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Research

Development of a clinical prediction model for sensitivity to combination therapy of Bcl-2 inhibitors and hypomethylating agents in elderly/unfit patients with acute myeloid leukemia

Yufeng Du[1,3] · **Chunhong Li**[1,3] · **Yonghong Chen**[4] · **Fang Xie**[1] · **Jinsong Yan**[1,2,3]

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Abstract

Objective This study aims to develop a clinical prediction model for sensitivity to Bcl-2 inhibitors combined with hypomethylating agents (HMAs) in elderly/unfit patients with acute myeloid leukemia (AML).

Methods Clinical data, including French-American-British (FAB) classification, chromosomal karyotype, and second-generation sequencing results, were retrospectively collected from consecutive elderly/unfit patients with AML treated with Bcl-2 inhibitors in combination with HMAs between September 2019 and March 2024. Treatment efficacy was assessed in all patients. Logistic regression and Akaike information criterion were used to identify risk variables affecting efficacy. A nomogram was developed based on these variables to assess patient sensitivity to the treatment regimen. The performance of the nomogram was evaluated using a receiver operating characteristic (ROC) curve, calibration plot, and decision curve analysis (DCA).

Results This study included 209 patients with AML. The FAB classification, AML type, AML status, prior HMAs exposure, chromosomal karyotype, and mutations in *ASXL1*, *FLT3*, *IDH*, *NPM1*, and *CEBPA* were screened to develop the nomogram. The area under the ROC curve indicated a discriminatory power of 0.900 (95% CI, 0.860–0.941). The calibration curve suggested favorable concordance between the predicted and actual occurrence probabilities ($P = 0.849$). DCA revealed a net clinical benefit when the threshold probability ranged from 0 to 0.98. Internal validation, performed 500 times using the bootstrap method, demonstrated a satisfactory model performance in the validation set.

Conclusion A prediction model was developed and validated to serve as a decision-making tool for physicians treating elderly/unfit patients with AML prior to initiating therapy with Bcl-2 inhibitors combined with HMAs.

Keywords Acute myeloid leukemia · Bcl-2 inhibitor · Hypomethylating agents · Nomogram · Sensitivity

Yufeng Du and Chunhong Li have share the first authorship.

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✉ Fang Xie, xiefang5105@163.com; ✉ Jinsong Yan, yanjsdmu@dmu.edu.cn | [1]Department of Hematology, Liaoning Medical Center for Hematopoietic Stem Cell Transplantation, the Second Hospital of Dalian Medical University, Dalian 116027, China. [2]Department of Pediatric, Pediatric Oncology and Hematology Center, The Second Hospital of Dalian Medical University, Dalian 116027, China. [3]Liaoning Key Laboratory of Hematopoietic Stem Cell Transplantation and Translational Medicine, Blood Stem Cell Transplantation Institute, Dalian Key Laboratory of Hematology, Diamond Bay Institute of Hematology, The Second Hospital of Dalian Medical University, Dalian 116027, China. [4]Yichang Central People's Hospital, The First College of Clinical Medical Science, Three Gorges University, Yichang 443000, China.

1 Introduction

Acute myeloid leukemia (AML) is a highly invasive hematological malignancy with the highest incidence and mortality rates among adult patients with leukemia. It predominantly affects the elderly population [1, 2]. The standard therapeutic approach for AML involves intensive chemotherapy (IC) for remission induction followed by sequential consolidation chemotherapy or hematopoietic stem cell transplantation. This regimen enables approximately 40% of young patients to achieve long-term survival [3]. However, elderly/unfit AML patients often have poor physical conditions or comorbidities, resulting in reduced tolerance to IC and an increased Chemotherapy-related mortality (CRM). Early mortality is 25–30% for patients aged 60–69 years and exceeds 50% for those aged ≥ 70 years [4]. To mitigate CRM, researchers explored alternative approaches for elderly/unfit AML patients, such as low-dose cytarabine (LDAC) or palliative treatments (PT). Although these strategies resulted in a lower CRM than IC, their efficacy was limited. The complete response (CR) rate for LDAC was merely 7.7–9%, with a 1-year overall survival (OS) rate of 13% [5, 6]. Subsequently, hypomethylating agents (HMAs) were introduced for AML treatment. Two key phase III clinical trials demonstrated CR/CRi (CR with incomplete blood count recovery) rates of 17.8% and 27.8% and 1-year OS rates of 32.1% and 46.5%, respectively [7, 8]. Real-world studies have reported a CR rate of 15.6% [9]. Although HMAs showed improved efficacy compared to LDAC, their effectiveness remains suboptimal [10]. Thus, improving therapeutic outcomes in elderly/unfit patients with AML remains an urgent challenge requiring immediate attention.

The B-cell lymphoma-2 (Bcl-2) protein family plays a crucial role in the regulation of apoptosis via mitochondrial outer membrane permeability. Bcl-2 family of proteins are categorized into three types: anti-apoptotic proteins, pro-apoptotic effector proteins (BAX/BAK), and BH3-only pro-apoptotic proteins. Under normal conditions, anti-apoptotic proteins inhibit BAX/BAK in the mitochondrial outer membrane and suppress apoptosis. In response to stress, BH3-only pro-apoptotic proteins bind to anti-apoptotic Bcl-2 family proteins, alleviating their inhibition of BAX/BAK, and ultimately activating the caspase cascade to facilitate apoptosis [11, 12]. Overexpression of Bcl-2 proteins plays a critical role in the development and progression of AML [13]. Venetoclax (Ven) is a selective Bcl-2 inhibitor that binds to Bcl-2 protein, reactivating the mitochondrial apoptotic process [14]. A phase II clinical trial demonstrated that Ven monotherapy had limited therapeutic efficacy in AML [15]. However, subsequent phase Ib and III clinical trials of Ven combined with HMAs (Ven-HMAs) for the treatment of newly diagnosed elderly/unfit AML showed promising results. These trials reported CR/CRi rates of 67% and 66.4%, respectively, with median OS periods of 17.5 months and 14.7 months [16, 17]. AML comprises a group of highly heterogeneous myeloid tumors with different subgroups exhibiting substantial variations in therapeutic responses to Ven-HMAs treatment. Studies have indicated factors influencing therapeutic efficacy, including AML type (de novo or secondary AML), AML status (newly diagnosed or refractory/relapsed AML), French-American-British (FAB) type, chromosomal karyotype, and molecular biological mutations [18–22]. These studies revealed that different AML subgroups exhibit varying benefits from Ven-HMAs treatment. Although these findings provide some guidance for clinical practice, a method for identifying patients more likely to benefit from this treatment has not yet been established.

To address this gap and facilitate the identification of AML patients who are more likely to benefit from Ven-HMAs treatment, there is an urgent need to construct a clinical prediction model to predict the sensitivity (CR/CRi) of AML patients to this treatment regimen. Therefore, based on a comprehensive analysis of the factors influencing the efficacy of Ven-HMAs in elderly/unfit AML patients, we developed and validated a clinical model for predicting the sensitivity of AML to the Ven-HMAs treatment regimen.

2 Materials and methods

This retrospective study was conducted in accordance with the Declaration of Helsinki principles and was approved by the Ethics Committee of the Second Affiliated Hospital of Dalian Medical University (Protocol No.: KY2024-183-01).

2.1 Participants and drug administration

This retrospective investigation analyzed the clinical data of elderly/unfit AML patients treated with Ven-HMAs at the Second Affiliated Hospital of Dalian Medical University and Yichang Central People's Hospital between June 2019 and March 2024. In this study,"elderly/unfit"referred to patients aged ≥ 60 years, or < 60 years with an Eastern Cooperative

Oncology Group (ECOG) performance status of 2–3 or comorbidities that preclude intensive chemotherapy. Patient information was extracted from the electronic medical records. AML classification and risk stratification followed the World Health Organization (WHO) 2016 criteria and 2022 European Leukemia Network (ELN) guidelines [23, 24]. The drug regimen consisted of Ven 100 mg d 1, 200 mg d 2, and 400 mg from d 3–28; azacitidine 75 mg/m^2 d 1–7, or decitabine 20 mg/m^2 d 1–5. The selection of HMAs was based on patient preferences or financial considerations. Ven dosage was reduced in patients concurrently receiving azoles (CYP3 A inhibitors) [25].

2.2 Chromosomal karyotype analysis and detection of AML gene mutations

Conventional karyotype analysis was conducted using the R-chromosome banding technique, with at least 20 metaphase divisions analyzed for each patient. Bone marrow fluid samples were analyzed by Shanghai Rightongene Biotechnology Co., Ltd., China, using next-generation sequencing to detect 62 common AML mutated genes (Supplemental table S1).

2.3 Data collection and definition of efficacy

Information regarding gender, age, blood cell count, AML type, FAB classification, AML status, chromosomal karyotype, and AML mutation genes of the enrolled patients was collected. Bone marrow morphology was assessed based on the FAB classification system. Refractory AML was defined as persistent leukemia without remission after at least two cycles of induction chemotherapy. Relapsed AML was defined as a recurrence of > 5% of bone marrow blasts after achieving CR/CRi. Secondary AML (S-AML) was a myelodysplastic syndrome/myeloproliferative neoplasm transformation or therapy-related AML. OS was defined as the time from treatment initiation to death from any cause, with patients alive at the last follow-up censored on their last known alive date. Treatment response outcomes were classified according to the ELN-2022 standards, including CR/CRi, Partial response (PR), overall response rate (ORR, CR/CRi + PR), and no response (NR). Treatment response was assessed on day 28 of the first cycle and on day 14 or 28 of the second cycle. Patients achieving CR/CRi in any assessment were deemed "sensitive". Those with only PR/NR across all assessments were categorized as "insensitive".

2.4 Development, assessment of the nomogram

Model development and evaluation were performed using the R (Version 4.3.1) software. Batch univariate logistic regression was conducted using custom functions, and variables (influencing factors) with $P < 0.1$ in the univariate analysis were selected for multivariate regression. Multivariate models were constructed using "forced entry, forward, backward, and forward–backward stepwise (both)" methods. The Akaike information criterion (AIC) was applied to compare the superiority and inferiority of each model. Eventually, the "forward–backward method" was adopted to construct the model, and the "regplot" package was used to present the nomogram of the model. The "pROC" package was used to draw the receiver operating characteristic (ROC) curve and calculate the area under the curve (AUC) to assess the discrimination of the model. The "fbroc" package was used to generate thebootstrap-corrected ROC. The "HLtest.R" package was used for the Hosmer–Lemeshow test and calibration curve for calibration evaluation. The "rms" package was used to draw the calibration curve and bootstrap resampling was conducted to draw the corrected curve. The net benefit of the model was evaluated by decision curve analysis (DCA) and internally validated by bootstrap, using the "rmda" package, which also generated the Clinical Impact Curve (CIC). The stability and reliability of the model were rigorously evaluated through bootstrap resampling method (B = 500 iterations). During the resampling process, we relied on the pre-established model structure rather than drawing repeated samples directly from the original dataset.

2.5 Statistical analysis

Data analysis and visualization were performed using R (version 4.3.1) and GraphPad Prism 9.2.0 software. Categorical variables were expressed as frequency (percentage). Continuous variables were tested for normality. Normally distributed data were described as mean ± standard deviation, while non-normally distributed data were described as median (P_{25}, P_{75}). Binary logistic regression analysis was applied to variables influencing the outcome, and odds ratio (OR) along with their 95% confidence interval (CI) were calculated. Survival curves were constructed using the Kaplan–Meier method, and differences in survival between groups were evaluated using the log-rank test. In all analyses, P values < 0.05 were considered statistically significant.

3 Result

3.1 Patient characteristics

The clinical information of 219 patients with AML was collected in this study. After applying the inclusion and exclusion criteria (Fig. S1 and Supplemental Table S2), 209 patients were included in the predictive model. The cohort comprised 122 males (58.4%) and 87 females (41.6%) with a median age of 66 (57–71) years. Among them, de novo AML accounted for 142 cases (67.9%), while S-AML accounted for 67 cases (32.1%). Newly diagnosed (ND) AML constituted 151 cases (72.2%) and refractory/relapsed (R/R) AML comprised 58 cases (27.8%). Cytogenetic analysis revealed normal karyotypes in 121 cases (57.9%), hyperdiploid or polyploid karyotypes in 30 cases (14.4%), and karyotypes with adverse prognosis in 58 cases (27.8%). Genes with mutation frequencies exceeding 20% included *ASXL1*, *DNMT3 A*, *K/NRAS*, *RUNX1*, *TET2,* and *FLT3*, whereas *IDH* gene mutations were observed in 19.6% of cases. Risk stratification according to the European LeukemiaNet 2022 (ELN-2022) criteria classified 16 cases (7.7%) as low-risk, 51 cases (24.4%) as intermediate-risk, and 142 cases (67.9%) as high-risk. Additionally, 21 patients (10.0%) had concurrent malignancies and 55 patients (26.3%) had previously received HMAs treatment. (Fig. 1 and Table 1).

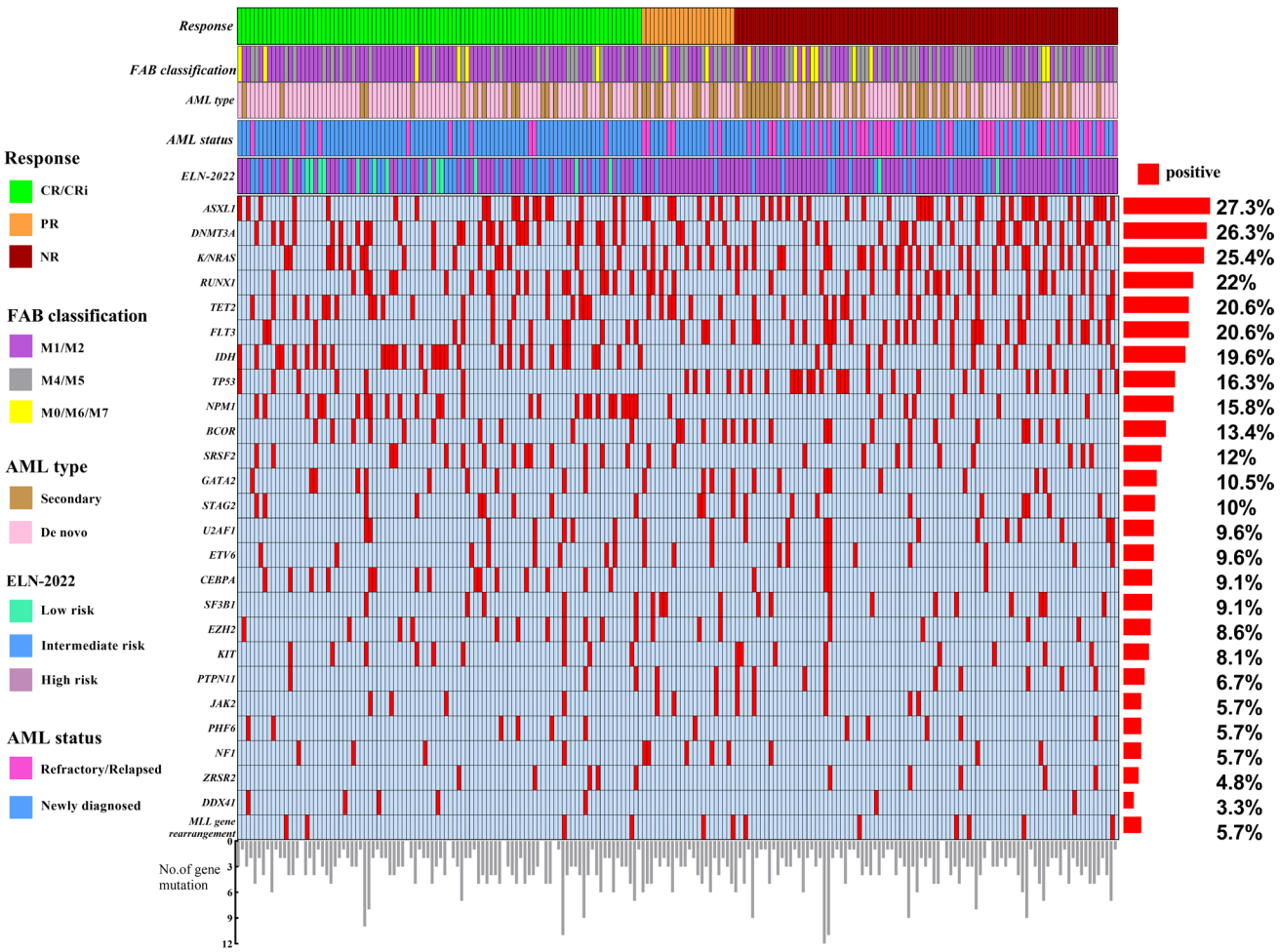

Fig. 1 The clinical characteristics of the enrolled patients (including treatment response, AML type, AML status, FAB classification, ELN-2022 risk stratification, and next-generation sequencing) were analyzed

Table 1 Characteristics of 209 AML patients

Baseline characteristics	Value
Sex [*n* (%)]	
Male	122 (58.4)
Female	87 (41.6)
Age [year, M (P_{25}, P_{75})]	66 (57, 71)
ECOG score [*n* (%)]	
0 ~ 1	83 (39.7)
2 ~ 3	126 (60.3)
Combination of other tumors [*n* (%)]	
Yes	21 (10.0)
No	188 (90.0)
FAB type [*n* (%)]	
M1/M2	124 (59.3)
M4/M5	68 (32.5)
M0/M6/M7	17 (8.1)
AML status [*n* (%)]	
Newly diagnosed	151 (72.2)
Refractory/Relapsed	58 (27.8)
AMLtype [*n* (%)]	
De novo AML	142 (67.9)
Secondary-AML	67 (32.1)
Median WBC count [(× 10^9/L), M (P_{25}, P_{75})]	4.77 (2.02, 12.53)
Median neutrophil count [(× 10^9/L), M (P_{25}, P_{75})]	1.43 (0.50, 3.75)
Median hemoglobin concentration [(× 10^9/L), M (P_{25}, P_{75})]	76 (62, 97)
Median platelet count[(× 10^9/L), M (P_{25}, P_{75})]	53 (26.5, 103)
Bone marrow blasts [%, M (P_{25}, P_{75})]	36.0 (24, 65.3)
Chromosome karyotype (According to ELN-2022) [*n* (%)]	
Normal karyotype	121 (57.9)
Hyperdiploid/polyploid karyotype	30 (14.4)
Adverse karyotype	58 (27.8)
Gene mutations (Top six)	
ASXL1	57 (27.3)
DNMT3 A	55 (26.3)
K/NRAS	53 (25.4)
RUNX1	46 (22.0)
TET2	43 (20.6)
FLT3	43 (20.6)
ELN-2022 risk stratification [*n* (%)]	
Low risk	16 (7.7)
Moderate risk	51 (24.4)
High risk	142 (67.9)
Prior_HMAs [*n* (%)]	
Yes	55 (26.3)
No	154 (73.7)
Cycles of Ven-HMAs [M (range)]	2 (1, 8)
Types of hypomethylating agents [*n* (%)]	
Azacitidine	166 (79.4)
Decitabine	43 (20.6)

Abbreviations *ECOG* Eastern Cooperative Oncology Group, *FAB* French-American-British, *WBC* White blood cell, *ELN-2022* European Leukemia Network-2022, *Prior_HMAs* Prior hypomethylating agents exposure, *Ven-HMAs* Venetoclax in Combination with hypomethylating agents

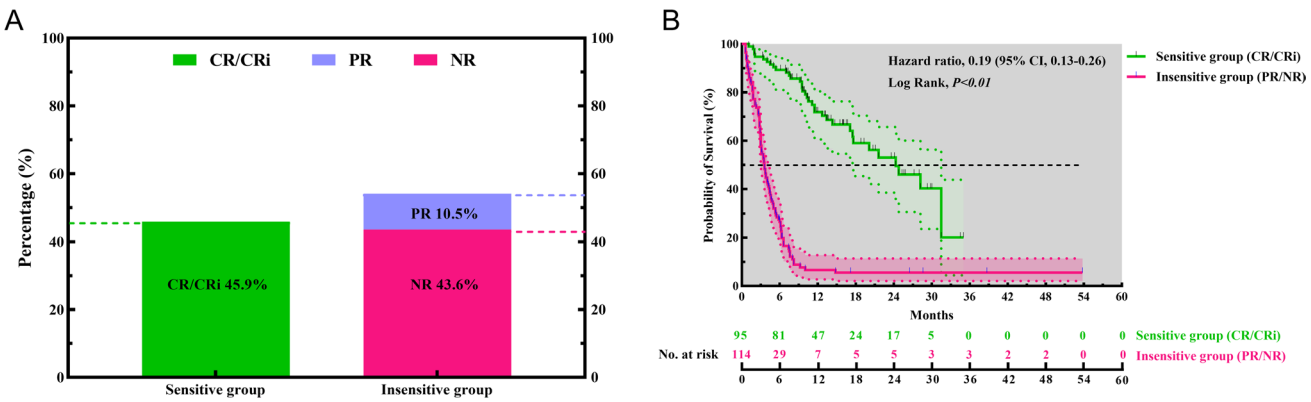

Fig. 2 Assessment of Ven-HMAs Efficacy in elderly/unfit Patients with AML. **A** Patients response to Ven-HMAs, divided into sensitive and non-sensitive groups. **B** Overall survival curves for the sensitive group and insensitive group

3.2 Assessment of therapeutic efficacy

Based on the assessment at post-treatment time points, the CR/CRi rate was 45.9% (96/209). The rate of achieving measurable residual disease (MRD) negativity was 35.4% (74/209), while the PR rate was 10.5% (22/209). The ORR was 56.5% (118/209). Notably, the median survival of the treatment-sensitive group was significantly higher than that of the treatment-insensitive group (HR 0.19, 95% CI 0.13–0.26, $P < 0.01$). (Fig. 2A–B).

3.3 Selection of model predictive variables

Potential predictive variables for treatment sensitivity (CR/CRi) encompassed demographic, clinical, and genetic factors. These included age, gender, ECOG score, FAB classification, AML type, AML status, concurrent malignancies, prior HMAs exposure (prior_HMAs), HMAs type, chromosomal karyotype, myeloid gene mutations (molecular mutations with more than 6 cases in the cohort occurring in more than six cases in the cohort), and *MLL* fusion gene status. Univariate logistic regression analysis was performed for these variables (Supplemental table S3). Subsequently 14 variables (FAB classification, AML type, AML status, prior_HMAs, chromosomal karyotype, *ASXL1*, *FLT3*, *IDH*, *NPM1*, *CEBPA*, *PTPN11*, *K/NRAS*, *SF3B1*, and *TP53*) were screened out with a threshold of $P < 0.1$ for inclusion in the multivariate logistic regression. Subsequently, a model was developed based on minimum AIC (AIC = 191.47). The final model incorporated 10 variables. Sensitive factors include include hyperdiploid/polyploid karyotype (β = 1.258), mutations in *IDH* (β = 1.058), *NPM1* (β = 1.816), and *CEBPA* (β = 1.950). Insensitive factors include FAB classification (M4/M5: β = – 0.923, M0/M6/M7: β = – 2.453), S-AML (β = – 1.322), R/R AML (β = – 2.093), adverse karyotype (β = – 1.620), mutations in *ASXL1* (β = – 0.728), and *FLT3* (β = – 1.622). (Table 2).

3.4 Establishment, assessment of the model

Based on the final model variables, a nomogram incorporating ten predictive factors was established (Fig. 3A). To further assess the performance of the predictive model, we plotted the ROC, calibration, DCA, and clinical impact curves. The AUC of the model's ROC curve was 0.900 (95% CI 0.860–0.941). The bootstrap-corrected AUC of the model's ROC curve was 0.900 (95% CI 0.852–0.941) (Fig. 3B–C), demonstrating that the model has robust discriminatory ability. The calibration curve of the model was plotted, and the results indicated good correspondence between the predicted probability of the model and the actual occurrence probabilities (Fig. 3D). The Hosmer–Lemeshow test yielded a chi-square value of 4.82 ($P = 0.849$), indicating no significant difference between the predicted and actual probabilities. The DCA curve was used to evaluate the net clinical benefit of the model. The applicable threshold probability range of the DCA for the model in this study was 0–0.98, whereas analysis of 500 bootstrap resampling iterations a range of 0.03–0.9 (Fig. 3E–F). Within the 0–0.98 threshold probability range, the net clinical benefit of intervention based on the model's predicted

Table 2 Model variables were selected using univariate and multivariate regression based on the AIC minimum criterion

Variables	Univariate logistic regression ($P < 0.1$)			Multivariate logistic regression and minimum AIC		
	β value	OR (95% CI)	*P* value	β value	OR (95% CI)	*P* value
FAB type						
M1/M2 *			0.008			**0.006**
M4/M5	− 0.932	0.394 (0.212–0.731)	0.003	− 0.923	0.397 (0.166–0.951)	0.038
M0/M6/M7	− 0.800	0.449 (0.156–1.291)	0.137	− 2.453	0.086 (0.015–0.482)	0.005
S-AML, yes	− 1.199	0.301 (0.160–0.568)	< 0.001	− 1.322	0.267 (0.102–0.696)	**0.007**
R/R AML, yes	− 2.002	0.135 (0.062–0.295)	< 0.001	− 2.093	0.123 (0.039–0.386)	**< 0.001**
Chromosome karyotype						
Diploid Karyotype *			< 0.001			**< 0.001**
Hyperdiploid/polyploid karyotype	0.743	2.078 (0.881–4.904)	0.095	1.258	3.517 (0.932–13.263)	0.063
Adverse karyotype	− 1.568	0.208 (0.099–0.440)	< 0.001	− 1.620	0.198 (0.072–0.544)	0.002
Prior_HMAs, yes	− 2.058	0.128 (0.057–0.288)	< 0.001	− 1.043	0.352 (0.111–1.120)	**0.077**
Gene mutations						
ASXL1	− 0.719	0.487 (0.258–0.920)	0.027	− 0.728	0.483 (0.178–1.311)	**0.153**
CEBPA	1.619	5.046 (1.614–15.775)	0.005	1.950	7.031 (1.321–37.423)	**0.022**
FLT3	− 0.836	0.433 (0.211–0.889)	0.023	− 1.622	0.197 (0.070–0.554)	**0.002**
IDH	1.592	4.912 (2.258–10.689)	< 0.001	1.058	2.879 (1.002–8.270)	**0.049**
NPM1	1.727	5.624 (2.316–13.662)	< 0.001	1.816	6.144 (1.728–21.843)	**0.005**
PTPN11	− 1.207	0.299 (0.081–1.105)	0.070			0.307
K/NRAS	− 0.665	0.514 (0.269–0.985)	0.045			0.274
SF3B1	− 0.945	0.389 (0.135–1.122)	0.080			0.964
TP53	− 1.384	0.251 (0.104–0.606)	0.002			0.221

Abbreviations: *reference, *S-AML* Secondary-AML, *R/R AML* Refractory/Relapsed AML, *Prior_HMAs* Prior hypomethylating agents exposure, *AIC* Akaike Information Criterion

The variables corresponding to bolded values were incorporated into the nomogram

probability was higher than that of no intervention (None) and intervention for all patients (All). The corresponding CIC is shown in Fig. 3G.

4 Discussion

In this study, we developed and validated a clinical model to predict the sensitivity of Ven-HMAs treatment in AML patients. The model incorporates AML gene mutations at diagnosis and other clinical information, including morphology and cytogenetics, as prediction parameters. The performance of the model was evaluated using the AUC index, calibration curve, DCA, and CIC, demonstrating good discrimination, accuracy, and net clinical benefit. Moreover, internal validation through bootstrap resampling method further confirmed the performance of the model.

Ven-HMAs have been approved for the treatment of newly diagnosed elderly or unfit AML patients, marking a significant shift in therapeutic modalities for this subgroup [26]. In recent years, the majority of efficacy reports on Ven-HMAs in AML have primarily originated from retrospective real-world studies. A systematic literature review revealed considerable variations in CR/CRi rates across hematological centers (14.0% to 75.0%), with inconsistent findings on factors influencing therapeutic efficacy [22, 27–29]. These discrepancies may be attributed to the distinct characteristics of the cohorts, sample sizes, and the treatment attributes of each study. Our study, encompassing 209 patients, reported CR/CRi and ORR rates of 45.6% and 56.5%, respectively, with a 35.4% rate of achieving MRD negativity. These outcomes were similar to those of Feld, Short, and Matthews et al. [30–32], but lower than those of Gangat and Chojecki et al. [33, 34], possibly due to the high proportion of high-risk patients (67.2%) and R/R AML (27.8%) in our cohort.

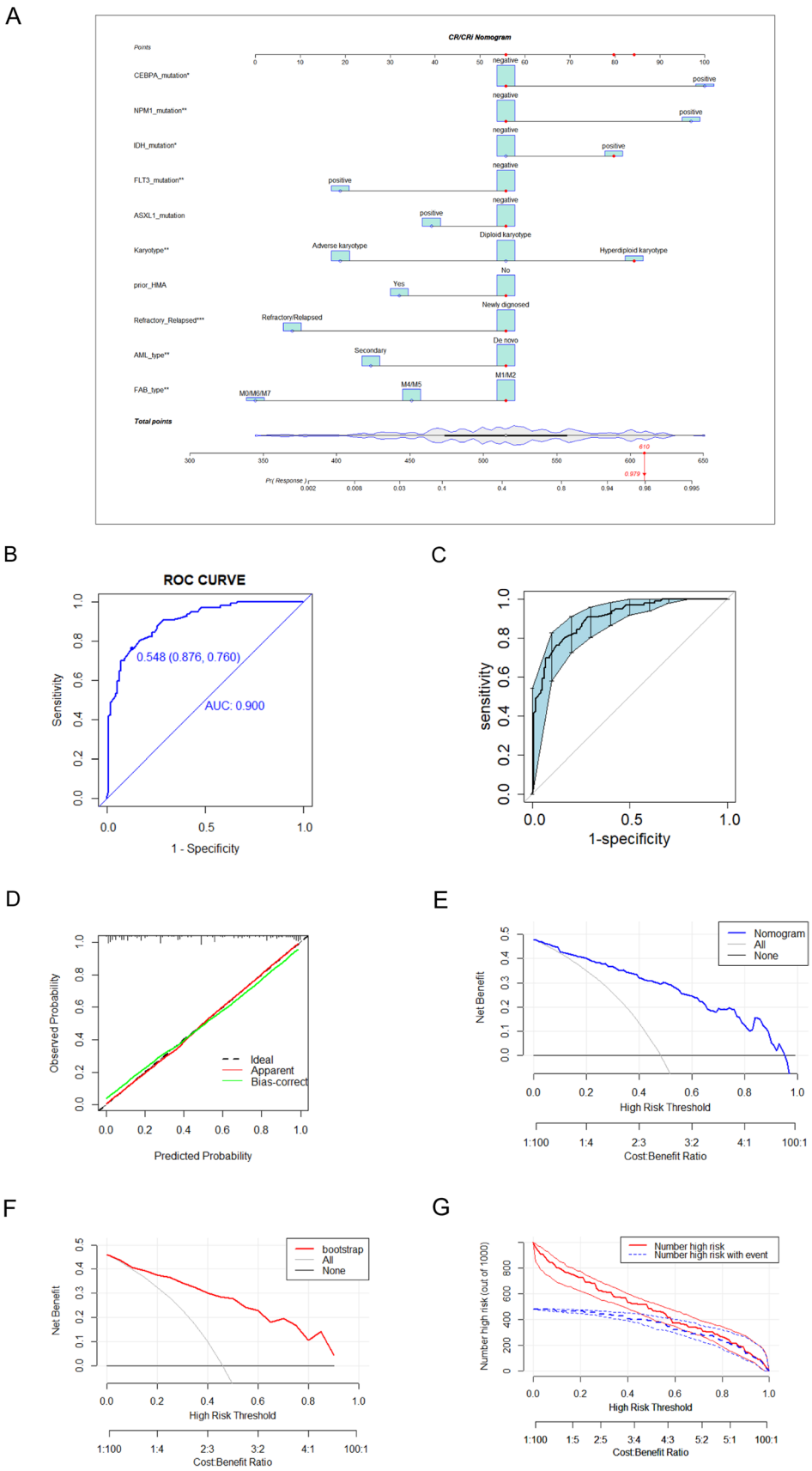

Fig. 3 Establishment, assessment of the model. **A** Nomogram for predicting sensitivity to Ven-HMAs in elderly/unfit Patients with AML. **B** ROC curve for the nomogram. **C** Bootstrap-corrected ROC curve for the nomogram. **D** Calibration curves for the nomogram. Ideal represents the ideal reference line, Apparent represents the model prediction curve, and Bias-correct represents bootstrap resampling method estimates the bias of the nomogram. **E** Decision curve analysis for the nomogram. **F** Decision curve analysis for the internal validation (bootstrap resampling method). **G** Clinical impact curves for the nomogram. The red line indicates the predicted number of outcome events according to the model, while the blue line represents the actual number of events that occurred

This study further explored the factors that influence the therapeutic effects of Ven-HMAs in AML. Univariate analysis was used to identify several risk factors for CR/CRi. These included specific FAB classification (M1/M2, M4/M5 and M0/M6/M7), S-AML, R/R AML, prior_HMAs, adverse chromosomal karyotypes, and mutations in the *ASXL1*, *FLT3*, *TP53*, and *K/NRAS* genes. Conversely, M1/M2 FAB classifications and mutations in *IDH*, *NPM1*, and *CEBPA* were associated with higher CR/CRi rates, consistent with previous studies [18–20, 35–38]. Subsequent multivariate analysis refined these findings, revealing that the *ASXL1*, *TP53*, and *K/NRAS* mutations did not significantly influence the CR/CRi rate. This study corroborates previous findings regarding the resistance of AML cells with monocytic differentiation to Ven. Additionally, it supports recent studies suggesting that AML with erythroid/megakaryocytic differentiation is also resistant to Ven. This resistance is proposed to be related to the high expression of Bcl-XL, which differs from the monocytic resistance mechanism [37]. The variables screened by multivariate regression analysis served as the foundation for constructing a model of sensitivity to Ven-HMAs treatment in patients with AML.

We employed multivariate regression to identify eight statistically significant variables. Subsequently, prior_HMAs and *ASXL1* mutations were incorporated into the final model, following the AIC minimum optimization model. However, the influence of *ASXL1* mutations on remission rates remains controversial. While Gangat and Johnson et al. [33, 39] argued that *ASXL1* mutation is a protective factor against CR/CRi, Winters et al. [35] presented contradictory findings. Our research suggests that Prior_HMAs and *ASXL1* mutations tend to lower the CR/CRi rate. The prediction model for Ven-HMAs treatment sensitivity in AML established in this study can estimate the probability of achieving CR/CRi in patients with AML based on their clinical characteristics. The AUC value of the model was relatively high, and the calibration curve revealed strong concordance between the predicted probabilities and actual event occurrence rates, indicating a considerable probability of accurately differentiating between sensitive and insensitive patients. Clinical net benefit evaluation using the DCA curve showed that adopting Ven-HMAs treatment within the threshold probability range of 0 to 0.98 yields clinical net benefits. The CIC curve further indicated good consistency between the predicted model probabilities and the actual occurrence probabilities when the risk threshold exceeded 0.6. Considering the current sample size limitations, we opted for internal validation using the bootstrap method, rather than data splitting [40]. The results suggest a robust model performance. This study constructed a prediction model for the sensitivity of elderly/unfit AML patients to Ven-HMAs treatment, differing from the drug resistance-focused model by Zong et al. [41] Key strengths of our study include: (1) Focusing directly on achieving CR/CRi, which is more clinically relevant than drug resistance. (2) Incorporating a broader range of predictive variables, including critical factors like *NPM1*, *CEBPA*, and *IDH* mutations that significantly influence the response to Ven-HMAs [42], beyond those in Zong et al.'s model. This may enable a more comprehensive assessment.

In summary, this study constructed and interally validated a prediction model for the sensitivity of Ven-HMAs to AML treatment. The model has the following advantages: First, it exhibits high discrimination, indicating a relatively high probability of identifying AML patients likely to benefit from Ven-HMAs treatment. Second, its DCA curve has a broad threshold range, suggesting a certain degree of clinical utility.

However, this study has several limitations that warrant consideration. First, this prediction model is based on a retrospective study, which might limit the level of evidence and require prospective studies to corroborate these findings. Second, the validation of this prediction model is internal, which, to a certain extent, may restrict its generalizability and applicability. External validation is necessary to verify the predictive ability of the model further. Third, as a prediction model, this study required expanding the sample size. Although efforts were made to include a substantial number of samples, this study would benefit from a larger dataset to optimize the model's performance and draw more robust conclusions.

Future research directions should focus on conducting prospective studies to validate the model's predictive accuracy, performing external validation across diverse patient populations and clinical settings, expanding the sample size to enhance the model's reliability and generalizability, and incorporating emerging biomarkers or genetic factors that may improve the model's predictive power. These efforts will contribute to refining the prediction model and enhancing its clinical utility in guiding Ven-HMAs treatment decisions for patients with AML.

5 Conclusion

In this study, we developed and internally validated a clinical model to predict the sensitivity of elderly or unfit AML patients to combination therapy with Ven-HMAs. This model demonstrates high discriminatory power, calibration, and clinical net benefit, potentially enhancing the precision of Ven-HMAs treatment in AML. This can potentially optimize treatment decisions, improve patient outcomes.

Author contributions Y. D. undertook data collection, data analysis, patient follow-up, and manuscript drafting; C. L. was accountable for data analysis and verification; Y. C. was responsible for data collection and verification; F. X. and J. Y. were responsible for supervision, review, and editing. All authors have read and consented to the publication version of the manuscript.

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Data availability The data provided in this study are available upon request from the corresponding author.

Declarations

Competing interests The authors declare no competing interests.

Informed consent statement Written informed consent was obtained from the patient for the publication of this paper.

Institutional review board statement This study was approved for implementation by the Ethics Committee of the Second Affiliated Hospital of Dalian Medical University (Lot Number: KY2024-183-01).

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