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Prognostic nomogram for adult patients with acute myeloid leukemia

A SEER database analysis

Cunte Chen, MD[a], Peipei Wang, MD[b], Caixia Wang, MD, PhD[a,*]

Abstract

Acute myeloid leukemia (AML) is hematopoietic malignancy. This study was designed to develop an individualized prognostic nomogram to predict cancer-specific survival (CSS) and overall survival (OS) of AML.

The clinical data of AML patients (n = 58,882) diagnosed from 1973 to 2014 were obtained from the Surveillance, Epidemiology, and End Results database. The patients were divided into training cohort (n = 29,441) and validation cohort (n = 29,441). The prognostic nomograms were designed with clinical variables selected by multivariate Cox regression model in training cohort. The concordance index (C-index), calibration curve, and receiver operating characteristic curve were used to assess the performance of the nomograms.

The predictors in nomogram for CSS were AML subtypes, age, sex, region, marital status, and chemotherapy, whereas the predictors for OS were AML subtypes, age, sex, region, race, marital status, and chemotherapy. The C-indexes of the nomograms in internal validation for CSS and OS were 0.712 and 0.703, respectively, whereas the C-indexes in external validation for CSS and OS were 0.712 and 0.705, respectively. The area under the curve of receiver operating characteristic curves for CSS and OS were 0.799 (95% confidence interval: 0.792–0.806) and 0.809 (95% confidence interval: 0.803–0.816), respectively.

The individualized prognostic nomogram could perform relatively accurate prediction of outcome in adult patients with AML.

Abbreviations: AML = acute myeloid leukemia, AUC = area under the curve, C-index = concordance index, CSS = cancer-specific survival, OS = overall survival, ROC = receiver operating characteristic, SEER = Surveillance Epidemiology and End Result.

Keywords: acute myeloid leukemia, cancer-specific survival, nomogram, overall survival, prognosis

1. Introduction

Acute myeloid leukemia (AML) is a highly heterogeneous hematological malignant disease derived from myeloid hematopoietic progenitor cells[1] and the most common type of myeloid malignancy in adults with an incidence of 3.7 per 100,000 persons.[2] The clinical outcome of AML patients are closely related to immune, molecular, and cytogenetic abnormalities,[3–5] as well as age at diagnosis, sex, marital status, insurance status, and county-level income.[6–8] Over the past few decades, diagnosis and treatment in patients with AML has improved, but the overall survival (OS) rate for AML is still low, less than 50%.[9] Therefore, prognostic models need to be established to provide evidence for diagnosis and treatment of AML in clinic.

The nomogram models have been validated in the prognosis of several malignancies, which can provide good statistical predictions on survival probability.[10–12] Recent research shows that nomogram models are built to analyze OS by integrating mutated genes for older patients with AML.[13]

In this study, we tried to design a nomogram model for predicting the survival probability of adult patients with AML, using the Surveillance Epidemiology and End Result (SEER) dataset between 1973 and 2014. The SEER program in the National Cancer Institute's Division of Cancer Control and Population Sciences is the most reliable and comprehensive source of population-based cancer information in the United States, which provides a large dataset for our nomogram models construction. AML subtypes, sex, age at diagnosis, region, race–ethnicities, marital status, and chemotherapy in SEER program were included into the nomogram models analysis. The visual format of the nomogram helps to understand the prognosis of an individual so that their physicians can make a corresponding treatment based on the prognosis.

2. Materials and methods

2.1. Data sources

The SEER program, involving in approximately 26% of the US population, is a publicly available database and primary source of cancer statistics that is supported by the Surveillance Research

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CC and PW contributed equally to this work.

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Program in the National Cancer Institute's Division of Cancer Control and Population Sciences.[14] The clinical data of AML patients diagnosed from 1973 to 2014 were obtained from the SEER database by using the SEER*Stat program (version 8.3.5).[14] A total of 65,535 records were obtained. In the SEER data, the AML subtypes were classified according to the 3rd edition of the International Classification of Disease Oncology (ICD-O-3) and WHO 2008 definitions.[15,16] The AML subtypes included in this study are as follows: 9840/3 – acute erythroid leukemia; 9861/3 – AML, NOS; 9865/3 – AML with t (6;9)(p23;q34), DEK-NUP214; 9866/3 –acute promyelocytic leukemia (AML with t (15;17)(q22;q12)) PML/RARA; 9867/3 – acute myelomonocytic leukemia; 9869/3 – AML. inv (3)(q21;q26.2) or t (3;3)(q21;q26.2), RPN1-EVI1; 9871/3 – AML with inv (16)(p13.1q22) or t (16;16)(p13.1;q22), CBFB-MYH11; 9872/3 – AML with minimal differentiation; 9873/3 – AML without maturation; 9874/3 – AML with maturation; 9891/3 – acute monoblastic and monocytic leukemia; 9895/3 – AML with myelodysplasia-related changes; 9896/3 – AML, t (8;21)(q22;q22) RUNX1-RUNX1T1; 9897/3 – AML with t (9;11)(p22;q23), MLLT3-MLL; 9910/3 – acute megakaryoblastic leukemia; 9911/3 – AML (megakaryoblastic) with t (1;22)(p13;q13), RBM15-MKL1; and 9920/3 – therapy-related myeloid neoplasm. Among the above AML subtypes, ICD-O3 codes 9840/3, 9861/3, 9865/3, 9867/3, 9869/3, 9871/3, 9872/3, 9873/3, 9874/3, 9891/3, 9895/3, 9896/3, 9897/3, 9910/3, 9911/3, and 9920/3 belonged to non-APL AML, whereas 9866/3 belonged to APL. The criteria of region were as follows: East includes Connecticut, Atlanta (Metropolitan), and Rural Georgia; Northern Plains include Detroit (Metropolitan) and Iowa; Pacific Coast includes San Francisco Oakland, Hawaii, Seattle (Puget Sound), San Jose-Monterey, and Los Angeles; and Southwest includes New Mexico and Utah.

The following cases were excluded: age at diagnosis <18 years; unknown survival time; unknown marital status; and unknown race/ethnicity. Owing to the small number of patients from Alaska, they might cause bias in survival analysis, so they were also excluded.

The following variables were analyzed: AML subtype, sex, age at diagnosis, region, race/ethnicity, marital status, chemotherapy, cause-specific death, and vital status. It is worth noting that the race/ethnicity of yellow included Chinese, Korean, and Japanese in this study. Additionally, in marital status, married included separated, whereas single included never married or unmarried. According to the prognosis of patients,[17,18] AML was divided into APL and non-APL. The follow-up time was recorded as the duration of time from the diagnosis to death or the last day of survival information documented in the SEER registry. The variable of "vital status recode" was used to determine the status of survive.

After exclusion of patients based on the above criteria, 58,882 AML patients were identified for OS analysis. Furthermore, after excluding patients with noncancer-specific death [noncancer-specific survival (CSS)], 42,652 patients were identified as entering CSS analysis. Ultimately, patients were randomly assigned to a training cohort and a validation cohort (1:1 ratio) for OS and CSS analysis (Fig. 1). The clinical information of adult AML are publicly available in the SEER program, so the approval of local ethics committee was not needed.

2.2. Statistical analysis

Qualitative variables were categorized prior to modeling based on clinical experience and significance. For continuous variables, the optimal cutoff of age was obtained using X-tile software version 3.6.1 (Yale University, New Haven, CT).[19] Univariate and multivariate analyses were performed by using the Cox proportional hazard regression models in SPSS Statistical Package version 22.0 (IBM, Chicago, IL) to clarify the independent prognostic value of clinical variables for OS and CSS. Clinically significant variables for OS and CSS, which were selected in multivariate Cox proportional hazard regression models in a backward stepwise manner based on the Akaike information criterion, were assessed for incorporating into the nomogram model. The foreign, rms, hmisc, lattice, survival, formula, and ggplot2 packages in R, version 3.5.1 (http://www.r-project.org/) were applied for nomogram model analysis. Model performance was assessed by internal and external validation, which was performed by discrimination with concordance index (C-index) and calibration curves using 1000 sample bootstrap. Then, all cohorts of patients were given a total score using standard points obtained from the nomogram models, which could predict survival rates of AML patients. The patients were randomly assigned using the Microsoft Excel 2007. The receiver operating characteristic (ROC) curves was used for predictive ability of nomogram in SPSS Statistical Package version 22.0 (IBM, Chicago, IL). A 2-tailed P value <.05 was considered to indicate statistical significance. This study was performed in accordance with the ethical principals of the Declaration of Helsinki for medical research involving human participants.[20]

3. Results

3.1. Cohort characteristics

The clinical characteristics of the patients in the training and validation cohorts for OS and CSS analysis were listed in Table 1.

3.2. X-tile for the optimal cutoff of age

X-tile software was used to determine the optimal cutoff value of age in total AML patients (n = 58,882) after screening, which was applied for univariate and multivariate Cox proportional hazard regression analysis, as well as nomogram model construction. As shown in Figure 2, the optimal cutoff of age for analysis were <62, 62–74, and >74 years, which indicated significant difference among cutoff values.

3.3. Cox regression analysis of training cohort

Univariate Cox proportional hazard regression analysis for OS and CSS suggested that there were significant differences in survival rates of AML subtypes, age, gender, region, race/ethnicity, marital, and chemotherapy, which could be further included in multivariate Cox regression analysis (Table 2). As shown in Table 3, multivariate Cox proportional hazard regression models demonstrated that AML subtypes, age, sex, region, race/ethnicity, marital status, and chemotherapy were independent prognostic factors of AML in the OS analysis, whereas AML subtypes, age, sex, region, marital status, and chemotherapy, except race/ethnicity, were independent prognostic factors of AML in the CSS analysis.

3.4. Nomograms of AML for CSS and OS

Clinical parameters after multivariate Cox regression selection were channeled into the construction of training cohort

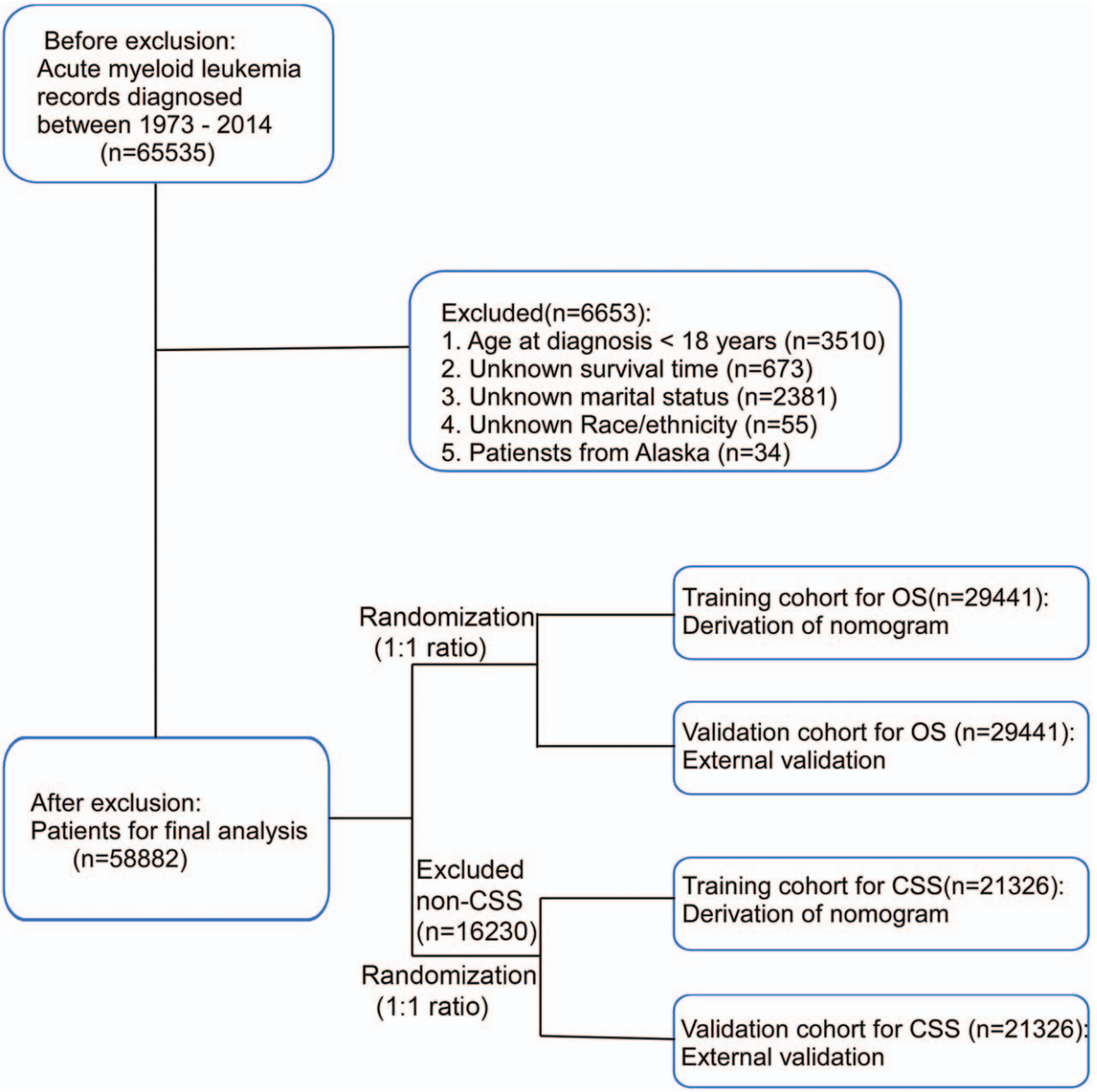

Figure 1. Flow diagram for data selection and research strategy.

nomogram (Fig. 3). However, due to $P < .05$ of multivariate Cox regression in the CSS, race/ethnicity could not be employed in nomogram. Details of the labels for tick marks and points in nomograms were shown in Table 4.

3.5. Internal validation

The C-indexes of 1000 sample bootstrap were 0.712 and 0.703 for the CSS and OS predictive nomograms, respectively, which indicated that nomograms for CSS and OS showed relatively precise ability of discrimination. Further calibration curves manifested that the probability of predicted 1, 3, and 5-year CSS and OS in nomograms were well consistent between the predicted outcome and actual observation (Fig. 4).

3.6. External validation

In the external validation cohort, the C-indexes of predictive accuracy for CSS and OS were 0.712 and 0.705, respectively (Fig. 5). The external calibration curves also illustrated good validation between predicted and observed 1, 3, and 5-year CSS and OS. The discrimination and calibration validation of external cohort definitely certificated that nomogram models in this study could be comparatively accurate enough to predict the CSS and OS rate of patients with AML.

3.7. ROC curves for CSS and OS

The predictive ability for CSS and OS in training cohorts is by using ROC curves. The area under the curve (AUC) of ROC

Table 1

Clinical characteristics of patients with AML.

Variables	Cancer-specific survival			Overall survival		
	Total (n = 58,882)	Training cohort (n = 29,441)	Validation cohort (n = 29,441)	Total (n = 42,652)	Training cohort (n = 21,326)	Validation cohort (n = 21,326)
Diagnosis, n (%)						
APL	3645 (6.2)	1816 (6.2)	1829 (6.2)	3104 (7.3)	1537 (7.2)	1567 (7.3)
Non-APL AML	55,237 (93.8)	27,625 (93.8)	27,612 (93.8)	39,548 (92.7)	19,789 (92.8)	19,759 (92.7)
Sex, n (%)						
Female	26,971 (45.8)	13,448 (45.7)	13,523 (45.9)	19,635 (46.0)	9801 (46.0)	9834 (46.1)
Male	31,911 (54.2)	15,993 (54.3)	15,918 (54.1)	23,017 (54.0)	11,525 (54.0)	11,492 (53.9)
Age, yr, n (%)						
<62	21,753 (37.0)	10,958 (37.2)	10,795 (36.7)	18,032 (42.3)	9057 (42.5)	8975 (42.1)
62–74	17,446 (29.6)	8613 (29.3)	8833 (30.0)	12,047 (28.2)	5978 (28.0)	6069 (28.5)
>74	19,683 (33.4)	9870 (33.5)	9813 (33.3)	12,573 (29.5)	6291 (29.5)	6282 (29.5)
Region, n (%)						
East	13,555 (23.0)	6776 (23.0)	6779 (23.0)	9481 (22.2)	4740 (22.2)	4741 (22.2)
Pacific Coast	30,845 (52.3)	15,424 (52.3)	15,421 (52.4)	22,508 (52.8)	11,255 (52.8)	11,253 (52.8)
Northern Plains	10,777 (18.3)	5388 (18.3)	5389 (18.3)	7726 (18.1)	3863 (18.1)	3863 (18.1)
Southwest	3705 (6.3)	1853 (6.3)	1852 (6.3)	2937 (6.9)	1468 (6.9)	1469 (6.9)
Race/ethnicity, n (%)						
Yellow	1888 (3.2)	927 (3.2)	961 (3.3)	1451 (3.4)	706 (3.3)	745 (3.5)
White	49,845 (84.7)	24,940 (84.7)	24,905 (84.6)	35,866 (84.1)	17,972 (84.3)	17,894 (83.9)
Black	4251 (7.2)	2125 (7.2)	2126 (7.2)	3037 (7.1)	1489 (7.0)	1548 (7.3)
Other	2898 (4.9)	1449 (4.9)	1449 (4.9)	2298 (5.4)	1159 (5.4)	1139 (5.3)
Marital, n (%)						
Married	36,044 (61.2)	17,981 (61.1)	18,063 (61.4)	26,112 (61.2)	13,069 (61.2)	13,043 (61.2)
Divorced	4373 (7.4)	2186 (7.4)	2187 (7.4)	3149 (7.4)	1618 (7.6)	1531 (7.2)
Single	8450 (14.4)	4256 (14.5)	4194 (14.2)	6656 (15.6)	3275 (15.4)	3381 (15.8)
Widowed	10,015 (17.0)	5018 (17.0)	4997 (17.0)	6735 (15.8)	3364 (15.8)	3371 (15.8)
Chemotherapy, n (%)						
Yes	38,810 (65.9)	19,447 (66.1)	19,363 (65.8)	29,723 (69.7)	14,873 (69.7)	14,850 (69.6)
No	20,072 (34.1)	9994 (33.9)	10,078 (34.2)	12,929 (30.3)	6453 (30.3)	6476 (30.4)

AML = acute myeloid leukemia, APL = acute promyelocytic leukemia.

curves for CSS and OS were 0.799 [95% confidence interval: 0.792–0.806, Fig. 6(A)] and 0.809 [95% confidence interval: 0.803–0.816, Fig. 6(B)], respectively.

4. Discussion

The nomogram model, compared with other predictive models, integrated different clinical variables to offer a more accurate and

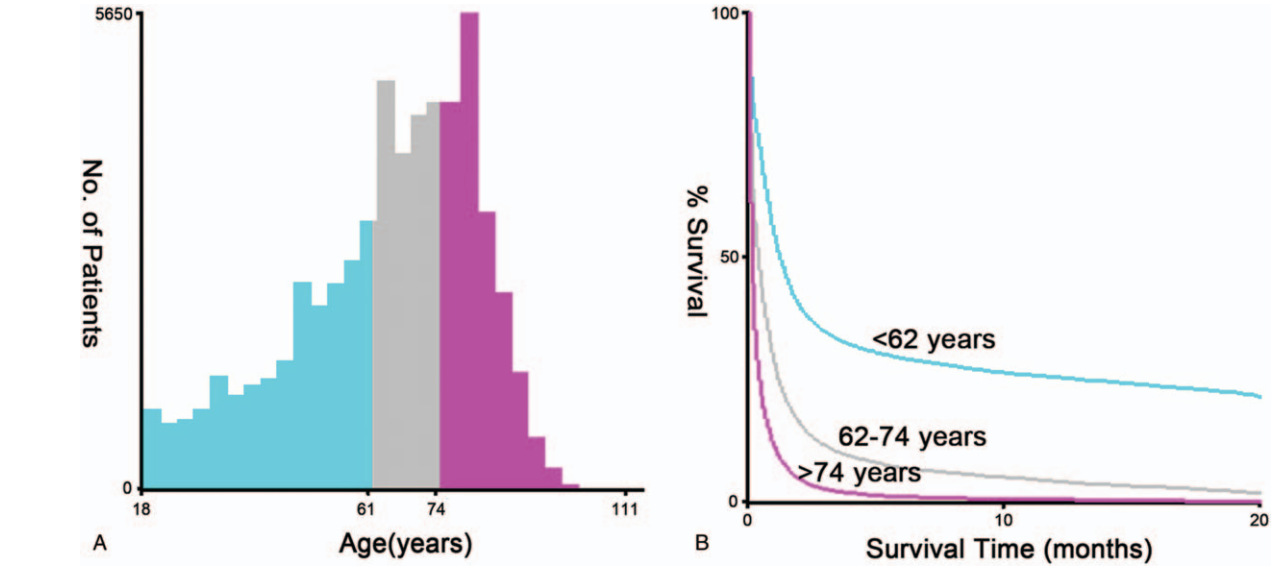

Figure 2. Optimal cutoff value of age obtained from X-tile software. (A) Distribution of the number of patients was showed in different age groups based on the cutoff values. (B) The survival curve was plotted on the basis of the optimal cutoff values, which revealed significant difference.

Table 2

Univariate Cox regression analysis of training cohort.

	Cancer-specific survival			Overall survival		
Variables	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Diagnosis (ref,APL)						
Non-APL AML	3.460	3.179–3.765	<.0001	3.001	2.801–3.216	<.0001
Sex (ref,Female)						
Male	1.081	1.048–1.114	<.0001	1.055	1.029–1.082	<.0001
Age, yr (ref,<62)						
62–74	2.167	2.085–2.252	<.0001	2.088	2.022–2.157	<.0001
>74	3.760	3.617–3.907	<.0001	3.409	3.301–3.520	<.0001
Region (ref,East)						
Pacific Coast	1.008	0.970–1.048	.679	0.989	0.959–1.020	.490
Northern Plains	1.245	1.188–1.305	<.0001	1.144	1.101–1.189	<.0001
Southwest	1.058	0.991–1.130	.093	0.970	0.917–1.026	.282
Race/Ethnicity (ref,Yellow)						
White	1.122	1.030–1.223	.008	1.213	1.128–1.306	<.0001
Black	1.033	0.932–1.144	.536	1.140	1.046–1.242	.003
Other	0.893	0.801–0.995	.041	0.974	0.888–1.069	.583
Marital (ref,Married)						
Divorced	0.995	0.939–1.055	.866	0.999	0.952–1.049	.974
Single	0.733	0.700–0.768	<.0001	0.757	0.729–0.787	<.0001
Widowed	1.901	1.826–1.979	<.0001	1.748	1.691–1.806	<.0001
Chemotherapy (ref,Yes)						
No	2.954	2.858–3.053	<.0001	2.691	2.620–2.764	<.0001

AML = acute myeloid leukemia, APL = acute promyelocytic leukemia, CI = confidence interval, HR = hazard ratio, ref = reference category.

personalized prognosis assessment system.[13,21–23] In this work, we developed 2 nomogram models based on the SEER database to predict CSS and OS for adult patients with AML. Although the predicted and observed probabilities of 1-year OS in the nomograms were not completely consistent, the C-indexes were all higher than 0.7, which achieved considerable prediction accuracy and repeatability when nomograms were applied to training and validation cohorts. Simultaneously, 3 and 5-year CSS and OS in nomograms showed good predictive accuracy. For the nomogram of AUC, the AUC were consistent with the C-index, indicating that the models could provide a good prognostic assessment system in patients with AML.

Here, some variables in the nomogram models were analyzed. Acute promyelocytic leukemia (APL) was generally characterized

Table 3

Multivariate Cox regression analysis of training cohort.

	Cancer-specific survival			Overall survival		
Variables	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Diagnosis (ref,APL)						
Non-APL AML	2.561	2.351–2.789	<.0001	2.276	2.123–2.441	<.0001
Sex (ref,Female)						
Male	1.114	1.079–1.150	<.0001	1.067	1.040–1.096	<.0001
Age, yr (ref,<62)						
62–74	1.802	1.731–1.876	<.0001	1.783	1.724–1.844	<.0001
>74	2.389	2.280–2.504	<.0001	2.291	2.206–2.379	<.0001
Region (ref,East)						
Pacific Coast	1.043	1.003–1.085	.035	1.029	0.997–1.063	.074
Northern Plains	1.198	1.143–1.255	<.0001	1.107	1.065–1.150	<.0001
Southwest	1.102	1.031–1.177	.004	1.009	0.953–1.067	.767
Race/Ethnicity (ref,Yellow)						
White	1.057	0.969–1.153	.211	1.122	1.041–1.208	.002
Black	1.105	0.996–1.227	.060	1.152	1.055–1.257	.002
Other	0.989	0.887–1.103	.843	1.093	0.996–1.200	.061
Marital (ref,Married)						
Divorced	1.091	1.028–1.157	.004	1.071	1.020–1.125	.006
Single	0.955	0.910–1.001	.057	0.964	0.927–1.003	.071
Widowed	1.175	1.123–1.229	<.0001	1.123	1.082–1.164	<.0001
Chemotherapy (ref,Yes)						
No	1.945	1.874–2.019	<.0001	1.886	1.831–1.943	<.0001

AML = acute myeloid leukemia, APL = acute promyelocytic leukemia, CI = confident interval, HR = hazard ratio, ref = reference category.

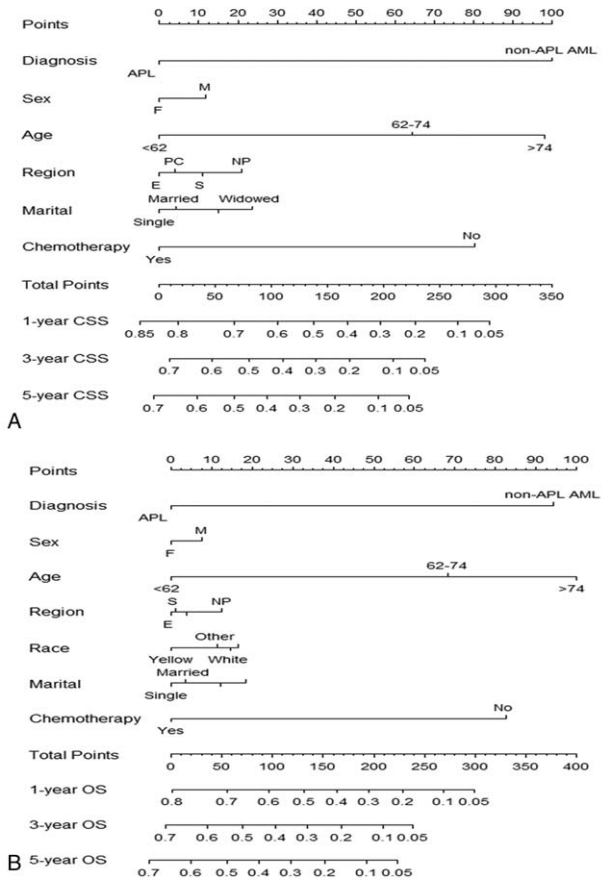

Figure 3. Nomogram models for CSS (A) and OS (B) of AML. First of all, the covariate of each patient was given a point based on the nomogram. Then, the total points were obtained by gathering the given points of all covariates of a patient. Finally, the survival probabilities of 1, 3, and 5-year CSS or OS corresponding to the total points could be showed by the nomogram. Additionally, a higher total point usually suggested a higher possibility of a lower predicted survival probability (CSS or OS). AML = acute myeloid leukemia, CSS = cancer-specific survival, OS = overall survival.

Table 4

Points for variables in nomograms.

Variables	Labels for tick marks	Points	
		Cancer-specific survival	Overall survival
Diagnosis			
APL	APL	0	0
Non-APL AML	Non-APL AML	100	94
Sex			
Female	F	0	0
Male	M	12	8
Age, yr			
<62	<62	0	0
62–74	62–74	64	68
>74	>74	98	100
Region			
East	E	0	0
Pacific Coast	PC	4	4
Northern Plains	NP	21	12
Southwest	S	11	1
Race/Ethnicity			
Yellow	Yellow	–	0
White	White	–	15
Black	Black	–	17
Other	Other	–	12
Marital			
Married	Married	4	4
Divorced	Divorced	15	12
Single	Single	0	0
Widowed	Widowed	24	18
Chemotherapy			
Yes	Yes	0	0
No	No	80	83

AML = acute myeloid leukemia, APL = acute promyelocytic leukemia.

by the t (15; 17)(q22; q21) chromosomal translocation to generate *PML-RAR* fusion gene, which was the target site for all-trans retinoic acid. Over the past years, due to the application of all-trans retinoic acid and arsenic trioxide (As_2O_3), the clinical complete remission (CR) rate and status of the disease-free survival of APL have been significantly improved, and the CR rate has been higher than 90%.[17] However, 3-year OS rate of non-APL AML was still poor, less than 30%.[18] In the present study, the points of non-APL AML in nomograms for CSS and OS were 100 and 94, respectively, indicating that subtype of AML was a strong predictor of prognosis in nomogram models established by the AML data of the SEER program.

With the prolonged life expectancy, the incidence of AML was rising in the aging population. Over the past few decades, with the great progress making in the diagnosis and treatment of AML, the outcome of young patients has been greatly improved, but the prognosis of elderly patients (>60 years old), whose long-term OS rate is less than 10%, was still very poor.[18,24] The risk ratios of age were more than 1.7 in multivariate Cox regression and the points of age in nomograms for CSS and OS were all more than 60, suggesting that age, especially >74 years old, was a strong predictor of outcome in patients with AML.

AML is hematopoietic malignancy progressing rapidly, whose natural process is of only a few months.[2] However, 50% to 60% patients with AML could achieve CR after intensive induction chemotherapy, and the long-term OS rate after chemotherapy could be improved to 15% to 30%.[25,26] We found that patients without chemotherapy had risk ratios of more than 1.8 and the points in the nomogram were all more than 80, which played an important role in predicting the outcomes of patients.

Studies have shown that sex, region, and marital status were predictors of outcomes in AML patients,[7,27] which were consistent with our findings. However, compared with AML subtype, age, and chemotherapy, the points of sex, region, and marital status in nomogram were low, showing that the predictive ability was relatively poor.

However, it is worth noting that population-based data of SEER program usually does not include detailed clinical data such as white blood cell,[28] relapse,[29] and risk stratification,[18] which may help to improve the reliability and accuracy of the nomogram models. Hence, larger clinical data was needed to validate the accuracy and repeatability of the nomogram models in the future.

Overall, in this study, the bootstrap-corrected and ROC curve-validated nomogram models could perform comparatively accurate prediction of 1, 3, and 5-year survival probabilities, which were clinically practical and relatively reliable in adult patients with AML. However, an independent external validation data will still be required to validate the nomogram models in the future, making the models more reliable.

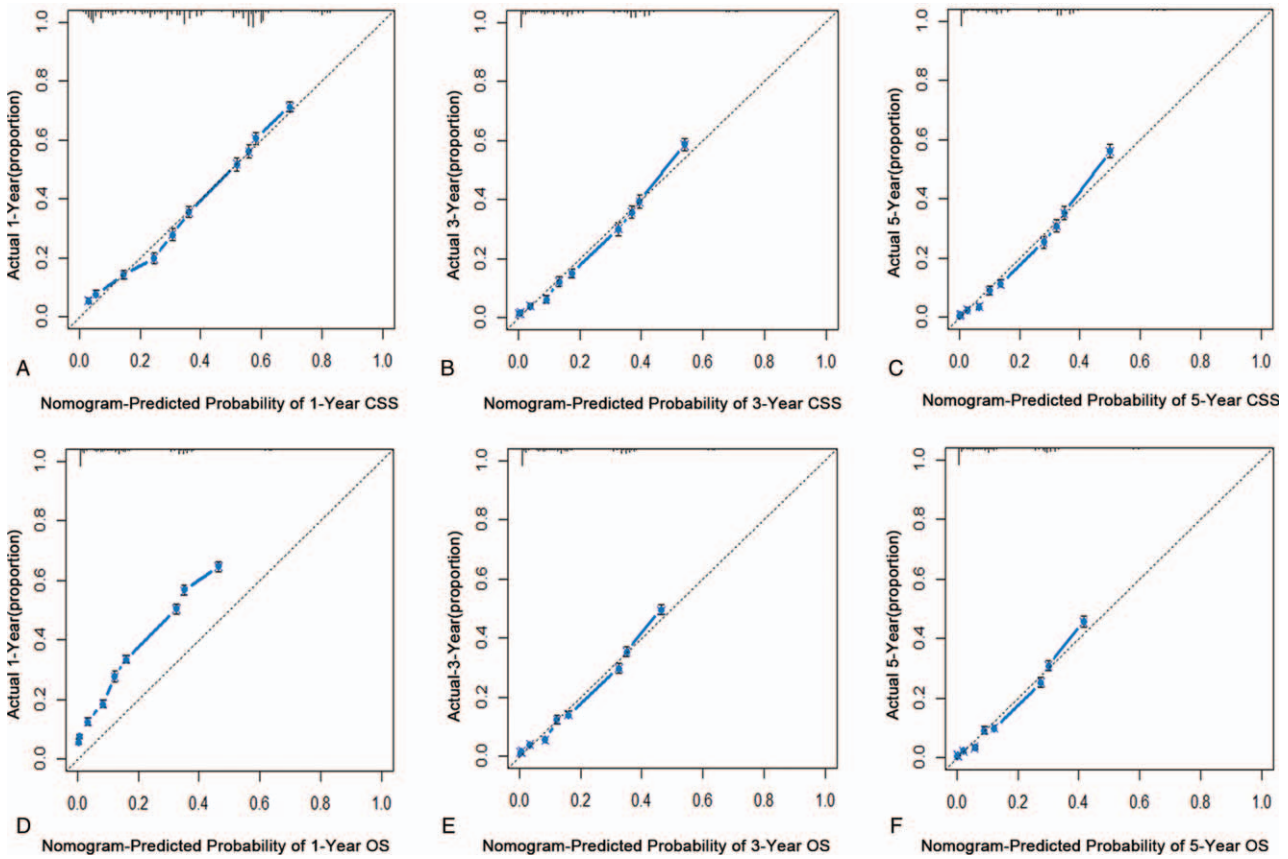

Figure 4. Internal validation of nomograms in the training cohorts. The predicted probabilities of 1, 3, and 5-year CSS (A–C) and OS (D–F) were consistent with the actual survival proportions of patients with AML. AML = acute myeloid leukemia, CSS = cancer-specific survival, OS = overall survival.

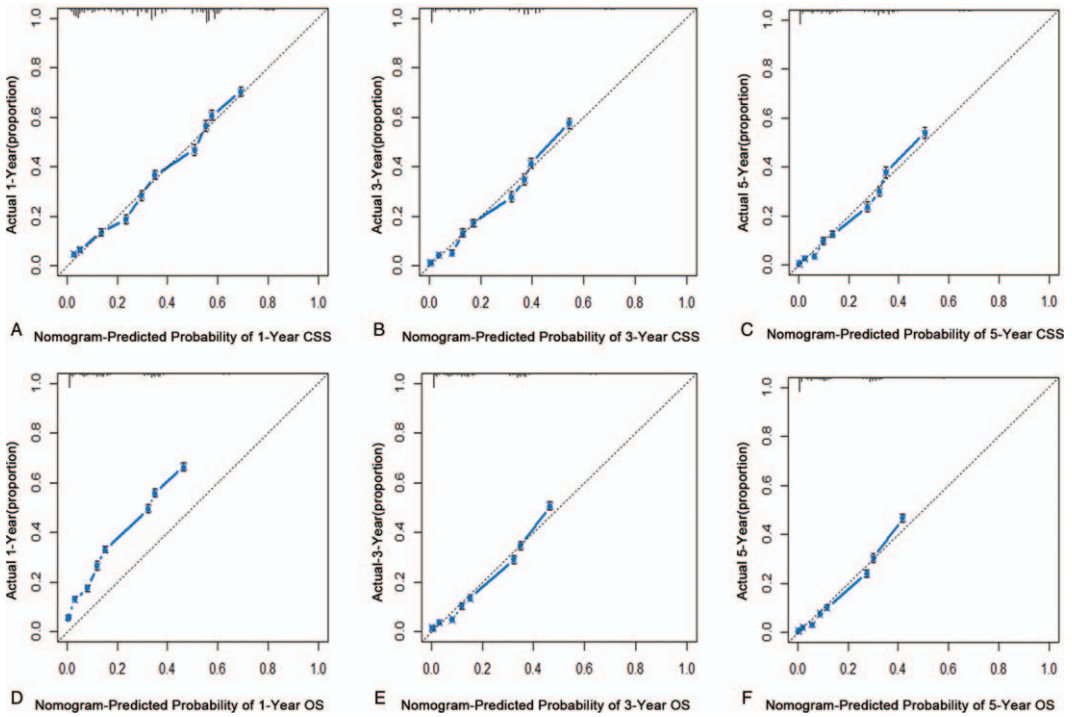

Figure 5. External calibration of nomograms in the validation cohorts. One thousand sample bootstrap calibration was used for external validation cohorts, indicating that the predicted probabilities of 1, 3, and 5-year CSS (A–C) and OS (D–F) were well related with the actual survival proportions. CSS = cancer-specific survival, OS = overall survival.

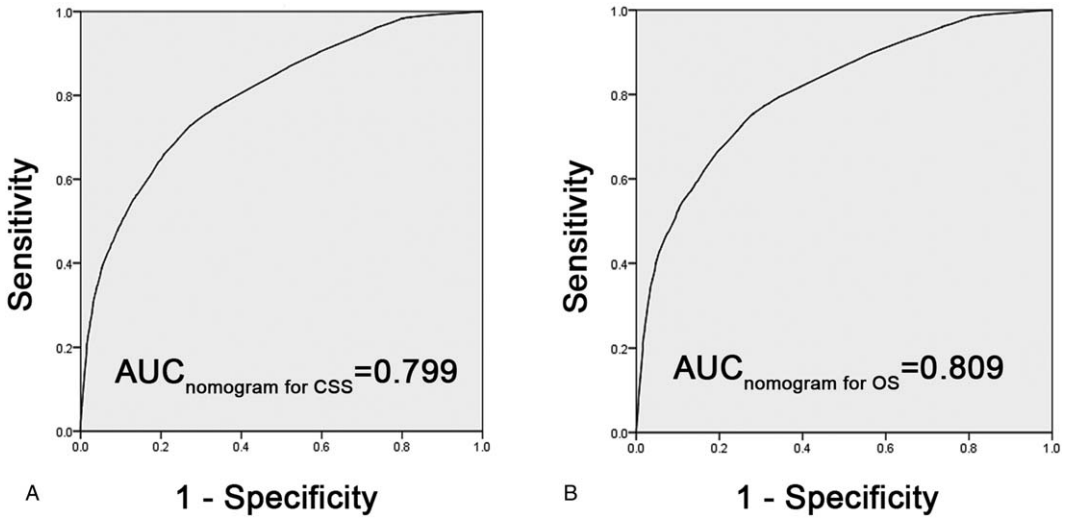

Figure 6. Predictive ability for cancer-specific survival (CSS) and overall survival (OS) in training cohorts. The AUC of ROC curves for CSS and OS were 0.799 (A) and 0.809 (B), respectively. AUC = area under the curve, ROC = receiver operating characteristic.

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