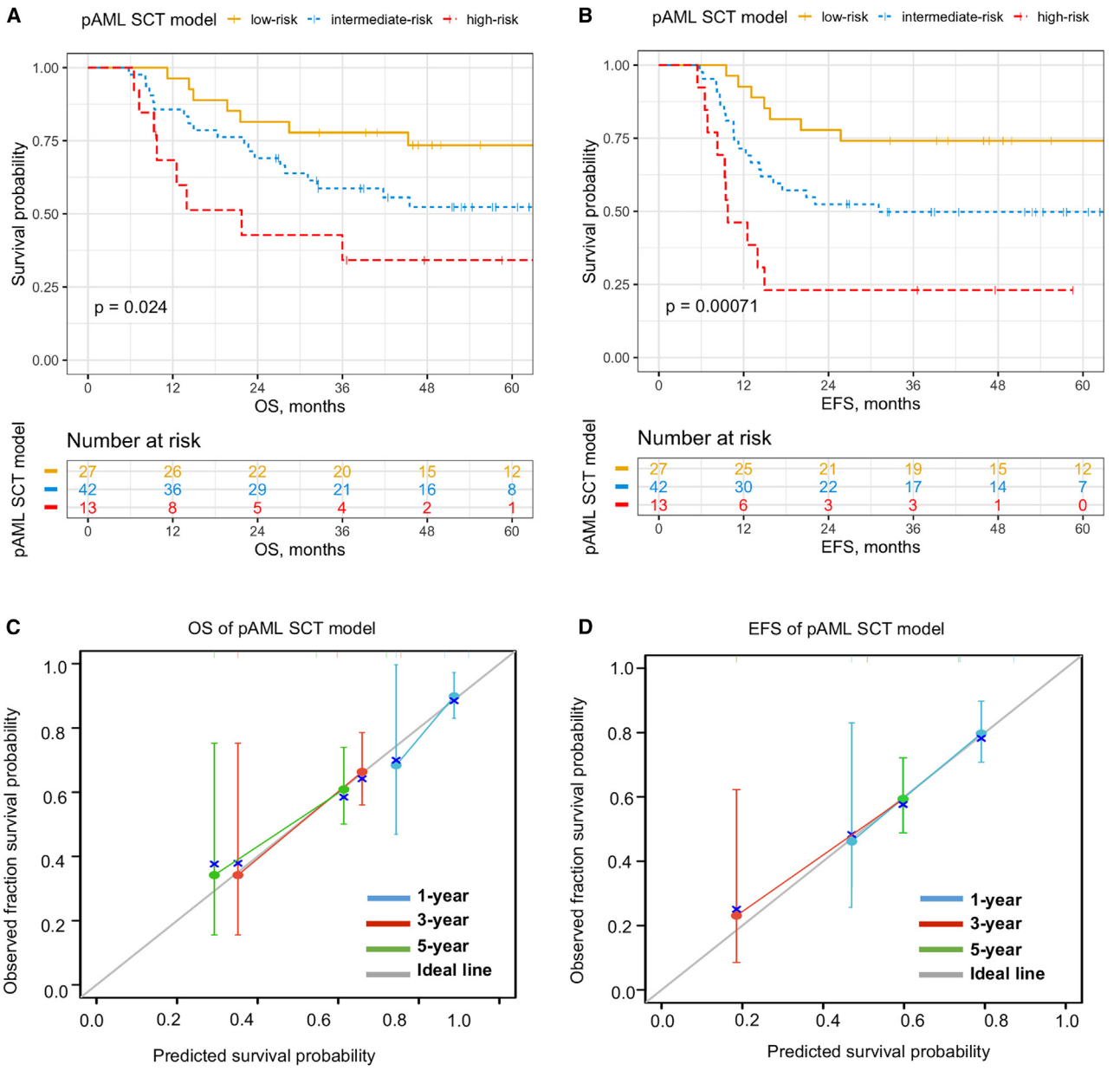


Figure 3. Performance evaluation of the pAML SCT model in the internal validation cohort

(A) The sequential decrease in OS was observed among patients in the high-, intermediate-, and low-risk groups in the internal validation cohort ($p = 0.024$).

(B) The sequential decrease in EFS was observed among patients in the high-, intermediate-, and low-risk groups ($p = 0.00071$) in the internal validation cohort. Yellow, low-risk, blue, intermediate-risk, red, high-risk for the Kaplan-Meier curves.

(C) The calibration curve graph for the internal validation cohort of OS.

(D) The calibration curve graph for the internal validation cohort of EFS. Blue, 1-year, red, 3-year, green, 5-year, gray, ideal line for the calibration curves. EFS, event-free survival; OS, overall survival; SCT, stem cell transplantation.

no significant differences were observed among the four risk groups ($p = 0.051$, Figure 5A). In the internal validation cohort of the same model, a notable overlap was identified between the high-risk and intermediate-risk groups, despite the presence of significant differences ($p = 0.019$, Figure 5B).

Then, the decision-making utility of the models was further evaluated using decision curve analysis (DCA) curves in the TARGET 308 cohort. The DCA curves, analyzed via OS (Figure 5C) and EFS (Figure 5D), revealed that the clinical utility of the pAML SCT model was promising and showed a better clinical utility to predict the death of patients than the study-defined risk group and the allogeneic HCT risk model at different points (1, 3, and 5 years) after SCT. These indicated that the pAML SCT model provides a higher net benefit in actual clinical

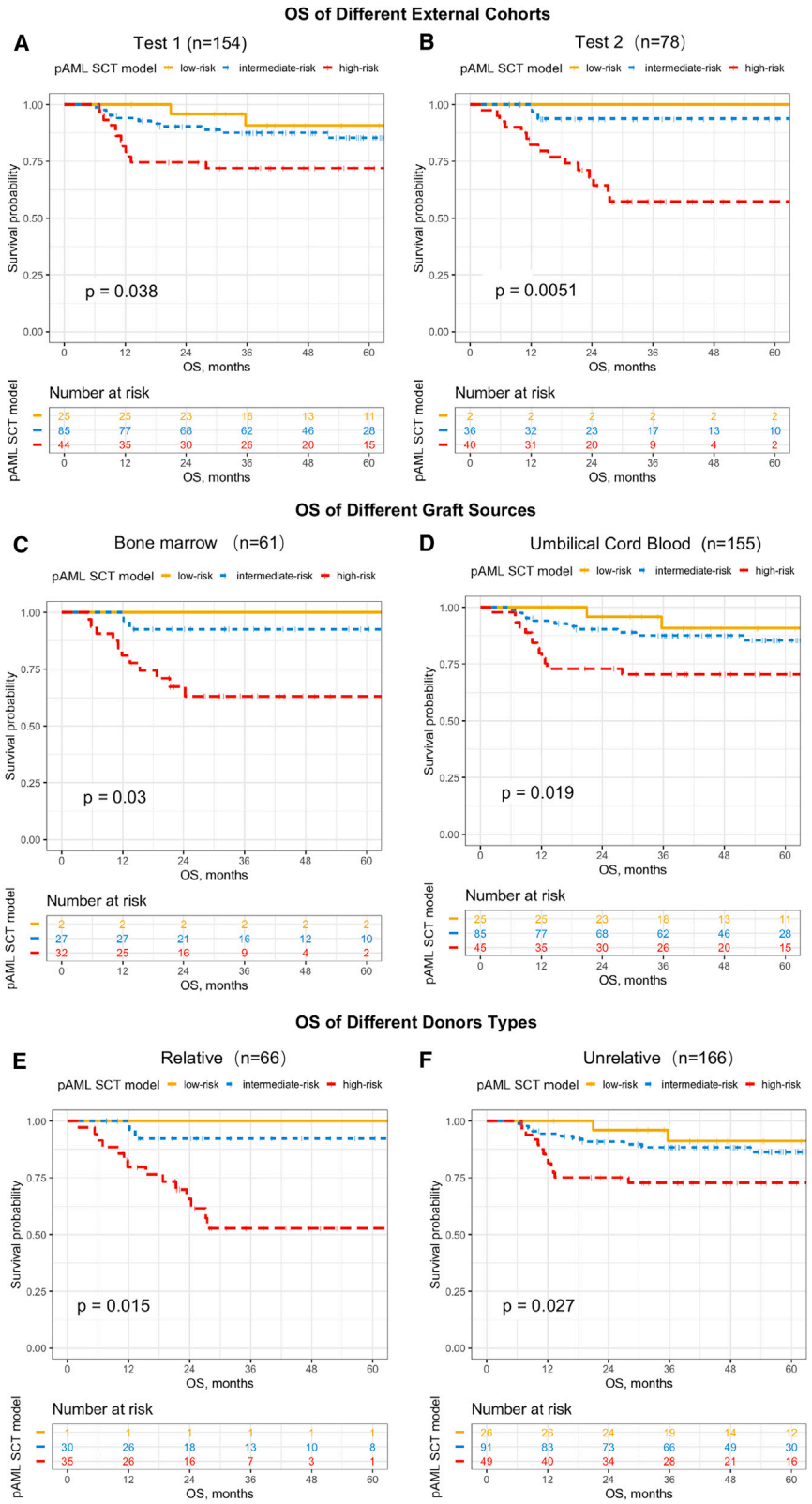


Figure 4. Further validation of the performance of the pAML SCT model in external validation cohorts

(A) The OS Kaplan-Meier curves (p = 0.038) of test 1 cohort.

(B) The OS Kaplan-Meier curves (p = 0.0051) of test 2 cohort.

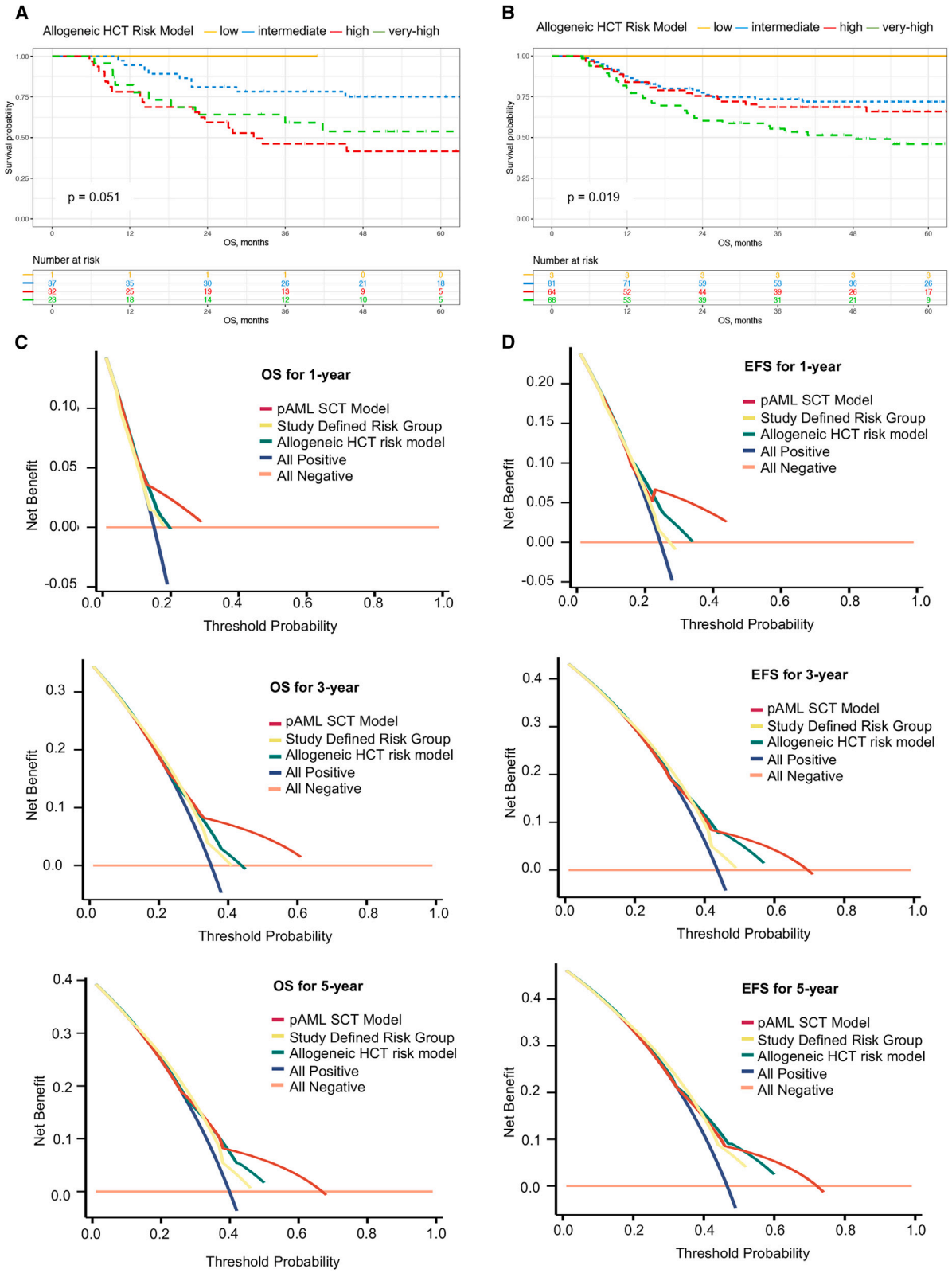
(C) Kaplan-Meier curves for OS (p = 0.03) in the bone marrow cohort.

(D) Kaplan-Meier curves for OS (p = 0.019) in the umbilical cord blood cohort.

(E) The OS Kaplan-Meier curves (p = 0.015) of the relative donors cohort.

(F) The OS Kaplan-Meier curves (p = 0.027) of the unrelative donors cohort.

Yellow, low-risk, blue, intermediate-risk, red, high-risk for the Kaplan-Meier curves. AUC, area under the curve; EFS, event-free survival; OS, overall survival; SCT, stem cell transplantation.



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decision-making and is more suitable for clinical practice. Comparison with different models showed that the pAML SCT model is currently the optimal SCT prognostic tool for AML patients.

Application of the final pAML SCT model for SCT candidate screening

Finally, we explore the clinical significance of our model through its application in pretransplant decision-making. The training cohort, validation cohort, and all non-SCT patients were combined. Among them, there were 662, 712, and 289 patients in the low-, intermediate- and high-risk groups, respectively. Among these groups, 84 (12.2%), 138 (19.4%), and 48 (16.6%) patients underwent SCT, respectively. Notably, SCT was unsuitable for patients in the high-risk group, who exhibited significantly lower OS compared to those who did not undergo SCT (p = 0.005, Figure S8A). Although SCT could significantly improve EFS in the intermediate-risk group ($p < 0.0001$, Figure S8B), it did not significantly improve OS in either the low-risk group (p = 0.45, Figure S8C) or the intermediate-risk group (p = 0.46, Figure S8B).

To further assist with pretransplant decision-making for low- and intermediate-groups patients, clinically important and recognized prognostic risk factors were incorporated into our model, based on the literature.[22,23] Since pAML patients with a high allelic ratio of FLT3/ITD mutations (>0.4; FLT3/ITD AR) are often considered high risk and recommended for SCT,[24,25] we used FLT3/ITD AR to refine the selection process for SCT candidates. A total of 237 pAML patients had FLT3/ITD AR data available for further analysis. The combination of the pAML SCT model and the FLT3/ITD AR led to the creation of the final pAML SCT model, which classifies patients into four subgroups, as shown in Figure 6A.

- No effect group: low-risk group with low FLT3/ITD AR;
- EFS prolonged group: low-risk group with high FLT3/ITD AR, and intermediate-risk group with low FLT3/ITD AR;
- OS and EFS prolonged group: intermediate-risk group with high FLT3/ITD AR;
- Harmful group: high-risk group.

The Kaplan-Meier survival curves for these four groups can be seen in Figures 6B–6E. Patients in the EFS prolonged group (Figure 6C) and the OS and EFS prolonged group (Figure 6D) are recommended for SCT, as it can extend their OS and/or EFS. However, SCT is not recommended for patients in the no effect group and the harmful group. For the no effect group, SCT does not improve OS or EFS (Figure 6B), suggesting that these patients could potentially avoid unnecessary SCT procedures and the associated risks. For the harmful group, SCT may lead to a reduction in OS (Figure 6E), regardless of whether FLT3/ITD AR is high or low (Figures S9A and S9B). Kaplan-Meier survival curves for OS and EFS for the four groups of patients are shown in Figures S10A and S10B. It is evident that our final pAML SCT model effectively identifies individuals who are not suitable for SCT and those who benefit from the procedure. Among patients undergoing SCT, the OS and EFS prolonged group had the best prognosis, while the EFS prolonged group ranked second. Patients in the harmful group had the worst prognosis.

Based on our final pAML SCT model, we identified 58 patients who were not suitable for transplantation but underwent SCT, including 10 patients (16.39%) in the no effect group and 48 patients (16.61%) in the harmful group. Additionally, we identified 81 patients who were suitable for transplantation but did not undergo SCT. Among them, 37 patients (45.12%) were in the OS and EFS prolonged group, and 44 patients (40%) were in the EFS prolonged group (Figure 6F). These results indicate that the final pAML SCT model can provide more valuable guidance for clinical decision-making compared to current SCT strategies.

DISCUSSION

In this study, we propose a simpler, robust, and externally validated stratification system, the pAML SCT model, which categorizes patients into three distinct groups. Moreover, the incorporation of FLT3/ITD AR enables the model to accurately identify patients suitable for SCT. As far as we know, this is the first SCT model specifically designed for pAML patients at CR1 that does not depend on cytomolecular risk stratification.

Despite considerable efforts made to improve the survival rates of pAML patients, the outcomes remain unpleasant. Global pAML consortia, including COG, I-BFM-SG, MRC, and JPLSG, have confirmed the prognostic significance of age at diagnosis,[19] KMT2A-r,[7,26–28] and MRD[19,29,30] in pAML. Based on previous studies, older pAML patients are more likely to face high transplant-related mortality[31,32] and experience shorter leukemia-free survival and OS[19]; in our study, age remained a crucial determinant of prognosis. Moreover, positive MRD before SCT is well-known to predict poor outcome.[13,19,33,34] However, due to the subclonal heterogeneity and clonal hematopoiesis of indeterminate potential of AML, using MRD assessment alone may not sufficiently reflect the disease state.[35] Hence, it is recommended to use a combination of several clinical factors upon MRD assessment.[19,35] Low-risk KMT2A-r predicts a better outcome in pAML, but patients who undergo SCT in the CR1 do not experience improved survival despite the risk status of KMT2A-r. This means that risk stratification for SCT patients should be performed using KMT2A-r along with other factors.[4]

The aforementioned studies indicated that integrating multiple indicators is a valid and necessary approach for accurately predicting the prognosis of SCT. Here, we identified age at diagnosis as a protective factor, and MRD1 and KMT2A-r positivity

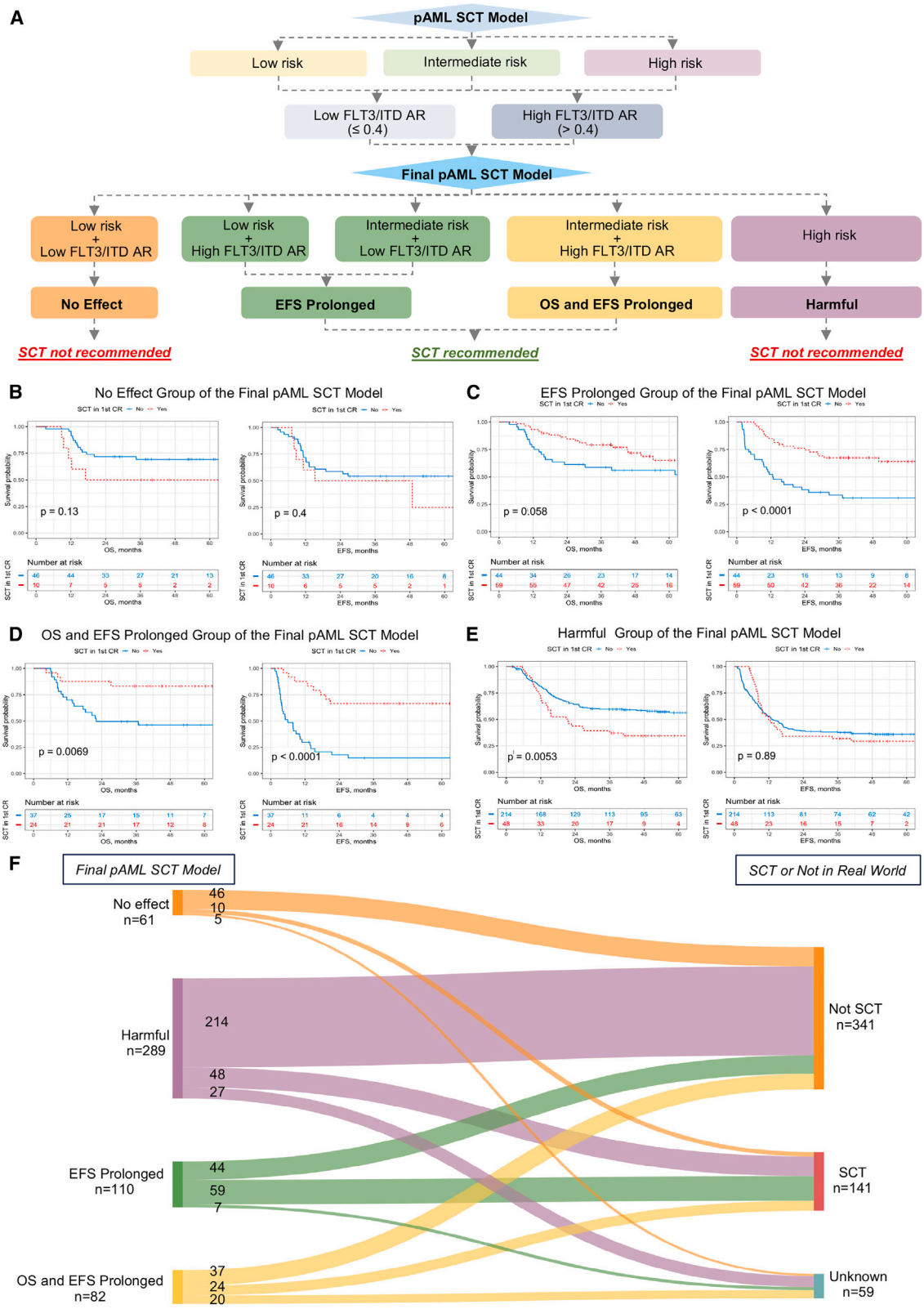
Figure 5. Comparison with existing pAML prognostic models guiding SCT

(A) In the training cohort, no statistically significant differences were observed between the four risk groups of the allogeneic HCT risk model (p = 0.051).

(B) In the internal validation cohort, significant differences were observed between the four risk groups of the allogeneic HCT risk model (p = 0.019) while the high-risk group overlapped with the intermediate group.

(C) The DCA curves for OS at the 1-, 3-, and 5-year timepoints.

(F) The DCA curves for EFS at the 1-, 3-, and 5-year timepoints. AUC, area under the curve; DCA, decision curve analysis; EFS, event-free survival; OS, overall survival.



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as risk factors after SCT for the survival of pAML. These results are consistent with those of previous studies. Notably, the pAML SCT model achieves satisfactory predictive performance using only three clinically accessible metrics, without incorporating cytomolecular risk stratification.

In the real world, SCT treatment for pAML is highly complex, with outcomes influenced by various factors, including donor, graft source, and chemotherapy regimen.[36] Our study has developed a widely applicable prognostic tool for pAML patients undergoing SCT. The TARGET dataset is predominantly composed of Western patients, while the external validation cohorts encompass Asian patients. Our model demonstrated reliable predictive accuracy across different ethnic cohorts. Significantly, the pAML SCT model maintained consistent predictive performance across different graft sources and donor types. For instance, significant OS differences were observed among risk groups in both bone marrow and cord blood transplant recipients, irrespective of the graft source. Likewise, the model accurately predicted outcomes in cohorts with both related and unrelated donors. With applicability across various clinical settings, the pAML SCT model provides clinicians with a more precise and dependable prognostic tool to enhance SCT treatment strategies for pAML patients with different ethnicities.

Expanding on the robust frameworks established by the study-defined risk group[5] and the allogeneic HCT risk model,[19] we have further refined our pAML SCT model. The COG has highlighted the critical role of the study-defined risk group in the prognostic evaluation of pAML patients and in identifying potential SCT candidates.[5,6] It is important to recognize that the study-defined risk group was not originally developed for SCT purpose. When applied to the SCT pAML population in our study, the study-defined risk group yielded suboptimal AUC values, underscoring the necessity for an SCT-specific prognostic tool. Our pAML SCT model, developed in this context, has shown enhanced predictive precision for the pAML population undergoing SCT, enabling a more precise forecast of treatment outcomes. The allogeneic HCT risk model was initially designed to classify pAML patients undergoing SCT into four risk groups based on age, cytogenetic risk, disease status, and MRD at transplantation. However, upon evaluation within the training and internal validation cohorts of this study, the allogeneic HCT risk model showed unsatisfactory discrimination of the high-risk group from other risk groups.

In this study, our pAML SCT model has made several improvements. Firstly, the standout feature of the pAML SCT model is its capacity to stratify SCT pAML patients into low-, intermediate-, and high-risk categories, without reliance on cytomolecular risk stratification. This attribute ensures broad applicability across various clinical contexts and time frames, while is easy to utilize in diverse healthcare settings. Secondly, by employing MRD1, the pAML SCT model enables clinicians to make informed SCT decisions earlier in the treatment process, specifically at the CR1 stage, as opposed to the CR2 utilized by the allogeneic HCT risk model. Thirdly, the pAML SCT model delivers greater net clinical benefit over the allogeneic HCT risk model, suggesting its enhanced suitability for practical application. Finally, while the allogeneic HCT risk model provides valuable prognostic information, it does not adequately guide the selection of SCT candidates. Our study overcomes this limitation by presenting a clear framework for identifying potential candidates suitable for SCT.

One of the significances of this study was to refine the precision of SCT screening for pAM patients. Existing guidelines advocate for the classification of high FLT3/ITD AR patients within the high-risk category, recommending SCT as a therapeutic option.[10,24] However, our findings suggest that SCT might lead to poor survival for those carrying the high FLT3/ITD AR, who are classified as harmful group in our model. Accordingly, high FLT3/ITD AR may not suffice as an independent indicator for transplantation decision-making and should be evaluated in tandem with other prognostic factors. Moreover, a subset of patients exhibited no obvious improvement following SCT, implying overtreatment situation. This aligns with prior research showing no prognostic benefit from SCT in the low FLT3/ITD AR group, a finding mirrored in our study's no effect group.[10] Based on our refined pAML SCT model, we advise against SCT for the harmful and no effect groups. Conversely, within the study's SCT recommended group, we discerned cases that might have benefited from SCT in terms of OS and/or EFS but were precluded due to their misclassification by COG criteria. In summary, our final pAML SCT model improves treatment precision and effectiveness through careful patient screening, reducing unnecessary treatment risks.

Limitations of the study

This study has some limitations. Firstly, as the study is a retrospective analysis, key variables such as low- and high-risk KMT2A-r, MRD2, and pre-SCT MRD may be missing or unrecorded. A prospective study to fully include these key variables is planned in the future to further improve the reliability of the

Figure 6. Application of the final pAML SCT model for SCT candidate screening

(A) This flowchart shows how the FLT3/ITD allelic ratio is incorporated into the final pAML SCT model, as well as how the risk groupings of the model are used to make SCT decisions. Patients in the final pAML SCT model were divided into four groups, where OS and EFS prolonged and EFS prolonged groups were recommended for SCT, and no effect and harmful groups were not.

(B) No significant difference was observed in OS ($p = 0.13$) and EFS ($p = 0.4$) between patients who underwent SCT and those who did not in the no effect group.

(C) SCT patients in the EFS prolonged group had longer EFS than non-SCT patients ($p < 0.001$). There was no significant difference in OS ($p = 0.058$) between the two groups in the EFS prolonged group.

(D) Longer OS ($p = 0.00069$) and EFS ($p < 0.0001$) were observed in SCT patients than in non-SCT patients in the OS and EFS prolonged group.

(E) SCT patients in the harmful group had a shorter OS than non-SCT patients ($p = 0.0053$). There was no significant difference in EFS ($p = 0.89$) within the harmful group.

(F) Sankey diagram illustrates the final pAML SCT model compared to the actual SCT population in the TARGET 308 cohort. Risk groups are illustrated by colored boxes, and the number of cases within them is included for each classifier. Middle areas indicate case redistribution flow. EFS, event-free survival; OS, overall survival; SCT, stem cell transplantation.

model in clinical applications. Moreover, it should be noted that the pAML SCT model is not a static tool and refinement should be made in the future when new information becomes available (such as new drugs including FLT3, menin inhibitors, and venetoclax); large-scale multicenter collaborations are needed to comprehensively assess the impact of evolving therapeutic regimens on SCT outcomes.

Conclusion

In summary, this study set out to present a simplified and robust risk stratification model specifically designed to predict SCT outcomes for pAML patients at CR1 stage. This model, independent of cytomolecular risk stratification, represents a collaborative, multi-institutional effort. The incorporation of variables that are routinely obtained enhances the applicability of the model in clinical practice. The pAML SCT model is pivotal for refining treatment decision accuracy in pAML, offering superior prognostic accuracy and facilitating the precise identification of SCT candidates.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Hua You (youhua307@163.com).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- The clinical and laboratory data for TARGET generated for this study are freely available from Genomic Data Commons Data Portal (https://portal.gdc.cancer.gov/).
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

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AUTHOR CONTRIBUTIONS

H. Yang, Y.X., L.W., and H. You designed the study, collected the data, and wrote the paper; Y.S. and H. You provided patient data for the center 3 cohort; Huihan Wang and Hongtao Wang provided patient data for the center 4 cohort; J.Y. provided patient data for the center 2 cohort; X. Zhang and X. Zhu provided patient data for the center 1 cohort. H. You directed the project, supervised the analysis, and revised the manuscript; H. Yang, Y.T., and R.L. participated in the modification of the figures. H. Yu provided recommendations for new data analysis methodologies. All authors read and approved the final manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
The clinical data from the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) project	GDC Data Portal	https://portal.gdc.cancer.gov/
Software and algorithms		
R Software (version 3.5.2)	R Foundation for Statistical Computing	https://www.r-project.org
ggplot_2_3.3.3	R core Team	https://ggplot2.tidyverse.org/
survival_3.5.8	R core Team	https://github.com/therneau/survival
survminer_0.4.9	R core Team	https://rpkgs.datanovia.com/survminer/
gtsummary_1.7.1	R core Team	https://github.com/ddsjoberg/gtsummary/releases
lattice_0.22.5	R core Team	https://www.rdocumentation.org/packages/lattice/versions/0.22-5
caret_6.0.94	R core Team	https://github.com/topepo/caret/
pROC_1.18.2	R core Team	https://xrobin.github.io/pROC/
rms_6.8.0	R core Team	https://cran.r-project.org/web/packages/rms/index.html
timeROC_0.4	R core Team	https://cran.r-project.org/web/packages/timeROC/index.html
devtools_2.4.5	R core Team	https://devtools.r-lib.org/
ggDCA_1.2	R core Team	https://github.com/yikeshu0611/ggDCA/blob/master/DESCRIPTION
ggprism_1.0.5	R core Team	https://cran.r-project.org/web/packages/ggprism/readme/README.html
SPSS (version 26.0)	IBM	https://www.ibm.com/support/pages/downloading-ibm-spss-statistics-26

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Training and internal validation cohorts

Demographic, clinical, and laboratory information on patients with pAML was collected based on data obtained through October 11, 2023 from the Treatment Applicability Research Generating Effective Treatments (TARGET) project (https://portal.gdc.cancer.gov/). The database included a total of 1941 cases of primary pAML (without M3 subtype), out of which 308 cases received SCT. These 308 cases, referred to as "TARGET 308″ were included in the study analysis. Additionally, three trials were registered as AAML03P1 (NCT00070174),[37] AAML0531 (NCT00372593),[24] and AAML1031 (NCT01371981)[38] involving pAML were accessed through the TARGET database. Inclusion and exclusion criteria are provided in Figure S1.

To develop the prognostic model, potential predictors of OS were analyzed. Explanations of the clinical data elements have been documented in a previous publication.[39] The training and validation subsets were randomly generated in a 7:3 ratio.[40] The basic clinical characteristics including the gender and age of the patients were summarized in Table S1 and Figure S2.

External validation cohorts

A total of 232 cases from four different centers for external validation, with initial diagnoses dating from January, 2012 to December, 2023. Inclusion and exclusion criteria are provided in Figure S1. Specifically, the patients from the First Affiliated Hospital of the University of Science and Technology of China (n = 154) formed the Test 1 cohort, while the patients from the Second Hospital of Dalian Medical University (n = 36), the Children's Hospital of Chongqing Medical University (n = 26), and Shengjing Hospital of China Medical University (n = 16) comprised the Test 2 cohort. Regarding source of transplants, 61 patients underwent bone marrow transplantation, 155 received umbilical cord blood transplants, and 16 had peripheral blood stem cell transplants. Concerning donor relationships, 66 had related donors (parents and siblings) and 166 had unrelated donors.

This study was performed in accordance with the Declaration of Helsinki, with approvals of the Institutional Review Board of First Affiliated Hospital of University of Science and Technology of China, Second Hospital of Dalian Medical University, Children's Hospital of Chongqing Medical University, and Shengjing Hospital of China Medical University.

METHOD DETAILS

Prognostic model construction

The prognostic model was developed by analyzing potential predictors of OS. Explanations of the clinical data elements have been documented in a previous publication.[39] The training and validation subsets were randomly generated in a 7:3 ratio.[40] The training cohort (n = 214) was used for model construction, the internal (n = 94) and external (n = 232) validation cohorts were used for model validation.

The primary endpoint was OS, defined as the time from study entry to death. The secondary endpoint was EFS, defined as the time from study entry to death or relapse. Univariate and multivariate Cox proportional hazards analyses were performed to assess the impact of various parameters on OS. Parameters with a p-value <0.05 in the multivariate analysis were included in the model. Risk scores were calculated for each subject based on the coefficients from the multivariate analysis, and patients were classified into low-, intermediate-, or high-risk categories using the 25th and 75th quartiles of the risk scores.

Prognostic model validation

OS and EFS probabilities were estimated using the Kaplan-Meier method, with survival curves compared using the log rank test. Model performance was evaluated using the AUC for discrimination, and calibration curves for calibration. The robustness and generalizability of the model were assessed using 5-fold cross-validation, with the TARGET 308 cohort randomly divided into five subsets.

Model comparison

Two mainstream prognostic models were selected for comparison with pAML SCT Model. The first one is the Study Defined Risk Group,[10] which is used to determine the risk stratification of patients with pAML, and patients categorized as high risk are recommended to receive SCT. The other model is the Allogeneic HCT Risk Model, currently the only reported transplantation prognostic model specifically designed for pediatric AML.[19] The AUC, and DCA were utilized to compare these prognostic models. The DCA curves were drawn by R-package (ggDCA), and was used to test the 1-, 3-, 5-year model values for clinical application.

QUANTIFICATION AND STATISTICAL ANALYSIS

The age at diagnosis cutoffs at 5 years for AML was determined statistically by using the Youden index. The chi-squared test was used to assess statistical differences between categorical variables. For quantitative variables, we used either the two-tailed Student's t-test or the Wilcoxon test. The Youden index was usually used to determine the best cut-off point for the continuous independent variable, which corresponds to the maximum value on the ROC curve. The R package caret[40] was used for cohort splitting. All statistical analyses were performed with R software (version 3.5.2) and SPSS (version 26.0). P valus <0.05 was considered statistically significant.