Am J Cancer Res 2026;16(5):1883-1906
www.ajcr.us /ISSN:2156-6976/ajcr0172946

Original Article

Establishment and validation of a 28-day clinical outcome prediction model for acute promyelocytic leukemia based on an early platelet-coagulation factor combined transfusion strategy

Shuaikui Zheng[1], Xiaocai Zheng[2], Zhanwei Li[3]

[1]Department of Blood Transfusion, Henan Provincial People's Hospital, People's Hospital of Zhengzhou University, Zhengzhou 450000, Henan, China; [2]Department of Gastroenterology and Hemorrhoid and Fistula Surgery, Jiaxian People's Hospital, Jia County, Pingdingshan 467100, Henan, China; [3]Department of Blood Transfusion, The First Affiliated Hospital of Henan University of Science and Technology, Luoyang 471000, Henan, China

Received March 28, 2026; Accepted May 15, 2026; Epub May 15, 2026; Published May 30, 2026

Abstract: Early mortality in acute promyelocytic leukemia (APL) remains a major challenge, and the Sanz risk stratification has limited predictive value. This retrospective multicenter study aimed to establish and externally validate a 28-day mortality risk prediction nomogram integrating an early platelet-coagulation factor (PLT-CF) combined transfusion strategy. A total of 631 newly diagnosed APL patients from two tertiary hospitals (2019-2024) were divided into a training cohort (n = 429) and an external validation cohort (n = 202). Independent predictors were identified by multivariate Cox regression and incorporated into a nomogram. Model performance was assessed by time-dependent ROC curves, calibration, decision curve analysis (DCA), and Kaplan-Meier survival analysis, with comparison against the Sanz system. The 28-day mortality rate was 19.02% (120/631). Six independent predictors were identified: decreased fibrinogen (HR = 0.254, P < 0.001), decreased hemoglobin (HR = 0.989, P = 0.034), age ≥ 45 years (HR = 2.037, P = 0.003), Charlson Comorbidity Index score 1-3 (HR = 1.877, P = 0.005), white blood cell count > 10 × 10^9/L (HR = 3.151, P < 0.001), and absence of early PLT-CF combined transfusion within 72 hours (HR = 2.713, P < 0.001). The nomogram showed excellent discrimination in the training cohort (28-day AUC = 0.890, C-index = 0.858) and validation cohort (AUC = 0.945, C-index = 0.913), with good calibration (Hosmer-Lemeshow P > 0.05) and net clinical benefit (DCA). High-risk patients had significantly higher 28-day mortality than low-risk patients (training: 67.1% vs. 8.1%; validation: 64.4% vs. 3.8%; both P < 0.0001). The nomogram significantly outperformed the Sanz risk stratification (AUC: 0.890 vs. 0.693 in training, 0.945 vs. 0.759 in validation; DeLong P < 0.001). In conclusion, this nomogram integrating early PLT-CF combined transfusion effectively predicts 28-day mortality in APL and is superior to the traditional Sanz system, aiding early identification of high-risk patients and individualized decision-making.

Keywords: Acute promyelocytic leukemia, early mortality, predictive model, nomogram, platelet-coagulation factors combined transfusion, external validation

Introduction

Acute promyelocytic leukemia (APL) is a special subtype of acute myeloid leukemia characterized by t(15;17)(q24;q21) chromosomal translocation and the resulting PML-RARα fusion gene [1]. All-trans retinoic acid (ATRA) and arsenic trioxide (ATO) has completely changed the treatment landscape for APL in clinics, transforming it from a highly lethal disease to the acute leukemia subtype with the highest cure rate [2, 3]. According to the findings of large-scale clinical studies, ATRA combined with ATO has achieved a complete remission rate exceeding 95% for APL, with long-term overall survival rates over 90% [4-6].

However, early mortality in APL still constitutes a major challenge. Early mortality refers to death occurring within 28 day after diagnosis or during induction therapy, with incidences ranging from 3% to 10% in clinical trials and reach-

https://doi.org/10.62347/AUHX4651

ing as high as 10% to 30% in real-world studies [7-9]. This discrepancy suggests that the true burden of early mortality in APL may be underestimated in clinical trials. In APL, hemorrhage (especially intracranial hemorrhage) is the leading cause of early mortality, which accounts for approximately 40%-60% of early deaths [10]. The procoagulant substances and plasminogen activators released by APL cells trigger severe disseminated intravascular coagulation (DIC) characterized by hypofibrinogenemia, as well as elevated D-dimer and fibrinogen degradation products (FDPs), a unique coagulopathy that constitutes the pathophysiological basis for the high bleeding risk in APL [11]. Moreover, differentiation syndrome and infection are also major causes of early mortality [12].

APL patients are classified into low-risk, intermediate-risk, and high-risk groups by white blood cell and platelet counts at initial diagnosis by the Sanz risk stratification system (currently widely used in clinics). This system is primarily applied to guide the intensity of induction chemotherapy and predict the risk of recurrence [13]. However, multiple studies indicate that the predictive value of Sanz stratification system for early mortality is limited, as the system does not include key factors that may influence early mortality, including coagulation parameters, patient baseline status, and early supportive therapies [14]. Previous studies have identified advanced age, comorbidities, and severe coagulation disorders as independent risk factors for early mortality in APL [9]. However, most of the existing studies are single-center, have limited sample sizes, and lack comprehensive prediction tools that have been externally verified.

Early identification of high-risk patients and targeted interventions are key strategies to reduce early mortality in APL. Aggressive supportive therapy, including platelet transfusion and coagulation factor replacement to maintain platelet counts ≥ 30-50 × 10^9/L and fibrinogen (FIB) levels ≥ 1.5 g/L, is considered important for bleeding prevention [2]. In recent years, predictive models and nomograms have gained widespread application in oncology as clinical tools that integrate multiple predictive factors to provide individualized risk assessments [15]. To construct a validated risk prediction model for early mortality in APL is expected to provide evidence-based support for the early identification of high-risk patients, resource allocation optimization, and individualized treatment decision-making in clinics.

Hence, the study aimed to comprehensively analyze risk factors influencing 28-day mortality using a large, multicenter cohort of APL patients. By integrating demographic characteristics, laboratory parameters, coagulation parameters, and early treatment factors, a risk prediction nomogram model for 28-day mortality in APL patients was established and validated. This model was compared with the traditional Sanz risk stratification system to provide a more precise predictive tool for clinical practice.

Materials and methods

Study design and sample size estimation

This is a retrospective mu lticenter cohort study. The Schoenfeld formula was used for sample size estimation for survival analysis [16]. The formula is as follows: $E = 4 \times (Z\alpha/2 + Z\beta)^2/[\ln(HR)]^2$. Where: E represents the number of events required; Zα/2 is the Z value corresponding to the two-sided significance level (when α = 0.05, Zα/2 = 1.96); Zβ is the Z value corresponding to the statistical power (when β = 0.20, i.e., 80% power, Zβ = 0.84); and HR represents the expected hazard ratio. According to previous reports, the hazard ratio (HR) for major risk factors for early mortality in APL patients (e.g., high white blood cell count and low FIB levels) is approximately 2.0 to 3.0 [17, 18]. Substituting HR = 2.5 into the calculation: $E = 4 \times (1.96 + 0.84)^2/[\ln(2.5)]^2 = 4 \times 7.84/0.84 \approx 37$ cases. Given that this study involves multivariate analysis, based on the rule of thumb for constructing predictive models, each candidate predictive variable requires at least 10-20 endpoint events to ensure model stability [19]. This study ultimately included six predictive variables, and at least 60 to 120 endpoint events were required. According to previous reports, the 28-day mortality rate in APL patients is approximately 15%-25% [17, 18]. Assuming an event incidence rate of P = 20%, the total sample size required N = E/P = 120/0.20 = 600 cases. This study ultimately included 631 patients, with a total of 120 deaths observed, meeting the aforementioned sample size requirements.

Study participants

Consecutive patients with newly diagnosed APL admitted to two tertiary medical institutions (Henan Provincial People's Hospital and the First Affiliated Hospital of Henan University of Science and Technology) from January 2019 and January 2024 were enrolled. Among them, patients from Henan Provincial People's Hospital were allocated for the construction of the predictive model (training cohort, n = 429), and patients from the the First Affiliated Hospital of Henan University of Science and Technology were allocated for the external validation of the model (validation cohort, n = 202). This retrospective study has obtained approval from the Henan Provincial People's Hospital Medical Ethics Committee and been exempted from informed consent.

Diagnosis criteria

The diagnosis of APL is based on bone marrow morphological features combined with molecular or cytogenetic evidence, requiring fulfillment of at least one of the following criteria: (1) Positive for PML::RARA fusion gene by reverse transcription-polymerase chain reaction (RT-PCR); (2) Positive for t(15;17)(q24;q21)/PML::RARA by fluorescence in situ hybridization (FISH); (3) Chromosomal karyotyping analysis indicating t(15;17) [20].

Inclusion and exclusion criteria: (1) Newly diagnosed APL patients aged ≥ 18 years; (2) Meeting the aforementioned APL diagnostic criteria; (3) Complete baseline clinical data and data on key laboratory parameters (including hematology and coagulation function) available upon admission or diagnosis; (4) Early transfusion records and 28 day survival outcome information available.

Exclusion criteria: (1) Non-APL cases or cases with insufficient diagnostic evidence; (2) Refractory or relapsed APL (non-initial diagnosis); (3) Transferred out shortly after admission, discharged voluntarily, or lost to follow-up, with 28 day survival outcomes not confirmed; (4) Critical variables severely missing, precluding the evaluation of early transfusion strategy or primary outcomes; (5) Complicated with other malignant hematologic tumors or concurrent participation in interventional clinical trials likely to significantly affect transfusion or treatment strategies.

Clinical data acquisition

Through the electronic medical record system, baseline data were retrospectively collected, including demographic characteristics (age (categorized into < 45 years and ≥ 45 years groups) and gender), performance status (assessed by the Eastern Cooperative Oncology Group performance status (ECOG PS) score, categorized into 0-1 and ≥ 2 groups) [21], comorbidity burden (assessed via the Charlson Comorbidity Index (CCI), categorized into 0 points and 1-3 points groups) [22], laboratory parameters (hematology and coagulation function parameters), and hematology parameters (white blood cell count (WBC), platelet count (PLT), and hemoglobin (Hb)). Based on the Sanz risk stratification system, participants were categorized into $\leq 10 \times 10^9$/L and $> 10 \times 10^9$/L groups using 10×10^9/L for WBC as the cutoff, and into $> 40 \times 10^9$/L and $\leq 40 \times 10^9$/L groups using 40×10^9/L for PLT as the cutoff. Coagulation function parameters were also collected, covering prothrombin time (PT), activated partial thromboplastin time (APTT), as well as international normalized ratio (INR), FIB, D-dimer, and fibrinogen degradation products (FDP).

Measurement methods

Using a fully automated hematology analyzer (Sysmex XN-9000, Sysmex, Japan), hematology tests/examinations were performed, including WBC, PLT, and Hb. All reagents used were original manufacturer-supplied reagents. Coagulation function testing was conducted with a fully automated coagulation analyzer (Sysmex CS-5100, Sysmex, Japan). PT, APTT, INR, and FIB were measured with the coagulation method using Dade® Behring coagulation reagents (Siemens, Germany). D-dimer testing employed an immunoturbidimetric assay using INNOVANCE® D-Dimer reagents (Siemens, Germany). FDP was measured with the latex agglutination turbidimetric assay, with supporting reagents (batch No.:). All tests/measurements were conducted in strict accordance with standard operating procedures, with daily internal quality control performed.

For molecular and cytogenetic testing, PML::RARA fusion gene was determined with RT-PCR using the leukemia fusion gene detection kit (Amoy Diagnostics Co., Ltd., batch No.:). FISH test employed PML/RARA dual color dual fu-

sion probes (Beijing Jinpujia Medical Technology Co., Ltd.). Chromosomal karyotyping was conducted using the G-banding technology, with karyotype descriptions following the *International System for Human Cytogenomic Nomenclature* (ISCN 2020).

Functional scoring criteria

Patient's performance status was assessed with the ECOG PS score [21]: a score of 0 indicates fully active, able to carry on all pre-disease performance without restriction; a score of 1 point indicates restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; a score of 2 indicates ambulatory and capable of all selfcare but unable to carry out any work activities, up and about more than 50% of waking hours; a score of 3 indicates capable of only limited selfcare, confined to bed or chair more than 50% of waking hours; a score of 4 indicates cannot carry on any selfcare; totally confined to bed or chair; a score of 5 indicates death. Here, scores of 0-1 was defined as good physical status and scores of ≥ 2 as poor physical status. CCI is a commonly used tool for assessing a patient's burden of comorbidities, covering 19 disease states. Based on severity, each disease is assigned a weight of 1-6 points, with the total score being the sum of all weights [22]. Here, a CCI score of 0 was defined as the absence of comorbidities, and scores of 1-3 as the presence of comorbidities.

Outcome definition

Time zero: the date of the patient's initial APL diagnosis or the start of ATRA therapy (consistent across the entire cohort). Primary outcome: death within 28 day, i.e., death from any cause occurring within 28 day after time zero. Secondary outcomes: death within 7 days, death within 14 days, and death within 21 days.

Statistical analysis

The R 4.5.1 and SPSS 27.0 software was employed for statistical analysis. For normally distributed measurement data, mean ± standard deviation (x ± s) was applied for presentation, with the independent samples t-test for intergroup comparisons. For non-normally distributed measurement data, median (interquartile range) [M (Q1, Q3)] was adopted for presentation, with the Mann-Whitney U test for intergroup comparisons. Enumeration data were presented by number of cases (percentages) [n (%)], with the chi-square test or the Fisher's exact test for intergroup comparisons. Using the LASSO regression, variables were selected, with the optimal penalty parameter λ determined via 10-fold cross-validation. Collinearity diagnosis was performed on the selected variables through the calculation of Pearson correlation coefficients and variance inflation factors (VIF). Variables with an absolute correlation coefficient > 0.6 or VIF > 5 were considered for removal. These thresholds were selected based on established statistical guidelines, where $|r| > 0.6$ indicates a strong correlation between two variables [23], and a VIF > 5 suggests moderate to severe multicollinearity that may affect the stability of regression estimates [24]. To identify candidate predictors associated with 28-day mortality, univariate Cox proportional hazards regression was adopted. For multivariate Cox regression analysis, variables with $P < 0.1$ were included. The Schoenfeld residuals was applied to test the proportional hazards assumption, and variables violating this assumption were excluded. A nomogram model predicting 28-day mortality risk in APL patients was constructed based on independent predictors screened from the multivariate Cox regression analysis. Model validation encompassed discrimination, calibration, and clinical utility assessment: The time-dependent receiver operating characteristic (ROC) curve was employed for model discrimination assessment at 7, 14, 21, and 28 days, with the area under the curve (AUC) and its 95% confidence interval (CI) calculated. The DeLong test was used to compare the differences in AUC between the predictive model and the Sanz risk stratification. Calibration curves were plotted to assess the consistency between predicted and observed probabilities, with concordance index (C-index), Hosmer-Lemeshow goodness-of-fit test, and Brier score calculated. Decision curve analysis (DCA) was applied to evaluate clinical net benefits of the model. The aforementioned assessments were replicated in the external validation cohort for model generalizability validation. On the basis of risk scores calculated from the nomogram, patients were categorized into high-risk and low-risk groups by optimal cutoff values. The optimal cutoff value was determined using the maximally selected log-rank

statistic implemented in the R package survminer. This method systematically evaluates all possible cutoff values of the risk score and selects the one that yields the most significant difference in survival between the two groups, i.e., the maximum log-rank chi-square statistic. The chosen cutoff was further validated by examining the Kaplan-Meier curves and ensuring a clinically meaningful sample size distribution between the risk groups. The Kaplan-Meier method was applied to plot survival curves, and log-rank tests were adopted to compare survival differences between groups. All statistical tests were two-sided, with $P < 0.05$ indicating statistically significant differences.

Results

Comparison of baseline characteristics between patients who died within 28 day and survivors in APL cohort

Here, 631 APL patients were included, and 120 (19.02%) of them died within 28 day. According to the comparison of baseline characteristic, patients in the mortality group were older ($P < 0.001$), with poorer ECOG performance status ($P < 0.001$) and higher CCI comorbidity scores ($P < 0.001$). Regarding laboratory parameters, patients in the mortality group exhibited higher WBC ($P < 0.001$), lower PLT ($P < 0.001$), and lower Hb ($P = 0.009$) at initial diagnosis, and more severe coagulation disorder, manifested by decreased FIB levels, prolonged PT and APTT, raised INR, and increased D-dimer and FDP levels (all $P < 0.001$). By Sanz risk stratification, the proportion of high-risk patients was notably higher in the mortality group ($P < 0.001$). In terms of early supportive therapy, the proportion of patients in the mortality group who received early PLT-CF combined transfusion ($P < 0.001$), PLT transfusion alone ($P < 0.001$), and CF/cryoprecipitate/FIB preparation transfusion ($P < 0.001$) within 72 hours was significantly lower than that in the survival group. No remarkable differences were seen between groups in gender ($P = 0.296$), induction therapy regimen ($P = 0.794$), or time from diagnosis to first ATRA administration ($P = 0.338$) (see Table S1).

Comparison of baseline characteristics between training and external validation cohorts

Totally 631 APL patients were enrolled and assigned to the training cohort (n = 429) or the external validation cohort (n = 202) in a ratio of approximately 2:1. Baseline characteristics comparison revealed no remarkable differences in demographic characteristics, including age ($P = 0.254$) and gender ($P = 0.694$). Clinical assessment measures, including ECOG performance status score ($P = 0.923$) and CCI comorbidity index ($P = 0.191$), were evenly distributed across both groups. Laboratory parameters including WBC at initial diagnosis ($P = 0.559$), PLT at initial diagnosis ($P = 0.810$), Hb at initial diagnosis ($P = 0.765$), FIB ($P = 0.786$), PT ($P = 0.914$), APTT ($P = 0.317$), INR ($P = 0.831$), D-dimer ($P = 0.957$), and FDP ($P = 0.842$) demonstrated no considerable differences between the two groups. Sanz risk stratification ($P = 0.841$) and survival status ($P = 0.458$) showed similar distributions. Regarding early supportive therapy, no considerable differences were seen between the two groups in early PLT-CF combined transfusion within 72 hours ($P = 0.338$), PLT transfusion alone ($P = 0.355$), or CF/cryoprecipitate/FIB preparation transfusion ($P = 0.312$). The induction therapy regimen ($P = 0.193$) and time from diagnosis to first ATRA administration ($P = 0.598$) were also comparable. These results indicate balanced baseline characteristics and reasonable data stratification between the training and external validation cohorts, making them suitable for predictive model development and validation (see **Table 1**).

Comparison of baseline characteristics between APL patients who died within 28 day and survivors in the training cohort

Among the 429 APL patients in the training cohort, 85 (19.81%) died within 28 day. Thrpigh the comparison of baseline characteristics, patients in the mortality group were older ($P < 0.001$), with poorer ECOG performance status ($P < 0.001$) and higher CCI comorbidity scores ($P < 0.001$). Regarding laboratory parameters, patients in the mortality group exhibited higher WBC ($P < 0.001$), lower PLT ($P < 0.001$), and lower Hb ($P = 0.021$) at initial diagnosis, and more severe coagulation disorder, manifested by decreased FIB levels, prolonged PT and APTT, raised INR, and increased D-dimer and FDP levels (all $P < 0.001$). By Sanz risk stratification, the proportion of high-risk patients was notably higher in the mortality group ($P < 0.001$). Regarding early supportive therapy, the proportion of patients in the mortality group

Table 1. Comparison of baseline characteristics between training and external validation cohorts in APL patients

Variable	Overall (n = 631)	Training cohort (n = 429)	External validation (n = 202)	Statistical value	*P*-value
Age				1.299	0.254
< 45 years	351 (55.63%)	232 (54.08%)	119 (58.91%)		
≥ 45 years	280 (44.37%)	197 (45.92%)	83 (41.09%)		
Gender				0.155	0.694
Male	357 (56.58%)	245 (57.11%)	112 (55.45%)		
Female	274 (43.42%)	184 (42.89%)	90 (44.55%)		
ECOG performance status score				0.009	0.923
0-1 points	495 (78.45%)	337 (78.55%)	158 (78.22%)		
Points	136 (21.55%)	92 (21.45%)	44 (21.78%)		
CCI Comorbidity Index				1.708	0.191
0 points	401 (63.55%)	280 (65.27%)	121 (59.90%)		
1-3 points	230 (36.45%)	149 (34.73%)	81 (40.10%)		
WBC at initial diagnosis				0.342	0.559
≤ 10 × 10^9/L	358 (56.74%)	240 (55.94%)	118 (58.42%)		
> 10 × 10^9/L	273 (43.26%)	189 (44.06%)	84 (41.58%)		
PLT at initial diagnosis				0.058	0.810
> 40 × 10^9/L	283 (44.85%)	191 (44.52%)	92 (45.54%)		
≤ 40 × 10^9/L	348 (55.15%)	238 (55.48%)	110 (54.46%)		
Sanz risk stratification				0.347	0.841
Low-risk	172 (27.26%)	115 (26.81%)	57 (28.22%)		
Intermediate-risk	186 (29.48%)	125 (29.14%)	61 (30.20%)		
High-risk	273 (43.26%)	189 (44.06%)	84 (41.58%)		
Early PLT-CF combined transfusion within 72 hours				0.917	0.338
Present	333 (52.77%)	232 (54.08%)	101 (50.00%)		
Absent	298 (47.23%)	197 (45.92%)	101 (50.00%)		
PLT transfusion within 72 hours				0.855	0.355
Present	501 (79.40%)	345 (80.42%)	156 (77.23%)		
Absent	130 (20.60%)	84 (19.58%)	46 (22.77%)		
CF/cryoprecipitate/FIB preparation transfusion within 72 hours				1.023	0.312
Present	457 (72.42%)	316 (73.66%)	141 (69.80%)		
Absent	174 (27.58%)	113 (26.34%)	61 (30.20%)		

Induction therapy regimen				3.295	0.193
ATRA + ATO	543 (86.05%)	367 (85.55%)	176 (87.13%)		
ATRA + chemotherapy	59 (9.35%)	38 (8.86%)	21 (10.40%)		
Other	29 (4.60%)	24 (5.59%)	5 (2.48%)		
Survival status				0.551	0.458
Survived	511 (80.98%)	344 (80.19%)	167 (82.67%)		
Died	120 (19.02%)	85 (19.81%)	35 (17.33%)		
Hb at initial diagnosis (g/L)	84.00 [72.00, 98.00]	84.00 [71.00, 98.00]	84.00 [73.00, 98.00]	0.298	0.765
FIB (g/L)	1.27 [0.86, 1.67]	1.27 [0.85, 1.64]	1.27 [0.86, 1.72]	0.271	0.786
PT (s)	17.55 ± 4.54	17.56 ± 4.45	17.52 ± 4.73	-0.108	0.914
APTT (s)	41.32 ± 9.26	41.06 ± 9.42	41.85 ± 8.91	1.001	0.317
INR	1.38 [1.16, 1.62]	1.38 [1.16, 1.61]	1.38 [1.17, 1.64]	0.213	0.831
D-dimer (mg/L)	6.68 [4.12, 9.64]	6.64 [4.28, 9.65]	7.00 [3.93, 9.59]	0.054	0.957
FDP (mg/L)	31.83 [20.52, 45.75]	32.04 [19.90, 45.85]	31.59 [21.63, 44.77]	0.199	0.842
Time from diagnosis/ATRA initiation to first ATRA administration (h)	7.00 [4.00, 10.00]	7.00 [4.00, 10.00]	7.00 [4.00, 10.00]	0.527	0.598

Note: APL, acute promyelocytic leukemia; ECOG, Eastern Cooperative Oncology Group; CCI, Charlson Comorbidity Index; ATRA, all-trans retinoic acid; ATO, arsenic trioxide; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio; FDP, fibrinogen degradation products.

Table 2. Comparison of baseline characteristics between patients who died within 28 day and survivors in the training cohort

Variable	Overall (n = 429)	Died within 28 day (n = 85)	Survived within 28 day (n = 344)	Statistical value	*P*-value
Age				23.555	< 0.001
< 45 years	232 (54.08%)	26 (30.59%)	206 (59.88%)		
≥ 45 years	197 (45.92%)	59 (69.41%)	138 (40.12%)		
Gender				0.362	0.548
Male	245 (57.11%)	51 (60.00%)	194 (56.40%)		
Female	184 (42.89%)	34 (40.00%)	150 (43.60%)		
ECOG performance status score				37.576	< 0.001
0-1 points	337 (78.55%)	46 (54.12%)	291 (84.59%)		
Points	92 (21.45%)	39 (45.88%)	53 (15.41%)		
CCI Comorbidity Index				19.771	< 0.001
0 points	280 (65.27%)	38 (44.71%)	242 (70.35%)		
1-3 points	149 (34.73%)	47 (55.29%)	102 (29.65%)		

WBC at initial diagnosis				35.885	< 0.001
≤ 10 × 10^9/L	240 (55.94%)	23 (27.06%)	217 (63.08%)		
> 10 × 10^9/L	189 (44.06%)	62 (72.94%)	127 (36.92%)		
PLT at initial diagnosis				13.088	< 0.001
> 40 × 10^9/L	191 (44.52%)	23 (27.06%)	168 (48.84%)		
≤ 40 × 10^9/L	238 (55.48%)	62 (72.94%)	176 (51.16%)		
Sanz risk stratification				36.844	< 0.001
Low-risk	115 (26.81%)	8 (9.41%)	107 (31.10%)		
Intermediate-risk	125 (29.14%)	15 (17.65%)	110 (31.98%)		
High-risk	189 (44.06%)	62 (72.94%)	127 (36.92%)		
Early PLT-CF combined transfusion within 72 hours				11.526	< 0.001
Present	232 (54.08%)	32 (37.65%)	200 (58.14%)		
Absent	197 (45.92%)	53 (62.35%)	144 (41.86%)		
PLT transfusion within 72 hours				6.507	0.011
Present	345 (80.42%)	60 (70.59%)	285 (82.85%)		
Absent	84 (19.58%)	25 (29.41%)	59 (17.15%)		
CF/cryoprecipitate/FIB preparation transfusion within 72 hours				2.380	0.123
Present	316 (73.66%)	57 (67.06%)	259 (75.29%)		
Absent	113 (26.34%)	28 (32.94%)	85 (24.71%)		
Induction therapy regimen				0.494	0.781
ATRA + ATO	367 (85.55%)	71 (83.53%)	296 (86.05%)		
ATRA + chemotherapy	38 (8.86%)	8 (9.41%)	30 (8.72%)		
Other	24 (5.59%)	6 (7.06%)	18 (5.23%)		
Hb at initial diagnosis (g/L)	85.34 ± 19.93	80.88 ± 20.06	86.44 ± 19.77	2.313	0.021
FIB (g/L)	1.27 [0.85, 1.64]	0.82 [0.55, 1.15]	1.42 [1.00, 1.78]	8.248	< 0.001
PT (s)	17.56 ± 4.45	20.53 ± 4.74	16.83 ± 4.07	-7.266	< 0.001
APTT (s)	41.06 ± 9.42	46.40 ± 10.37	39.74 ± 8.70	-6.073	< 0.001
INR	1.40 ± 0.38	1.65 ± 0.45	1.34 ± 0.33	-7.361	< 0.001
D-dimer (mg/L)	6.64 [4.28, 9.65]	10.60 [7.13, 14.10]	6.06 [3.73, 8.58]	8.306	< 0.001
FDP (mg/L)	32.04 [19.90, 45.85]	48.64 [30.14, 58.99]	29.06 [18.71, 40.86]	6.471	< 0.001
Time from diagnosis/ATRA initiation to first ATRA administration (h)	7.00 [4.00, 10.00]	7.00 [4.00, 11.00]	7.00 [4.00, 10.00]	0.528	0.598

Note: APL, acute promyelocytic leukemia; ECOG, Eastern Cooperative Oncology Group; CCI, Charlson Comorbidity Index; ATRA, all-trans retinoic acid; ATO, arsenic trioxide; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio; FDP, fibrinogen degradation products.

who received early PLT-CF combined transfusion (P < 0.001) and PLT transfusion alone (P = 0.011) within 72 hours was significantly lower than that in the survival group. No significant differences were observed between groups in gender (P = 0.548), CF/cryoprecipitate/FIB preparation transfusion within 72 hours (P = 0.123), induction therapy regimen (P = 0.781), or time from diagnosis to first ATRA administration (P = 0.598) (see **Table 2**).

Predictive variable selection using LASSO regression

Cox-LASSO regression was employed to screen predictive variables among 429 APL patients in the training cohort. Via 10-fold cross-validation, the optimal penalty parameter lambda.min (λ = 0.0179) was determined, and 14 candidate predictive variables were initially screened. Collinearity diagnostics were then performed on the screened variables. Correlation analysis revealed that the absolute values of Pearson correlation coefficients between all variables were less than 0.6, eliminating the need for variable exclusion. Variance inflation factor (VIF) analysis showed that all variables had VIF values below 5 (maximum: 1.585), indicating no severe multicollinearity. The final 14 variables included in the predictive model were: Hb, FIB, PT, APTT, D-dimer, time from diagnosis to ATRA administration, age, gender, ECOG PS score, CCI, WBC at initial diagnosis, PLT at initial diagnosis, early PLT-CF combined transfusion within 72 hours, and PLT transfusion within 72 hours (see **Figure 1**).

Cox proportional hazards hypothesis testing and model optimization

The initial Cox regression model (Model A, comprising 14 variables) constructed for the training cohort underwent Schoenfeld residuals tests to evaluate the proportional hazards (PH) assumption. Results indicated that the overall PH assumption was not met in the initial model (Global Chi-sq = 38.650, P < 0.001). Specifically, PT (P = 0.001), APTT (P = 0.003), D-dimer (P = 0.001), and ECOG PS score (P = 0.029) violated the PH assumption, indicating that their hazard ratios varied over time rather than remaining constant (see **Figure 2**).

To satisfy the PH assumption for Cox regression, a simplified model (Model D, comprising 10 variables) was established after excluding the aforementioned 4 variables that violated the assumption. The overall PH test for the adjusted model satisfied the assumption (Global Chi-sq = 11.400, P = 0.327). Schoenfeld residuals for all included variables remained stable over time, indicating constant hazard ratios throughout the observation period (see **Figure 3**). The final model incorporated 10 predictive variables: age, gender, CCI, WBC at initial diagnosis, PLT at initial diagnosis, Hb, FIB, time from diagnosis to ATRA administration, early PLT-CF combined transfusion within 72 hours, and CF/cryoprecipitate/FIB preparation transfusion within 72 hours.

Univariate and multivariate Cox regression analysis of risk factors for 28-day mortality in APL patients

In the training cohort, univariate Cox regression analysis was soncudcted to identify potential risk factors for 28-day mortality in APL patients. Results indicated that initial Hb (P = 0.016), FIB (P < 0.001), age (P < 0.001), CCI comorbidity index (P < 0.001), WBC at initial diagnosis (P < 0.001), PLT at initial diagnosis (P < 0.001), early PLT-CF combined transfusion within 72 hours (P < 0.001), and CF/cryoprecipitate/FIB preparation transfusion within 72 hours (P = 0.017) were significantly linked to the risk of 28-day mortality. Time from diagnosis to ATRA administration (P = 0.416) and gender (P = 0.527) showed no remarkable association with the risk of 28-day mortality.

Variables with P < 0.1 in univariate analysis were subject to multivariate Cox regression analysis. Results showed that decreased FIB (P < 0.001), reduced Hb at initial diagnosis (P = 0.034), age ≥ 45 years (P = 0.003), CCI comorbidity index of 1-3 points (P = 0.005), WBC > 10 × 10^9/L at initial diagnosis (P < 0.001), and absence of early PLT-CF combined transfusion within 72 hours (P < 0.001) were independent risk factors for 28-day mortality in APL patients. PLT at initial diagnosis (P = 0.080) and CF/cryoprecipitate/FIB preparation transfusion within 72 hours (P = 0.287) did not demonstrate independent predictive value in multivariate analysis (see **Table 3**).

Construction of a nomogram for predicting 28 day survival in APL patients

Based on 6 independent predictive factors selected through multivariate Cox regression analysis, a nomogram for predicting 28 day sur-

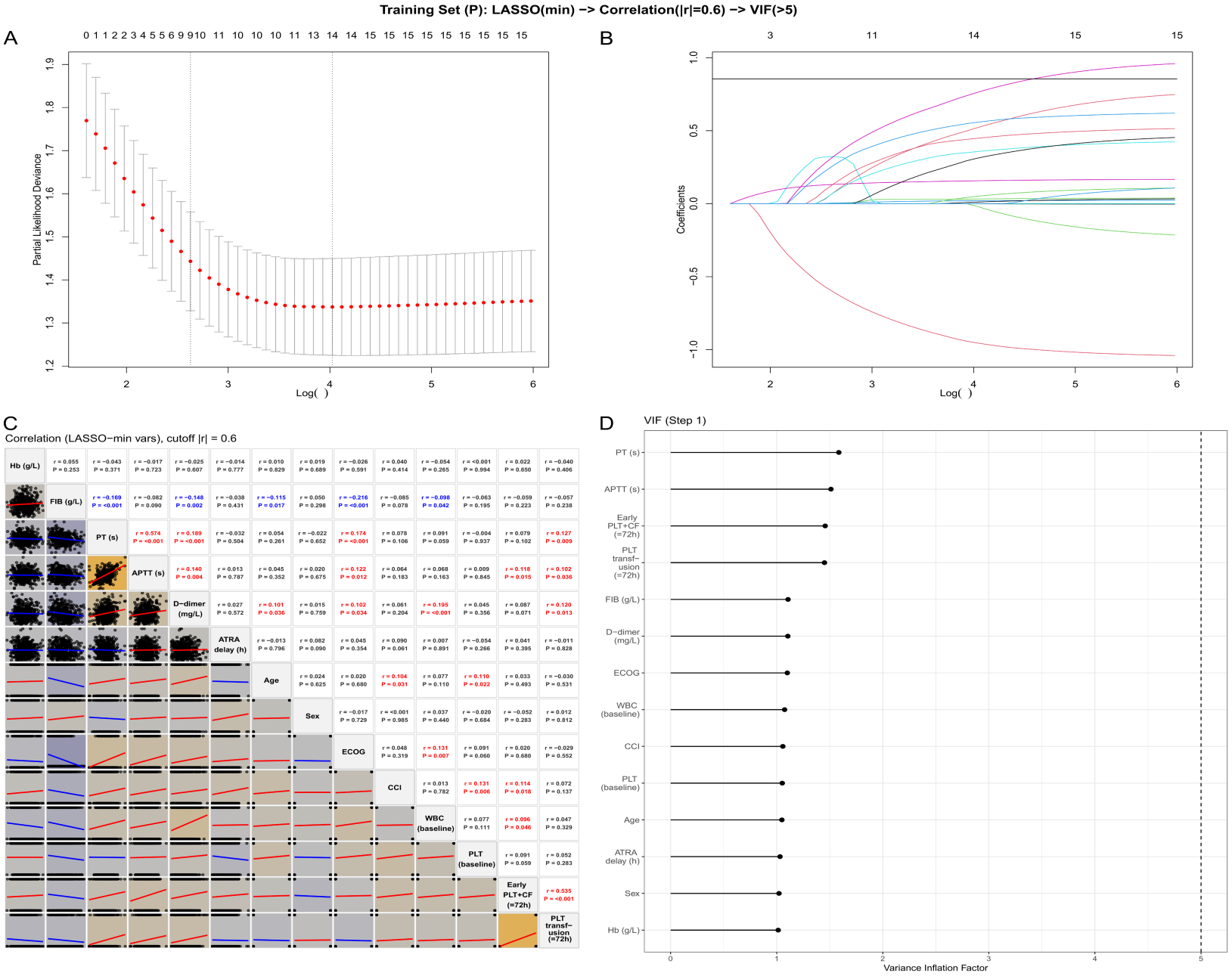
Training Set (P): LASSO(min) –> Correlation(|r|=0.6) –> VIF(>5)
A
0 1 1 2 2 3 4 5 5 6 9 9 10 11 10 10 10 11 13 14 14 15 15 15 15 15 15 15 15 15
Partial Likelihood Deviance
Log( )
B
3 11 14 15 15
Coefficients
Log( )
C
Correlation (LASSO−min vars), cutoff |r| = 0.6
Hb (g/L)
FIB (g/L)
PT (s)
APTT (s)
D−dimer (mg/L)
ATRA delay (h)
Age
Sex
ECOG
CCI
WBC (baseline)
PLT (baseline)
Early PLT+CF (=72h)
PLT transf−usion (=72h)
D
VIF (Step 1)
PT (s)
APTT (s)
Early PLT+CF (=72h)
PLT transf−usion (=72h)
FIB (g/L)
D−dimer (mg/L)
ECOG
WBC (baseline)
CCI
PLT (baseline)
Age
ATRA delay (h)
Sex
Hb (g/L)
Variance Inflation Factor

Figure 1. Variable selection process using LASSO regression with collinearity diagnostics in the training cohort. A. Cross-validated partial likelihood deviance curve for LASSO regression with optimal lambda values indicated. B. LASSO coefficient paths as a function of log(λ). C. Correlation matrix of LASSO-selected variables with Pearson correlation coefficients and *P* values. D. Variance inflation factor (VIF) assessment for multicollinearity diagnosis. Note: LASSO, least absolute shrinkage and selection operator; VIF, variance inflation factor; Hb, hemoglobin; FIB, fibrinogen; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio; ATRA, all-trans retinoic acid; ECOG, Eastern Cooperative Oncology Group; CCI, Charlson Comorbidity Index; WBC, white blood cell; PLT, platelet; CF, coagulation factor.

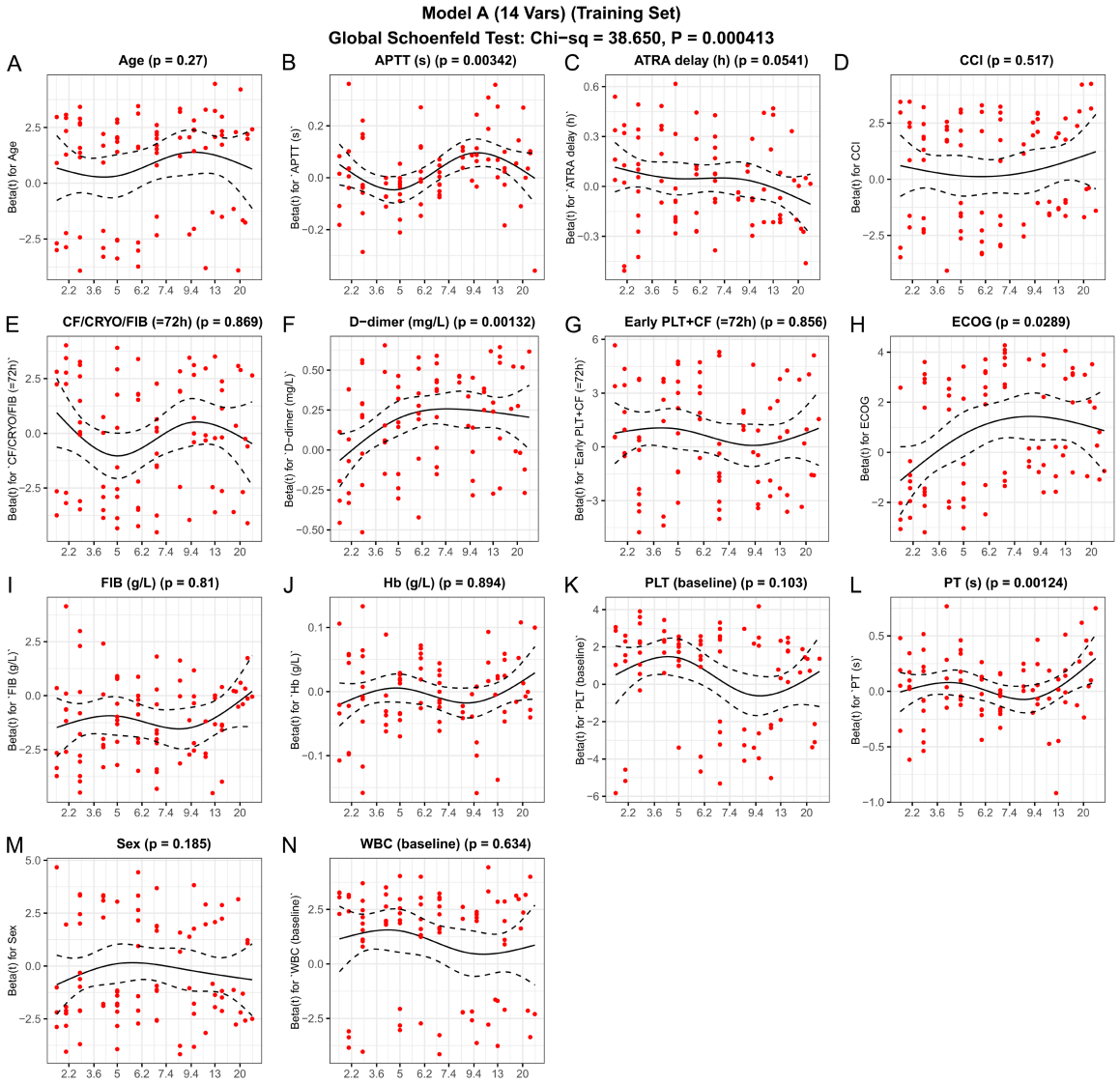

Figure 2. Schoenfeld residual plots for proportional hazards assumption testing of the initial Cox regression model (Model A) in the training cohort. A-N. Scaled Schoenfeld residuals plotted against time for each of the 14 variables in Model A. The solid line represents a smoothing spline fit, and the dashed lines indicate the 95% confidence interval. Variables with P < 0.05 indicate violation of the proportional hazards assumption. Global Schoenfeld test: Chi-sq = 38.650, P < 0.001. Note: PH, proportional hazards; PT, prothrombin time; APTT, activated partial thromboplastin time; ECOG, Eastern Cooperative Oncology Group; CCI, Charlson Comorbidity Index; ATRA, all-trans retinoic acid; FIB, fibrinogen; Hb, hemoglobin; WBC, white blood cell; PLT, platelet; CF, coagulation factor; CRYO, cryoprecipitate.

vival was constructed for APL patients. The predictive variables included in this nomogram included Hb at initial diagnosis (Hb), FIB (FIB), age (Age), CCI (CCI), WBC at initial diagnosis

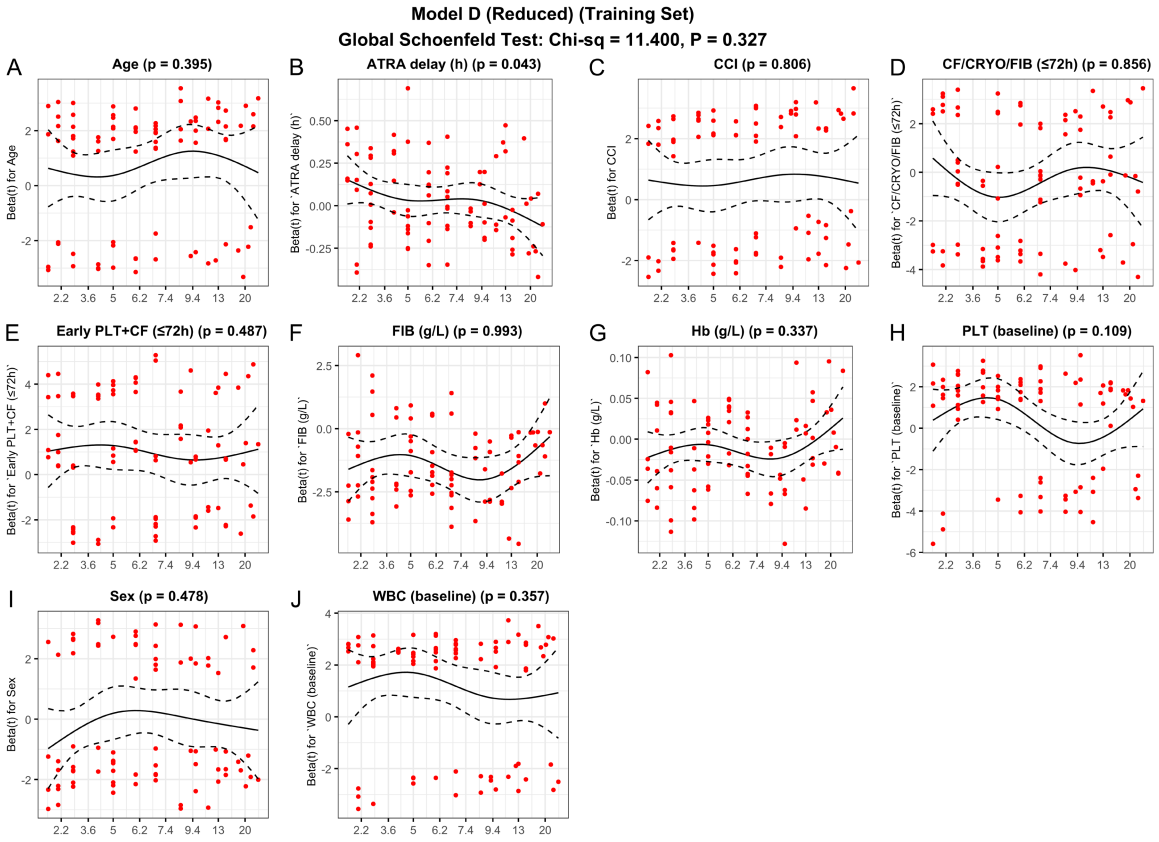

Figure 3. Schoenfeld residual plots for proportional hazards assumption testing of the reduced Cox regression model (Model D) in the training cohort. A-J. Scaled Schoenfeld residuals plotted against time for each of the 10 variables in Model D after excluding variables violating the proportional hazards assumption. Global Schoenfeld test: Chi-sq = 11.400, P = 0.327. Note: PH, proportional hazards; PT, prothrombin time; APTT, activated partial thromboplastin time; ECOG, Eastern Cooperative Oncology Group; CCI, Charlson Comorbidity Index; ATRA, all-trans retinoic acid; FIB, fibrinogen; Hb, hemoglobin; WBC, white blood cell; PLT, platelet; CF, coagulation factor; CRYO, cryoprecipitate.

(WBC), and early PLT-CF combined transfusion within 72 hours (EarlyTransfusion). When using the tool, the specific values of each predictive variable for the patient were first determined. Then, the corresponding scores were obtained by aligning these values with the top scale. The scores of all variables were summed up to calculate the Total Points. Subsequently, the predicted 28 day survival probability for the patient was acquired by aligning the Total Points with the bottom scale. The nomogram indicates that FIB levels contributed most significantly to the predictive score, followed by WBC at initial diagnosis and the status of early PLT-CF combined transfusion within 72 hours (see **Figure 4**).

Time-dependent ROC curve analysis of the predictive model

The predictive models' discriminatory capabilities at different time points were assessed with time-dependent ROC curves. In the training cohort, the AUC values for predicting 7-day, 14-day, 21-day, and 28-day mortality risks were 0.896 (95% CI: 0.859-0.933), 0.906 (95% CI: 0.872-0.939), 0.902 (95% CI: 0.869-0.935), and 0.890 (95% CI: 0.853-0.926), respectively. In the external validation cohort, the model demonstrated superior discriminatory capability, with for predicting 7-day, 14-day, 21-day, and 28-day mortality risks of 0.934 (95% CI: 0.884-0.984), 0.946 (95% CI: 0.910-0.983), 0.946 (95% CI: 0.912-0.981), and 0.945 (95% CI: 0.911-0.979), respectively. With 28-day mortality as endpoint, at the optimal cutoff value, the training cohort showed a sensitivity of 84.71%, specificity of 80.23%, and accuracy of 81.12%; the validation cohort showed a sensitivity of 94.29%, specificity of 83.23%, and accuracy of 85.15%. The results above indicate that the predictive model demonstrates strong discrimination capabilities in both the training cohort

Table 3. Univariate and multivariate Cox regression analysis of risk factors for 28-day mortality in APL patients (training cohort)

Variable	Univariate			Multivariate		
	β	*P*-value	HR (95% CI)	β	*P*-value	HR (95% CI)
Hb at initial diagnosis (g/L)	-0.014	0.016	0.987 (0.976-0.997)	-0.012	0.034	0.989 (0.978-0.999)
FIB (g/L)	-1.649	< 0.001	0.192 (0.126-0.293)	-1.372	< 0.001	0.254 (0.166-0.388)
Time from diagnosis/ATRA initiation to first ATRA administration (h)	0.02	0.416	1.02 (0.972-1.071)			
Age						
< 45 years			Ref			Ref
≥ 45 years	1.087	< 0.001	2.965 (1.869-4.705)	0.711	0.003	2.037 (1.267-3.274)
Gender						
Male			Ref			
Female	-0.14	0.527	0.869 (0.563-1.342)			
CCI comorbidity index						
0 points			Ref			Ref
1-3 points	0.96	< 0.001	2.611 (1.702-4.005)	0.63	0.005	1.877 (1.208-2.918)
WBC at initial diagnosis						
≤ 10×10^9/L			Ref			Ref
> 10×10^9/L	1.388	< 0.001	4.007 (2.482-6.469)	1.148	< 0.001	3.151 (1.939-5.122)
PLT at initial diagnosis						
> 40×10^9/L			Ref			Ref
≤ 40×10^9/L	0.876	< 0.001	2.401 (1.488-3.875)	0.442	0.080	1.556 (0.949-2.551)
Early PLT-CF combined transfusion within 72 hours						
Present			Ref			Ref
Absent	1.109	< 0.001	3.03 (1.91-4.808)	0.998	< 0.001	2.713 (1.575-4.676)
CF/cryoprecipitate/FIB preparation transfusion within 72 hours						
Present			Ref			Ref
Absent	0.537	0.017	1.711 (1.1-2.662)	-0.282	0.287	0.754 (0.449-1.268)

Note: HR, hazard ratio; CI, confidence interval; ATRA, all-trans retinoic acid; CCI, Charlson Comorbidity Index; Ref, reference.

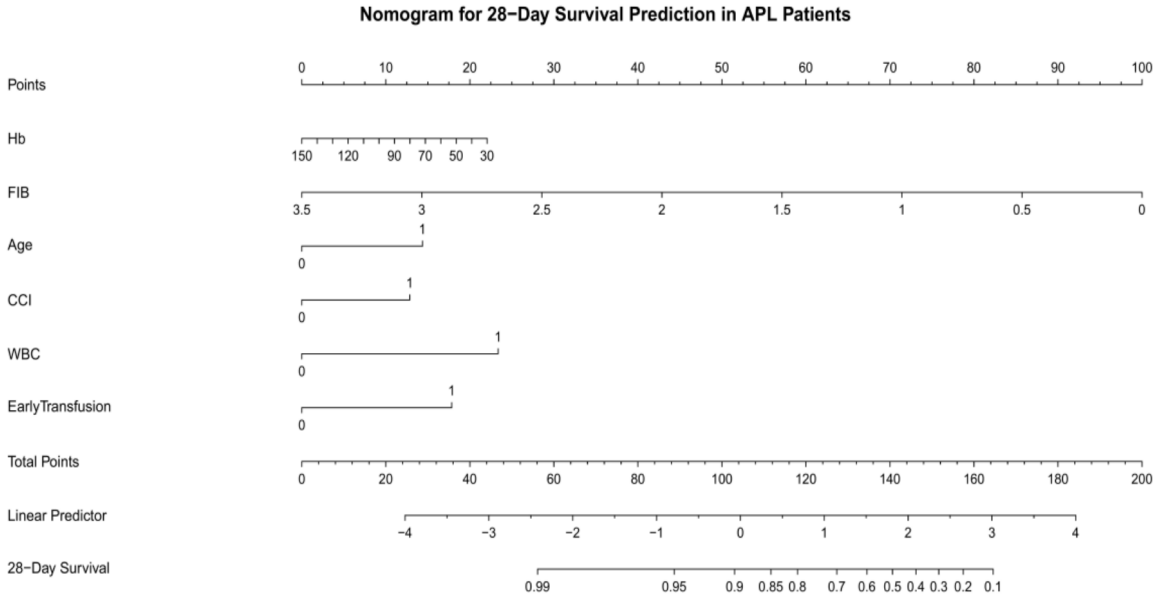

Figure 4. Nomogram for predicting 28 day survival probability in APL patients. Note: APL, acute promyelocytic leukemia; Hb, hemoglobin; FIB, fibrinogen; CCI, Charlson Comorbidity Index; WBC, white blood cell count; EarlyTransfusion, early platelet-coagulation factor combined transfusion within 72 hours.

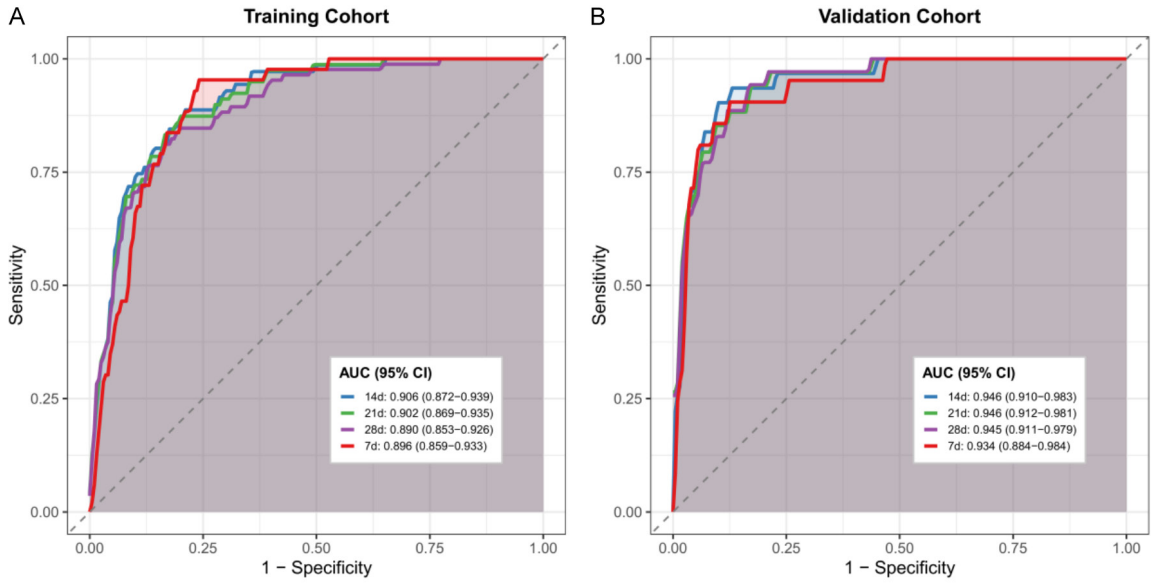

Figure 5. Time-dependent ROC curves for the prediction model in training and validation cohorts. A. Time-dependent ROC curves at 7, 14, 21, and 28 days in the training cohort. B. Time-dependent ROC curves at 7, 14, 21, and 28 days in the validation cohort. Shaded areas represent the AUC for each time point. Note: ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval.

and the external validation cohort (see **Figure 5**).

Calibration curve analysis of the predictive model

The calibration performance of the predictive model was assessed with calibration curves. In the training cohort, the model achieved a C-index of 0.858 (95% CI: 0.827-0.890), with a *P*-value of 0.125 by Hosmer-Lemeshow test and a Brier score of 0.1024. The Brier score measures the mean squared difference between predicted probabilities and actual outcomes; it ranges from 0 to 1, with lower values indicating better calibration. A Brier score < 0.25 is generally considered informative for clinical prediction models, and values < 0.1 indicate excellent calibration. In the external validation cohort, the model achieved a C-index of 0.913 (95% CI: 0.880-0.946), with a *P*-value of 0.317 by Hosmer-Lemeshow test and a Brier score of 0.0732, further confirming the model's outstanding calibration performance. The *P*-values by Hosmer-Lemeshow test were > 0.05 for both groups, indicating no significant difference between predicted probabilities and observed probabilities. The calibration curve demonstrates favorable consistency between predicted probabilities and observed probabilities, with predicted points distributed near the diagonal line. This indicates good calibration performance of the model in both the training and external validation cohorts (see **Figure 6**).

Decision curve analysis of the predictive model

Decision curve analysis (DCA) was employed to evaluate the clinical utility of the predictive model. In the training cohort, when the threshold probability ranged from 0-60%, the net benefit curve of the predictive model remained above the "treat all" and "treat none" strategies. The maximum net benefit reached 0.1270, corresponding to an optimal threshold probability of 20.0%. In the external validation cohort, the predictive model also demonstrated a net benefit superior to the extreme strategy, with a maximum net benefit of 0.1303 and a corresponding optimal threshold probability of 18.0%. These results indicate that across a broad range of threshold probabilities, using this predictive model to guide clinical decision-making yields a net benefit for patients, suggesting its strong clinical utility (see **Figure 7**).

Kaplan-Meier survival analysis stratified by predictive model-based risks

On the basis of risk scores calculated via the predictive model, patients were categorized into high-risk and low-risk groups by the opti-

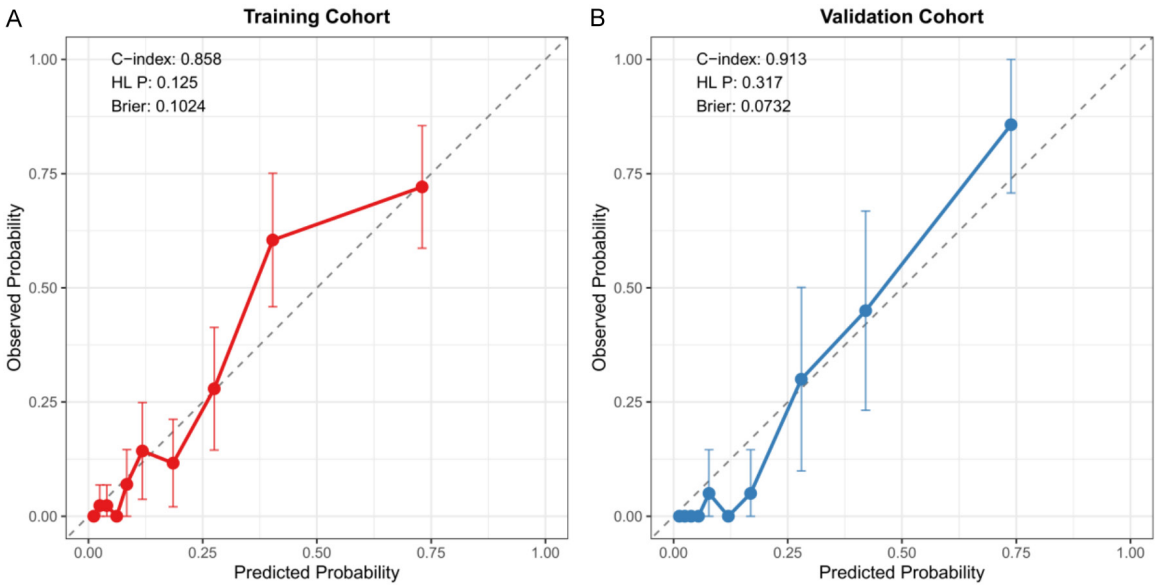

Figure 6. Calibration curves for the prediction model in training and validation cohorts. A. Calibration curve for 28-day mortality prediction in the training cohort. B. Calibration curve for 28-day mortality prediction in the validation cohort. The dashed diagonal line represents perfect calibration. Error bars indicate 95% confidence intervals. Note: C-index, concordance index; HL, Hosmer-Lemeshow.

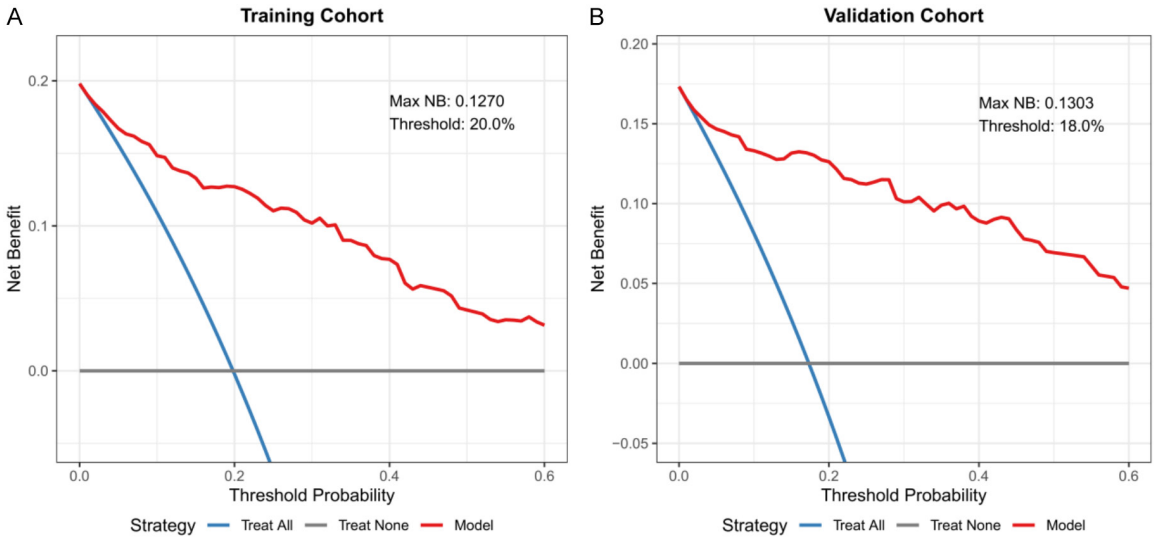

Figure 7. Decision curve analysis for the prediction model in training and validation cohorts. A. Decision curve analysis for 28-day mortality prediction in the training cohort. B. Decision curve analysis for 28-day mortality prediction in the validation cohort. The red line represents the prediction model, the blue line represents the "Treat All" strategy, and the gray line represents the "Treat None" strategy. Note: DCA, decision curve analysis; NB, net benefit.

mal cutoff value (1.2389). In the training cohort, there were 344 cases in the low-risk group and 85 cases in the high-risk group; in the external validation cohort, there were 157 cases in the low-risk group and 45 cases in the high-risk group. According to the Kaplan-Meier survival analysis, the 28 day survival rates of patients in the high-risk group in both the training cohort and external validation cohort were remarkably lower than those in the low-risk group (both $P < 0.0001$ by log-rank test). For the training cohort, 28 cases (8.1%) in the low-risk group and 57 cases (67.1%) in the high-risk group died within 28 day; for the external validation cohort, 6 cases (3.8%) in the low-risk group and 29 cases (64.4%) in the high-risk group died within 28

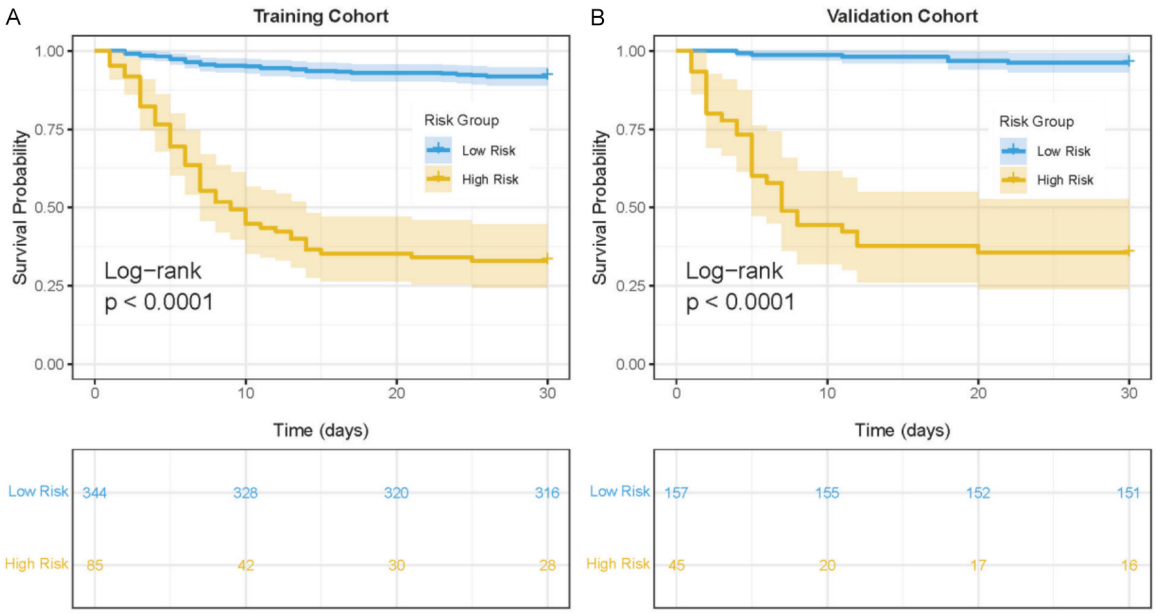

Figure 8. Kaplan-Meier survival curves stratified by risk groups in training and validation cohorts. A. Kaplan-Meier survival curves for low-risk and high-risk groups in the training cohort with risk table. B. Kaplan-Meier survival curves for low-risk and high-risk groups in the validation cohort with risk table. Patients were stratified based on the optimal risk score cutoff of 1.2389. Note: K-M, Kaplan-Meier.

day. The results above indicate that the predictive model effectively identified high-risk individuals among APL patients (see **Figure 8**).

Comparison of discrimination capability between the predictive model and Sanz risk stratification

The discriminatory ability of the predictive model versus the traditional Sanz risk stratification in assessing the 28-day mortality risk among patients with acute pancreatitis was compared using the ROC curves. In the training cohort, the AUC of the predictive model was 0.890 (95% CI: 0.853-0.926), significantly higher than the AUC (0.693, 95% CI: 0.639-0.746) of the Sanz risk stratification, with $P < 0.001$ by the DeLong test. In the external validation cohort, the AUC of the predictive model was 0.945 (95% CI: 0.910-0.979), also significantly superior to the AUC (0.759, 95% CI: 0.687-0.830) of the Sanz risk stratification, with $P < 0.001$ by the DeLong test. The results above prove that the predictive model established in this study significantly outperforms the traditional Sanz risk stratification system in distinguishing the 28-day mortality risk among APL patients, demonstrating superior predictive efficacy (see **Figure 9**).

Discussion

APL is a kind of acute myeloid leukemia with the optimal prognosis; its long-term survival rate exceeds 90% with the combination of ATRA and ATO [2]. However, early mortality is still a major obstacle affecting the overall prognosis of APL, with real-world studies reporting a 28-day mortality rate as high as 10%-30%, far exceeding the 3%-10% documented in clinical trials [25, 26]. Based on a cohort of 631 APL patients from two tertiary hospitals, a 28-day mortality rate of 19.02% was reported in this study, consistent with findings from previous real-world studies. The 28-day mortality risk prediction nomogram model integrating an early PLT-CF combined transfusion strategy was successfully constructed and validated. As a model, incorporating six independent predictive factors, it demonstrated excellent discrimination capability and good calibration in both the training and external validation cohorts. Moreover, it demonstrates significantly superior predictive performance relative to the traditional Sanz risk stratification system, providing a more precise tool for early identification of high-risk patients.

As for early mortality rates in APL, there is a significant disparity between clinical trials and

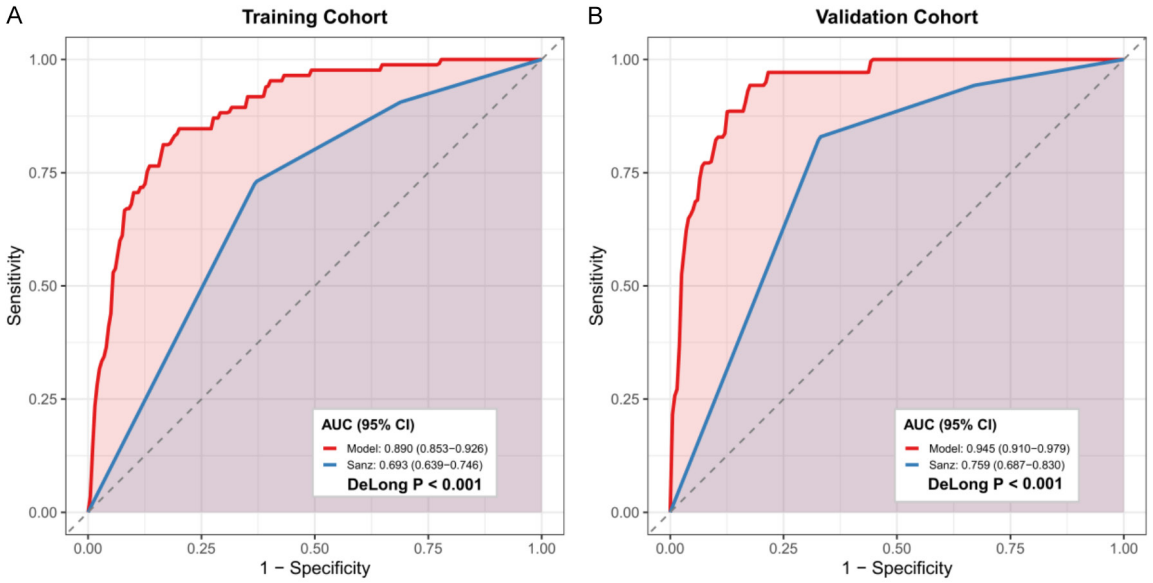

Figure 9. Comparison of ROC curves between the prediction model and Sanz risk stratification for 28-day mortality prediction. A. ROC curves comparing the prediction model (red) and Sanz risk stratification (blue) in the training cohort. B. ROC curves comparing the prediction model (red) and Sanz risk stratification (blue) in the validation cohort. DeLong test was used to compare the AUCs between the two methods. Note: ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval.

real-world studies, primarily attributable to the following factors. First, patients who are elderly, have poor performance status, or present with multiple comorbidities are generally excluded from clinical trials, yet they are precisely at higher risk for early mortality [27]. Second, diagnosis confirmation and treatment initiation are faster in clinical trials, as well as more standardized supportive care; additionally, medical centers involved in clinical trials usually have more extensive experience in APL diagnosis and treatment [28]. Hemorrhage is the leading cause of early mortality in APL, accounting for approximately 40%-65% of early deaths, with intracranial hemorrhage being the most fatal [29]. APL cells express tissue factor and procoagulant substances and release plasminogen activator, resulting in a unique coagulopathy characterized by disseminated intravascular coagulation (DIC) and primary hyperfibrinolysis [30]. This complex coagulation disorder is the pathophysiological basis for the high bleeding risk in APL. The Sanz risk stratification system, which is currently widely used in clinical practice, categorizes patients into low-risk, intermediate-risk, and high-risk groups by WBC and PLT at initial diagnosis. However, this system has limited predictive ability for early mortality, as it was primarily designed to predict recurrence risk and guide chemotherapy intensity [31]. Hence, specialized predictive tools for early mortality are urgently needed in clinics.

Through multivariate Cox proportional hazards regression analysis, six independent predictors of 28-day mortality were identified: hypofibrinogenemia (FIB, reflecting DIC consumption and hyperfibrinolysis), elevated initial WBC (> 10 × 10^9/L, indicating high tumor burden and procoagulant release), age ≥ 45 years (associated with reduced organ reserve), a CCI score of 1-3 (capturing baseline comorbidity burden), low hemoglobin (indicating bone marrow suppression or bleeding), and absence of early platelet-coagulation factor (PLT-CF) combined transfusion within 72 hours (depriving timely correction of the dual hemostatic defect). The strongest predictor was FIB levels (HR = 0.254), whose reduction notably increased the risk of early mortality. Hypofibrinogenemia is a core feature of APL-related coagulopathy, primarily caused by both DIC consumption and hyperfibrinolysis degradation [32]. FIB levels at diagnosis are an independent predictor of fatal bleeding during the induction phase of APL, with hypofibrinogenemia significantly linked to increased risk of early mortality [33]. According to international guidelines, active supplementation with FIB preparations is recommended in APL patients to maintain levels ≥ 1.5 g/L [2]. The results

obtained herein further confirm the pivotal role of FIB in the prediction of early mortality in APL.

A WBC > 10 × 10^9/L at initial diagnosis notably increases the risk of early mortality (HR = 3.151), consistent with findings from a recent real-world study [34]. Elevated WBC reflects high tumor burden, and APL cells release increased procoagulant substances that exacerbate DIC; additionally, patients with elevated WBC also face a notably heightened risk of APL differentiation syndrome [35]. Age ≥ 45 years is identified as an independent risk factor (HR = 2.037). Reduced organ function reserve, increased comorbidities, and poor tolerance to chemotherapy and supportive care are observed in elderly patients, and they are more prone to severe bleeding and infections [10]. The CCI reflects patients' health status at baseline: a CCI score of 1-3 denotes increased risk of mortality (HR = 1.877), indicating that comorbidity burden notably affects early prognosis in APL patients. The U.S. SEER database and the European HARMONY platform have also revealed that APL patients with underlying conditions (e.g., cardiovascular disease, diabetes, or renal insufficiency) experience a substantially increased risk of early mortality [17, 36]. Reduced hemoglobin levels are also an independent risk factor (HR = 0.989). Although the HR value was close to 1, the statistical significance was clear (P = 0.034). Low Hb levels may be associated with the degree of bone marrow suppression, blood loss, or poor nutritional status. Tissue hypoxia caused by anemia may further impair organ function, resulting in reduced tolerance to complications in patients [37].

The core finding of this study is the association between early PLT-CF combined transfusion within 72 hours and the risk of 28-day mortality. Patients who did not receive the combined transfusion had a 2.713-fold higher risk of death than those who received the combined transfusion (P < 0.001), which holds significant clinical implications and biological plausibility. APL-associated coagulopathy is considered distinctive due to the concurrent presence of PLT decreased (bone marrow infiltration and DIC consumption) and CF deficiency (DIC consumption and fibrinolytic degradation); besides, single-component transfusion may be insufficient to correct this complex coagulation disorder [38]. PLTs are central to primary hemostasis, while CFs are key to secondary hemostasis. Hemostatic function can be effectively restored only through their coordinated action. APL patients should maintain PLT ≥ 30-50 × 10^9/L and prothrombin levels ≥ 1.5 g/L [39] according to a recent review by Sanz and Montesinos in 2023, which reflects the principle of concurrent correction of PLT and CF deficiencies. The clinical data obtained herein proved the importance of this strategy.

From a biological standpoint, it is plausible that the protective effect of early PLT-CF combined transfusion may differ according to the severity of coagulopathy and tumor burden. Patients with severe hypofibrinogenemia and hyperleukocytosis represent a particularly high-risk subgroup in whom both platelet and coagulation factor consumption are pronounced, and combined dual-component transfusion may theoretically confer greater hemostatic benefit than single-component transfusion [38, 39]. However, formal interaction or stratified subgroup analyses were not performed in the present study. The identification of FIB and WBC as independent predictors alongside early combined transfusion in the multivariate model suggests that these factors contribute additively to mortality risk rather than through a demonstrated statistical interaction. Whether the benefit of early combined transfusion is modified by baseline FIB levels or WBC count re mains a hypothesis that requires dedicated investigation in future studies with larger sample sizes and pre-specified subgroup analyses.

Of note, the time window for early transfusion was defined as within 72 hours, as multiple recent registry studies and systematic reviews indicate that early mortality in APL predominantly occurs within the first few days to 1-2 weeks after diagnosis, with the first week being a particularly high-risk window [9]. To correct coagulation disorders actively within this critical time window may represent an effective strategy to reduce the risk of bleeding and early mortality. Here, the proportion of patients in the mortality group who received PLT-CF combined transfusion within 72 hours (26.67%) was substantially lower relative to the survival group (58.90%), exhibiting the protective effect of early combined transfusion. However, the association between combined transfusion and mortality may be influenced by confounding factors because of the retrospective nature of this study. For example, critically ill patients

may fail to receive scheduled transfusion therapy because of rapid deterioration (reverse causality), or inherently conservative transfusion strategies may be employed in some hospitals. To control for confounding factors, baseline coagulation parameters (FIB), PLT, and WBC that indicate disease severity were incorporated into the multivariate Cox regression model. Additionally, we conducted a sensitivity analysis by repeating the analysis after excluding cases of death that occurred within 72 hours and found that combined transfusion remained an independent protective factor (data not shown). Nevertheless, further prospective studies are required to validate its causal relationship.

In terms of model performance, 28-day mortality was utilized as the time-to-event outcome, Cox proportional hazards regression was employed for predictive model construction, and a comprehensive evaluation was initiated based on the 28 day cumulative risk probability predicted by the model. As indicated by the results, this model showed excellent discrimination capability in both cohorts: the 28 day time-dependent AUC was 0.890 (95% CI: 0.853-0.926) in the training cohort and 0.945 (95% CI: 0.911-0.979) in the external validation cohort, both meeting the evaluation criteria for an excellent predictive model (AUC > 0.85). Furthermore, the AUC values remained stable overall when conducting time-dependent analyses at different time points (7 days, 14 days, 21 days, and 28 day), indicating consistent and reliable predictive capability of the model throughout the entire early observation period. Of note, the AUC in the external validation cohort exceeded that in the training cohort. This phenomenon has also been reported in studies on clinical prediction model and may be attributed to the following: First, the small sample size and limited number of events in the external validation cohort may lead to increased variability of the AUC estimate; Second, the APL diagnosis and treatment processes at the external validation center may be more standardized, so that the patient case mix is more homogeneous; Third, patient sources, referral patterns, and supportive treatment strategies may vary between the two centers. Nevertheless, the 95% confidence interval for the AUC of the external validation cohort still indicated a degree of uncertainty. According to the latest recommendations from the TRIPOD + AI Statement, any predictive model must undergo external validation on additional independent populations before being deployed in practice to further confirm its robustness and generalization ability [40]. Regarding calibration, favorable agreement was seen between the model-predicted probabilities and the actual observed outcomes. Prediction errors was evaluated with the time-dependent Brier score via inverse probability of censoring weighting (IPCW). At the 28 day time point, the Brier scores for the training and validation cohorts were 0.1024 and 0.0732, respectively, both at low levels, suggesting high predictive accuracy of the model. DCA revealed that this model yielded positive net benefit within the 0-60% threshold probability range when it was applied to guide clinical decision-making, with an optimal threshold probability of approximately 18%-20%, indicating strong practical applicability in clinics [41].

The model demonstrates significant advantages in predicting early mortality among APL patients compared with the traditional Sanz risk stratification system. In the training cohort, the 28 day AUC was 0.890 for the model and 0.693 only for the Sanz stratification; in the external validation cohort, the AUC was 0.945 for the model and 0.759 for the Sanz stratification. The Bootstrap resampling method exhibited statistically significant differences in AUC between the two models. Multiple real-world studies have also indicated that the Sanz stratification system (primarily based on WBC and PLT at initial diagnosis) has limited predictive capability for early mortality, as it was designed to guide the intensity of induction therapy and predict recurrence risk [34, 42, 43]. In recent years, there have been attempts to establish predictive models or risk scoring systems for early mortality in APL. For example, Österroos et al. constructed a risk scoring model to predict early mortality in APL based on real-world cohorts, which is superior to traditional Sanz stratification in distinguishing early mortality risk [42]. A 28 day early mortality risk stratification model was developed and validated in a multicenter cohort by Kim et al., emphasizing the importance of incorporating patient baseline status and disease severity into compre-

hensive assessment [34]. The nomogram model established by Hao et al. demonstrated that coagulation parameters and supportive therapy-related variables can provide significant incremental value in early mortality prediction [43]. Compared with the aforementioned models, a higher and more stable time-dependent AUCs was obtained in this study by integrating coagulation function, physiological reserve status, and early supportive treatment strategies, which further highlights the potential advantages of multidimensional risk assessment in early mortality prediction in APL. Neverthless, this model is not intended to replace the Sanz stratification system but rather to complement it: the Sanz stratification system is mainly applied to guide induction therapy regimens and assess recurrence risk, while this model focuses specifically on risk assessment of early mortality. It is recommended to use these two tools in combination in clinics to achieve more comprehensive and precise risk stratification for APL patients.

Patients were categorized into high-risk and low-risk groups by optimal cutoff values based on risk scores calculated from the nomogram. Kaplan-Meier survival analysis showed remarkable differences in 28 day survival rates between the two groups: in the training cohort, the 28-day mortality rate was 67.1% in the high-risk group and only 8.1% in the low-risk group; in the validation cohort, the 28-day mortality rate was 64.4% in the high-risk group and 3.8% in the low-risk group (both $P < 0.0001$ by log-rank test). With the remarkable risk stratification capability, the nomogram is highly valuable in clinical applications. The following clinical interventions may be adopted for patients identified as high-risk: more aggressive blood product support (to raise the thresholds for PLT and FIB transfusions), closer monitoring of coagulation parameters (tests/examinations repeated every 6-12 hours), admission to an ICU or hematology laminar-flow ward, early identification and management of bleeding signs, and referral to centers with extensive experience in APL diagnosis and treatment when necessary [44]. The visual characteristics of nomogram allows for rapid clinical assessment of individual risk, which may serve as an auxiliary tool in doctor-patient communication and informed consent.

There are certain limitations in the study. First, the retrospective nature may introduce selection bias and information bias, as some data depended on the accuracy and completeness of medical records. Second, although the model demonstrated excellent discrimination in both cohorts, the AUC and C-index in the external validation cohort (0.945 and 0.913) were numerically higher than those in the training cohort (0.890 and 0.858), which deviates from the typical pattern where model performance is expected to be lower in an independent validation sample. Several factors may account for this observation. The 95% CIs of the AUCs overlapped substantially (training: 0.853-0.926; validation: 0.911-0.979), indicating that the difference may not be statistically significant. The relatively small validation sample ($n = 202$) with a limited number of events ($n = 35$) increases estimate variability, and an upward fluctuation of the point estimate cannot be excluded. Such a phenomenon has been documented in clinical prediction model research, where models may show numerically higher discrimination in external samples with more homogeneous case-mix or less variability in unmeasured confounders. Furthermore, high discrimination does not equate to perfect calibration; the model's calibration was independently confirmed in the validation cohort (Brier score 0.0732, Hosmer-Lemeshow $P = 0.317$). Nevertheless, these results must be interpreted with caution, and further external validation in larger, geographically diverse cohorts is warranted to confirm the model's generalizability. Third, the early combined transfusion strategy was not randomly assigned. Although we adjusted for baseline coagulation parameters and disease severity in the multivariate analysis and performed sensitivity analyses (excluding cases of death within 72 hours), prospective studies or randomized controlled trials are required to confirm the causal relationship between combined transfusion and mortality. In the future, propensity score matching or weighting methods may be considered to control for confounding factors, or center effects may be incorporated into the model as random effects. Fourth, several potential confounders closely related to transfusion decision-making - including baseline bleeding severity (e.g., WHO bleeding grade), the presence and site of active hemorrhage at presentation, and the urgency of

clinical intervention - were not systematically recorded in the electronic medical records and could not be adjusted for. These unmeasured factors may have influenced both the decision to administer early combined transfusion and the risk of early mortality, thereby further limiting the causal inference regarding the observed protective association of early PLT-CF combined transfusion. This association should therefore be interpreted with caution, and confirmation through prospective studies or randomized controlled trials with standardized bleeding assessment is warranted. Fifth, this study did not include all potential predictors (e.g., lactate dehydrogenase, creatinine, specific bleeding sites, the occurrence of differentiation syndrome; these factors may provide incremental predictive value to the model). Sixth, we defined all-cause mortality within 28 days as the endpoint without distinguishing between causes (e.g., hemorrhagic mortality, differentiation syndrome-related mortality, or infectious mortality). Specialized predictive models targeting specific causes of death should be developed in future studies. Seventh, potential effect modification between early combined transfusion and coagulation parameters (particularly FIB) or tumor burden (WBC) was not formally assessed through interaction terms or stratified subgroup analyses. The mechanistic discussion regarding differential transfusion benefit across risk strata should therefore be considered hypothesis-generating and requires verification in future studies. Last, the data for this study spans from 2019 to 2024. Current treatment concepts and supportive care strategies may differ from those in earlier periods, and the applicability of the model in other timeframes requires validation.

Conclusion

This study successfully established and validated a risk prediction nomogram model integrating an early PLT-CF combined transfusion strategy for predicting 28-day mortality in ALP patients. The model incorporates six readily accessible clinical predictors (FIB, WBC, age, CCI, Hb level, and the status of early PLT-CF combined transfusion within 72 hours), showing favorable discrimination, calibration, and clinical utility, which is superior to the traditional Sanz risk stratification system in predictive performance. The findings highlight the critical role of FIB levels and early combined transfusion strategies in risk assessment of early mortality in APL, providing evidence-based support for identifying high-risk patients and optimizing individualized supportive care strategies in clinics.

Disclosure of conflict of interest

None.

Address correspondence to: Shuaikui Zheng, Department of Blood Transfusion, Henan Provincial People's Hospital, People's Hospital of Zhengzhou University, No. 7, Weiwu Road, Jinshui District, Zhengzhou 450000, Henan, China. Tel: +86-0371-65580575; E-mail: zhengskky@163.com

References

[1] Lo-Coco F, Avvisati G, Vignetti M, Thiede C, Orlando SM, Iacobelli S, Ferrara F, Fazi P, Cicconi L, Di Bona E, Specchia G, Sica S, Divona M, Levis A, Fiedler W, Cerqui E, Breccia M, Fioritoni G, Salih HR, Cazzola M, Melillo L, Carella AM, Brandts CH, Morra E, von Lilienfeld-Toal M, Hertenstein B, Wattad M, Lübbert M, Hänel M, Schmitz N, Link H, Kropp MG, Rambaldi A, La Nasa G, Luppi M, Ciceri F, Finizio O, Venditti A, Fabbiano F, Döhner K, Sauer M, Ganser A, Amadori S, Mandelli F, Döhner H, Ehninger G, Schlenk RF and Platzbecker U. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med 2013; 369: 111-121.

[2] Sanz MA, Fenaux P, Tallman MS, Estey EH, Löwenberg B, Naoe T, Lengfelder E, Döhner H, Burnett AK, Chen SJ, Mathews V, Iland H, Rego E, Kantarjian H, Adès L, Avvisati G, Montesinos P, Platzbecker U, Ravandi F, Russell NH and Lo-Coco F. Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet. Blood 2019; 133: 1630-1643.

[3] Cicconi L, Platzbecker U, Avvisati G, Paoloni F, Thiede C, Vignetti M, Fazi P, Ferrara F, Divona M, Albano F, Efficace F, Sborgia M, Di Bona E, Breccia M, Borlenghi E, Cairoli R, Rambaldi A, Melillo L, La Nasa G, Fiedler W, Brossart P, Hertenstein B, Salih HR, Annibali O, Wattad M, Lubbert M, Brandts CH, Hanel M, Rollig C, Schmitz N, Link H, Frairia C, Fozza C, Maria D'Arco A, Di Renzo N, Cortelezzi A, Fabbiano F, Dohner K, Ganser A, Dohner H, Amadori S, Mandelli F, Voso MT, Ehninger G, Schlenk RF and Lo-Coco F. Long-term results of all-trans retinoic acid and arsenic trioxide in non-high-risk acute promyelocytic leukemia: update of the APL0406 Italian-German randomized trial. Leukemia 2020; 34: 914-918.

[4] Abaza Y, Kantarjian H, Garcia-Manero G, Estey E, Borthakur G, Jabbour E, Faderl S, O'Brien S, Wierda W, Pierce S, Brandt M, McCue D, Luthra R, Patel K, Kornblau S, Kadia T, Daver N, DiNardo C, Jain N, Verstovsek S, Ferrajoli A, Andreeff M, Konopleva M, Estrov Z, Foudray M, McCue D, Cortes J and Ravandi F. Long-term outcome of acute promyelocytic leukemia treated with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab. Blood 2017; 129: 1275-1283.

[5] Iland HJ, Bradstock K, Supple SG, Catalano A, Collins M, Hertzberg M, Browett P, Grigg A, Firkin F, Hugman A, Reynolds J, Di Iulio J, Tiley C, Taylor K, Filshie R, Seldon M, Taper J, Szer J, Moore J, Bashford J and Seymour JF. All-trans-retinoic acid, idarubicin, and IV arsenic trioxide as initial therapy in acute promyelocytic leukemia (APML4). Blood 2012; 120: 1570-1580; quiz 1752.

[6] Burnett AK, Russell NH, Hills RK, Bowen D, Kell J, Knapper S, Morgan YG, Lok J, Grech A, Jones G, Khwaja A, Friis L, McMullin MF, Hunter A, Clark RE and Grimwade D. Arsenic trioxide and all-trans retinoic acid treatment for acute promyelocytic leukaemia in all risk groups (AML17): results of a randomised, controlled, phase 3 trial. Lancet Oncol 2015; 16: 1295-1305.

[7] Bidikian A, Bewersdorf JP, Kewan T, Stahl M and Zeidan AM. Acute promyelocytic leukemia in the real world: understanding outcome differences and how we can improve them. Cancers (Basel) 2024; 16: 4092.

[8] Zhu HH, Ma YF, Yu K, Ouyang GF, Luo WD, Pei RZ, Xu WQ, Hu HX, Mo SP, Xu XH, Lan JP, Shen JP, Shou LH, Qian SX, Feng WY, Zhao P, Jiang JH, Hu BL, Zhang J, Qian SY, Wu GQ, Wu WP, Qiu L, Li LJ, Lang XH, Chen S, Chen LL, Guo JB, Cao LH, Jiang HF, Xia YM, Le J, Zhao JZ, Huang J, Zhang YF, Lv YL, Hua JS, Hong YW, Zheng CP, Wang JX, Hu BF, Chen XH, Zhang LM, Tao S, Xie BS, Kuang YM, Luo WJ, Su P, Guo J, Wu X, Jiang W, Zhang HQ, Zhang Y, Chen CM, Xu XF, Guo Y, Tu JM, Hu S, Yan XY, Yao C, Lou YJ and Jin J. Early death and survival of patients with acute promyelocytic leukemia in ATRA plus arsenic Era: a population-based study. Front Oncol 2021; 11: 762653.

[9] Infante JB. Predictors of early death in acute promyelocytic leukemia. Med Sci (Basel) 2025; 13: 300.

[10] Jillella AP, Lee SJ, Altman JK, Luger SM, Tallman MS, Foran JM, Bradshaw D, Law LY, Bryan LJ, Abou Zahr A, Begna KH, Perl AE, Vadakara JJL, Qamar R, Bergan RC, Fisch MJ, Carlos RC, Wagner LI, Kota VK and Litzow MR. Academic community partnership in acute promyelocytic leukemia and early mortality: the ECOG-ACRIN EA9131 trial. JAMA Oncol 2025; 11: 400-407.

[11] Ding Y, Qi X, Li Y, Sun Y, Wan J, Luo C, Huang Y, Li Q, Wu G, Zhu X and Xu S. Albumin-to-fibrinogen ratio is an independent prognostic parameter in de novo non-M3 acute myeloid leukemia. Clin Exp Med 2023; 23: 4597-4608.

[12] Zhao Y, Yu X, Yan L, Shi D, Li J, Hou W, Zhang Q, Zhu Y and Zhang Y. Study on clinical features of early death in older patients with acute promyelocytic leukemia. Ann Hematol 2025; 104: 183-192.

[13] Voso MT, Guarnera L, Lehmann S, Döhner K, Döhner H, Platzbecker U, Russell N, Dillon R, Thomas I, Ossenkoppele G, Haferlach T, Vignetti M, La Sala E, Piciocchi A, Fazi P, Ramiro AV, Giménez LT, Gurnari C, Bullinger L and Hernández-Rivas JM. Acute promyelocytic leukemia: long-term outcomes from the HARMONY project. Blood 2025; 145: 234-243.

[14] Li AY, Kashanian SM, Hambley BC, Zacholski K, Duong VH, El Chaer F, Holtzman NG, Gojo I, Webster JA, Norsworthy KJ, Smith BD, DeZern AE, Levis MJ, Baer MR, Kamangar F, Ghiaur G and Emadi A. FLT3-ITD allelic burden and acute promyelocytic leukemia risk stratification. Biology (Basel) 2021; 10: 243.

[15] Riley RD, Ensor J, Snell KIE, Harrell FE Jr, Martin GP, Reitsma JB, Moons KGM, Collins G and van Smeden M. Calculating the sample size required for developing a clinical prediction model. BMJ 2020; 368: m441.

[16] Riley RD, Debray TPA, Collins GS, Archer L, Ensor J, van Smeden M and Snell KIE. Minimum sample size for external validation of a clinical prediction model with a binary outcome. Stat Med 2021; 40: 4230-4251.

[17] Baysal M, Gürsoy V, Hunutlu FC, Erkan B, Demirci U, Bas V, Gulsaran SK, Pinar IE, Ersal T, Kirkizlar TA, Atli EI, Kirkizlar HO, Ümit EG, Gürkan H, Ozkocaman V, Ozkalemkas F, Demir AM and Ali R. The evaluation of risk factors leading to early deaths in patients with acute promyelocytic leukemia: a retrospective study. Ann Hematol 2022; 101: 1049-1057.

[18] Wang A, Zhang Z, Zhu T, Liu X and Duan Q. Clinical characteristics and analysis of related factors associated with early death in newly diagnosed patients with acute promyelocytic leukemia. Discov Oncol 2024; 15: 375.

[19] Peduzzi P, Concato J, Kemper E, Holford TR and Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996; 49: 1373-1379.

[20] Roshan R, Shah MH, J S, Parry AF and Bhat JR. Assessing the Impact of All-Trans Retinoic Acid (ATRA)- and Arsenic Trioxide (ATO)-based therapy in pediatric acute promyelocytic leukemia: a single-center study. Cureus 2025; 17: e89081.

[21] Brown JR, Seymour JF, Jurczak W, Aw A, Wach M, Illes A, Tedeschi A, Owen C, Skarbnik A, Ly-

sak D, Eom KS, Šimkovič M, Pavlovsky MA, Kater AP, Eichhorst B, Miller K, Munugalavadla V, Yu T, de Borja M and Ghia P. Fixed-duration acalabrutinib combinations in untreated chronic lymphocytic leukemia. N Engl J Med 2025; 392: 748-762.

[22] Klinge PM, Ma KL, Leary OP, Sastry RA, Sayied S, Venegas O, Brinker T and Gokaslan ZL. Charlson comorbidity index applied to shunted idiopathic normal pressure hydrocephalus. Sci Rep 2023; 13: 5111.

[23] Mukaka MM. Statistics corner: a guide to appropriate use of correlation coefficient in medical research. Malawi Med J 2012; 24: 69-71.

[24] O'brien RM. A caution regarding rules of thumb for variance inflation factors. Qual Quant 2007; 41: 673-690.

[25] Lehmann S, Deneberg S, Antunovic P, Rangert-Derolf Å, Garelius H, Lazarevic V, Myhr-Eriksson K, Möllgård L, Uggla B, Wahlin A, Wennström L, Höglund M and Juliusson G. Early death rates remain high in high-risk APL: update from the Swedish Acute Leukemia Registry 1997-2013. Leukemia 2017; 31: 1457-1459.

[26] Venkitachalam R, Szabo A and Guru Murthy GS. Population-level outcomes of pediatric acute promyelocytic leukemia in the United States. J Pediatr 2020; 223: 114-119, e115.

[27] Matsuda K, Oyama T, Maki H, Nakazaki K, Yasunaga M, Honda A, Masamoto Y and Kurokawa M. Prompt Initiation of conventional chemotherapy to avoid early death in patients with newly diagnosed acute promyelocytic leukemia. Intern Med 2023; 62: 2181-2185.

[28] Kantarjian HM, DiNardo CD, Kadia TM, Daver NG, Altman JK, Stein EM, Jabbour E, Schiffer CA, Lang A and Ravandi F. Acute myeloid leukemia management and research in 2025. CA Cancer J Clin 2025; 75: 46-67.

[29] Chean D, Kemp H, Fodil S, Darmon M, Azoulay E and Dupont T. Early mortality in patients with acute promyelocytic leukemia: a systematic review and meta-analysis. Crit Care 2025; 29: 490.

[30] Infante JB, Esteves GV, Raposo J and de Lacerda JF. Disseminated intravascular coagulation score evolution in 48 h predicts early death in acute promyelocytic leukemia patients. Eur J Haematol 2024; 112: 840-844.

[31] Burnett AK, Hills RK and Russell N. Twenty five years of UK trials in acute myeloid leukaemia: what have we learned? Br J Haematol 2020; 188: 86-100.

[32] Cao M, Li T, He Z, Wang L, Yang X, Kou Y, Zou L, Dong X, Novakovic VA, Bi Y, Kou J, Yu B, Fang S, Wang J, Zhou J and Shi J. Promyelocytic extracellular chromatin exacerbates coagulation and fibrinolysis in acute promyelocytic leukemia. Blood 2017; 129: 1855-1864.

[33] Zhao S, Ge Y, Li Z and Yang T. Influence of cytokines on early death and coagulopathy in newly diagnosed patients with acute promyelocytic leukemia. Front Immunol 2023; 14: 1100151.

[34] Kim S, Jung J, Ahn SY, Kim M, Jeon SY, Lee CH, Kim DS, Lee SR, Sung HJ, Choi CW, Kim BS, Kim HJ, Kwak JY, Park Y, Ahn JS and Yhim HY. Risk stratification for early mortality in newly diagnosed acute promyelocytic leukemia: a multicenter, non-selected, retrospective cohort study. Front Oncol 2024; 14: 1307315.

[35] Wen J, Xu F, Zhou Q, Shi L, Liu Y, Yue J, Zhang Y and Liang X. Effects of peripheral blood leukocyte count and tumor necrosis factor-alpha on early death in acute promyelocytic leukemia. BMC Cancer 2023; 23: 27.

[36] Dhakal P, Lyden E, Joshi U, Pyakuryal A, Loh KP, Klepin H and Bhatt VR. Comorbidity burden and outcomes of older adults with acute promyelocytic leukemia: a National Cancer Database analysis of 2221 patients. Leuk Lymphoma 2023; 64: 691-697.

[37] Fontes HMF, de Freitas JP, Oliveira JHV, de Sousa Moraes É A, Rego EM and Melo RAM. Causes and risk factors for early death in adult patients with acute promyelocytic leukemia: a real-life experience. Hematol Transfus Cell Ther 2024; 46 Suppl 6: S122-S128.

[38] Sabljic N, Thachil J, Pantic N and Mitrovic M. Hemorrhage in acute promyelocytic leukemia-fibrinolysis in focus. Res Pract Thromb Haemost 2024; 8: 102499.

[39] Li S, Gao Y, Li F, Zheng Y and Su Y. Value of the FDP/FIB ratio in predicting early severe bleeding events in patients with newly diagnosed acute promyelocytic leukemia. Ann Hematol 2023; 102: 787-794.

[40] Collins GS, Moons KGM, Dhiman P, Riley RD, Beam AL, Van Calster B, Ghassemi M, Liu X, Reitsma JB, van Smeden M, Boulesteix AL, Camaradou JC, Celi LA, Denaxas S, Denniston AK, Glocker B, Golub RM, Harvey H, Heinze G, Hoffman MM, Kengne AP, Lam E, Lee N, Loder EW, Maier-Hein L, Mateen BA, McCradden MD, Oakden-Rayner L, Ordish J, Parnell R, Rose S, Singh K, Wynants L and Logullo P. TRIPOD+AI statement: updated guidance for reporting clinical prediction models that use regression or machine learning methods. BMJ 2024; 385: e078378.

[41] Van Calster B, Wynants L, Verbeek JFM, Verbakel JY, Christodoulou E, Vickers AJ, Roobol MJ and Steyerberg EW. Reporting and interpreting decision curve analysis: a guide for investigators. Eur Urol 2018; 74: 796-804.

[42] Österroos A, Maia T, Eriksson A, Jädersten M, Lazarevic V, Wennström L, Antunovic P,

Cammenga J, Deneberg S, Lorenz F, Möllgård L, Uggla B, Ölander E, Aguiar E, Trigo F, Höglund M, Juliusson G and Lehmann S. A risk score based on real-world data to predict early death in acute promyelocytic leukemia. Haematologica 2022; 107: 1528-1537.

[43] Hao L, Yao Y and Yang L. Thromboembolism in adult patients with acute promyelocytic leukemia: clinical characteristics, risk factors, and a predictive nomogram. Ann Hematol 2025; 104: 973-983.

[44] de Figueiredo-Pontes LL, Catto LFB, Chauffaille M, Pagnano KBB, Madeira MIA, Nunes EC, Hamerschlak N, de Andrade Silva MC, Carneiro TX, Bortolheiro TC, de Freitas TT, Bittencourt RI, Maranhão Fagundes E and Magalhães Rego E. Diagnosis and management of acute promyelocytic leukemia: Brazilian consensus guidelines 2024 on behalf of the Brazilian association of hematology, hemotherapy and cellular therapy. Hematol Transfus Cell Ther 2024; 46: 553-569.

Table S1. Comparison of baseline characteristics between patients who died within 28 day and survivors in APL cohort

Variable	Overall (n = 631)	Died within 28 day (n = 120)	Survived within 28 day (n = 511)	Statistical value	*P*-value
Age				32.106	< 0.001
< 45 years	351 (55.63%)	39 (32.50%)	312 (61.06%)		
≥ 45 years	280 (44.37%)	81 (67.50%)	199 (38.94%)		
Gender				1.093	0.296
Male	357 (56.58%)	73 (60.83%)	284 (55.58%)		
Female	274 (43.42%)	47 (39.17%)	227 (44.42%)		
ECOG performance status score				62.854	< 0.001
0-1 points	495 (78.45%)	62 (51.67%)	433 (84.74%)		
Points	136 (21.55%)	58 (48.33%)	78 (15.26%)		
CCI Comorbidity Index				35.478	< 0.001
0 points	401 (63.55%)	48 (40.00%)	353 (69.08%)		
1-3 points	230 (36.45%)	72 (60.00%)	158 (30.92%)		
WBC at initial diagnosis				64.033	< 0.001
≤ 10×10^9/L	358 (56.74%)	29 (24.17%)	329 (64.38%)		
> 10×10^9/L	273 (43.26%)	91 (75.83%)	182 (35.62%)		
PLT at initial diagnosis				23.604	< 0.001
> 40×10^9/L	283 (44.85%)	30 (25.00%)	253 (49.51%)		
≤ 40×10^9/L	348 (55.15%)	90 (75.00%)	258 (50.49%)		
Sanz risk stratification				65.157	< 0.001
Low-risk	172 (27.26%)	10 (8.33%)	162 (31.70%)		
Intermediate-risk	186 (29.48%)	19 (15.83%)	167 (32.68%)		
High-risk	273 (43.26%)	91 (75.83%)	182 (35.62%)		
Early PLT-CF combined transfusion within 72 hours				40.522	< 0.001
Present	333 (52.77%)	32 (26.67%)	301 (58.90%)		
Absent	298 (47.23%)	88 (73.33%)	210 (41.10%)		
PLT transfusion within 72 hours				14.683	< 0.001
Present	501 (79.40%)	80 (66.67%)	421 (82.39%)		
Absent	130 (20.60%)	40 (33.33%)	90 (17.61%)		
CF/cryoprecipitate/FIB preparation transfusion within 72 hours				11.454	< 0.001
Present	457 (72.42%)	72 (60.00%)	385 (75.34%)		
Absent	174 (27.58%)	48 (40.00%)	126 (24.66%)		
Induction therapy regimen				0.463	0.794
ATRA + ATO	543 (86.05%)	101 (84.17%)	442 (86.50%)		
ATRA + chemotherapy	59 (9.35%)	13 (10.83%)	46 (9.00%)		
Other	29 (4.60%)	6 (5.00%)	23 (4.50%)		
Hb at initial diagnosis (g/L)	84.00 [72.00, 98.00]	80.00 [67.75, 95.25]	85.00 [73.00, 100.00]	2.626	0.009
FIB (g/L)	1.27 [0.86, 1.67]	0.82 [0.55, 1.14]	1.42 [1.00, 1.81]	10.180	< 0.001
PT (s)	17.55 ± 4.54	20.72 ± 4.79	16.80 ± 4.15	-9.033	< 0.001
APTT (s)	41.32 ± 9.26	46.65 ± 10.12	40.06 ± 8.59	-7.297	< 0.001
INR	1.40 ± 0.38	1.68 ± 0.45	1.33 ± 0.33	-9.543	< 0.001
D-dimer (mg/L)	6.68 [4.12, 9.64]	10.49 [7.14, 14.18]	6.05 [3.71, 8.78]	9.534	< 0.001
FDP (mg/L)	31.83 [20.52, 45.75]	48.62 [31.14, 60.40]	28.88 [19.24, 41.52]	7.675	< 0.001
Time from diagnosis/ATRA initiation to first ATRA administration (h)	7.00 [4.00, 10.00]	7.00 [4.00, 11.00]	7.00 [4.00, 10.00]	0.958	0.338

Note: APL, acute promyelocytic leukemia; ECOG, Eastern Cooperative Oncology Group; CCI, Charlson Comorbidity Index; ATRA, all-trans retinoic acid; ATO, arsenic trioxide; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio; FDP, fibrinogen degradation products.