Clinical and Cytogenetical Characteristics-Related Nomograms for Assessing Outcome of Acute Myeloid Leukemia Patients Post IA Induction

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Abstract

Background: Acute myeloid leukemia(AML) is a highly heterogeneous hematological malignancy. Despite, increase in treatment options for AML over the past decade, prognosis for AML remain dismal. Numerous prognostic models have been developed for this disease, however nomograms predicting long-term survival in AML patients after induction chemotherapy(IA regimen) have not been described.

Method: We constructed nomograms to predict disease-free survival(DFS) and overall survival(OS) by analyzing the cohort of patients with *de novo* non-M3 AML patients who underwent induction chemotherapy between June 2008 to August 2019. We utilized univariable and multivariable Cox proportional hazards regression analyses to obtain the selected variables for the nomograms. The discriminative ability and calibration were tested using C statistics, calibration plots, and Kaplan-Meier curves.

Results: A total of 360 patients who underwent induction chemotherapy with IA regimen were included in the study. Of these 55% were male with a median age was 48 years. Using the univariate and multivariate analyses, the following variables were identified in the prediction of DFS: age(HR, 1.770; 95%CI, 1.160-2.702; P = 0.008), Hb(HR, 0.634; 95%CI, 0.462-0.870; P = 0.005), albumin(HR, 0.473; 95%CI, 0.363-0.615; P < 0.001) and cyto/molecular risk group(intermediate vs. favorable: HR, 1.614; 95%CI, 1.128-2.309; P = 0.001; poor vs. favorable: HR, 2.459; 95%CI, 1.645-3.676; P < 0.001) at the time of diagnosis, and allo-HSCT treatment(HR, 0.341; 95%CI, 0.234-0.497; P < 0.001). Factors which predicted OS were Hb (HR, 0.616; 95%CI, 0.438-0.866; P = 0.005), albumin (HR, 0.448; 95%CI, 0.340-0.591; P < 0.001), cyto/molecular risk group (intermediate vs. favorable: HR, 1.558; 95%CI, 1.068-2.275; P = 0.021; poor vs. favorable: HR, 2.348; 95%CI, 1.523-3.620; P < 0.001), allo-HSCT treatment (HR, 0.256; 95%CI, 0.166-0.396; P < 0.001), and age (HR, 1.528; 95%CI 0.980-2.382; P = 0.061). The discriminative ability and calibration of the nomograms revealed good predictive ability as indicated by the C statistics (0.715 for DFS and 0.731 for OS).

Conclusion: Independent predictors of survival and relapse risk after IA regimen for AML can be utilized to obtain survival nomograms. These nomograms were able to predict DFS and OS while having good calibration accuracy and discriminative ability on internal validation.

Background

Acute myeloid leukemia(AML) is the most common type of acute leukemia, with the estimated 19,940 new cases and 11,180 deaths in the United States in 2020[1]. For patients with non-M3 [acute promyelocytic leukemia(APL)] *de novo* AML, IA regimen [idarubicin(IDA) and cytarabine(Ara-C)] as induction therapy remains the best intervention for long-term survival.[2, 3] Unfortunately, AML is a highly lethal malignancy, with up to 39-49% of patients suffering from relapse at 5-year.[4-6] Furthermore, 5-year overall survival (OS) for patients with non-M3 AML range from 24% to 40%.[7-10]

Currently, several factors which can aid with prognostication and prediction of clinical outcomes [e.g., risk stratification, age, white blood cell (WBC) count, coexisting comorbidities and a history of an antecedent hematologic disorder].[2, 3, 11-17] The European Leukemia Net(ELN)[3] and National Comprehensive Cancer Network(NCCN)[2] risk stratifications are the most widely used criteria to stratify patients with AML. Although the risk stratification is an important factor for the prediction of survival, it is important to incorporate other clinical factors(e.g., age) to optimize prediction system.

Despite the presence of several clinicopathological factors used to predict prognosis, the accuracy of these prognosticative models remains a challenge. Thus, there have been various prognostication models developed recently to address this issue. Sorror *et al.* developed a novel AML composite model, which included cytogenetic risk, age, regimen intensity and comorbidities, to predict 1-year mortality.[11] Shouval, *et al.* constructed an auto-AML nomogram, which contained age and cytogenetic risk, to predict leukemia-free survival from autologous stem cell transplantation (auto-SCT).[18] Considering that these models were constructed based on different populations and outcomes, the availability of predictive models is restrictive.

Therefore, we aimed to develop and validate nomograms, which include clinicopathological factors, for estimate the probability of disease-free survival(DFS) and overall survival(OS) in patients with non-M3 AML undergoing “3+7” IA regimen as induction chemotherapy.

Methods

Patient Population and Data Collection

We conducted a retrospective study, based on data collected by review of electronic medical records for 360 patients treated at the First Affiliated Hospital of Wenzhou Medical University between June 2008 to August 2019. All patients were newly diagnosed with *de novo* non-M3 AML. Only patients who received

conventional “3+7” IA(IDA 8-10 mg/m2 at day 1-3 and Ara-C 100 mg/m2 at day 1-7) regimen as initial induction chemotherapy were included in the study group. Secondary AML patients with preceding hematological disorders were excluded. Patients with missing values on follow-up data were not included in the study. This study was approved by the institutional review board. No additional patient informed consent was required due to retrospective nature of this study. All data were collected and analyzed in accordance with the Declaration of Helsinki.

Variables concerning clinicopathological characteristics were reviewed, including age, sex, WBC count, hemoglobin(Hb), platelet(PLT), serum albumin, blasts at bone marrow(BM) and peripheral blood(PB), morphological immunophenotypic, cytogenetic and molecular features of myeloid blasts at the time of diagnosis before chemotherapy. Additionally, variables concerning subsequent therapeutic data were extracted, such as initial chemotherapy regimen, allogeneic hematopoietic stem cell transplantation(allo-HSCT) treatment and remission status after treatment. *De novo* AML was diagnosed and classified according to FAB [19] and ELN 2017 criteria[3].

Outcome

The outcomes of interest in this study were OS and DFS. OS was calculated from the date of diagnosis to the death or last follow-up, and DFS was calculated from the date of complete remission(CR) to relapse, death or last follow-up. The criteria of CR included low residual blast percentages (<5), morphologically normal hematopoiesis, recovery of peripheral blood cell counts to normal levels, and without extramedullary disease.[20-23] Relapse was defined as reoccurrence of high blast percentages (≥5%) in BM unrelated to recovery from prior chemotherapy [3, 24].

Statistical Analysis

Numerical variables were reported as medians with interquartile ranges (IQRs), and categorical variables were reported as absolute and relative frequencies. Numerical predictors (e.g., WBC, Hb and PLT) were categorized by receiver operating characteristic(ROC) curve, and the optimal cut-off was made by combination of Youden index and clinical use.

The associations of each variable with DFS and OS were first assessed by univariable cox proportional hazards regression analysis for investigating the independent risk factors. All variables associated with DFS and OS at a significant level were subsequently analyzed by stepwise multivariate analysis. Variables with a p value <0.05 in multivariable analysis and variables with clinical importance identified by previously published articles [3, 4, 11, 12, 14, 15], were selected to incorporate in the nomograms to predict the probability of 1-year, 2-year and 3-year DFS and OS rates.

The nomograms were then constructed based on proportionally turning each regression coefficient in multivariate analysis to a 0- to 100-point scale. The performance of nomograms were measured using the concordance index(C-index) as per Harrell *et al.*[25] To further assess discriminative ability of the model, the Kaplan-Meier curves of DFS and OS were plotted, stratified by the quartile of the total points calculated from the nomograms. The calibration of nomograms were evaluated by calibration curve, with bootstrap resampling to decrease the overfit bias. Statistical analyses was performed with R version 3.6.1(https://www.r-project.org/). Significance level was defined as p value <0.05.

Results

Baseline Characteristics

A total of 360 AML patients were enrolled in this study who baseline characteristics as listed in Table 1. The median age of the patient population was 48 years(IQR, 33-59 years), 55% of patients were male(Table 1). The median WBC count was 18.25×109/L(5.54-54.33). The median Hb level was 82.50g/L(66.00-103.25), and median PLT count was 40.50×10^9/L(19.75-86.25). The median percentages of blasts in PB and BM were 54.00% (21.50-78.00) and 66.00% (45.80-83.28) respectively. The median albumin level was 35.95g/L (32.75-39.52). In total, 70(19.44%), 195(54.17%) and 83(23.06%) patients

displayed favorable, intermediate, and poor risk groups, respectively. In total, 21.39% of the patients underwent allo-HSCT.

The study was censored on January 22, 2020. The median follow-up time was 15.4 months (range,0.2-132.8). By the time of censor, 65(18.06%) patients did not reach CR after induction and re-induction chemotherapy, 138(38.33%) patients relapsed, and 226(62.78%) patients died. Among them, 28 patients died of induction-related toxic effects, 21 patients died during re-induction chemotherapy, 15 patients died during maintenance and consolidation chemotherapy, 24 patients died of lack of response to induction, 124 patients died of disease-progression, 11 patients died of complications of HSCT and 3 patients died of other reasons(eTable). The unadjusted median DFS was 9.2 months (95% CI, 7.0-14.8), and the unadjusted median OS was 21.2months (95% CI, 16.6-27.6). The 1-year, 2-year, and 3-year DFS percentages were 47.6%(95% CI, 42.6-53.1), 36.0%(95% CI, 31.2-41.5), and 29.8%(95% CI, 25.2-35.3), respectively, while the OS percentages were 59.2%(95% CI, 54.2-64.5), 46.4%(95% CI, 41.4-52.1), and 37.8%(95% CI, 32.8-43.6), respectively(eFigure).

Independent Prognostic Factors

The results of univariate and multivariate analyses of DFS and OS are summarized in Table 2 and Table 3. The univariate and multivariate Cox proportional hazards regression modeling found: age(HR, 1.770; 95%CI, 1.160-2.702; P = 0.008), Hb (HR, 0.634; 95%CI, 0.462-0.870; P = 0.005), albumin (HR, 0.473; 95%CI, 0.363-0.615; P < 0.001) and cytogenetic /molecular risk group (intermediate vs. favorable: HR, 1.614; 95%CI, 1.128-2.309; P = 0.001; poor vs. favorable: HR, 2.459; 95%CI, 1.645-3.676; P < 0.001) at the time of diagnosis, and allo-HSCT treatment (HR, 0.341; 95%CI, 0.234-0.497; P < 0.001) were independent predictors for DFS. Similarly, the following 4 variables were found to be associated with OS: Hb (HR, 0.616; 95%CI, 0.438-0.866; P = 0.005), albumin(HR, 0.448; 95%CI, 0.340-0.591; P < 0.001), cyto/molecular risk group(intermediate vs. favorable: HR, 1.558; 95%CI, 1.068-2.275; P = 0.021; poor vs. favorable: HR, 2.348; 95%CI, 1.523-3.620; P < 0.001), and allo-HSCT treatment(HR, 0.256; 95%CI, 0.166-0.396; P < 0.001). Although the association of age and OS was not significant (HR, 1.528; 95%CI 0.980-2.382; P = 0.061), age was still selected as candidate for nomogram due to its clinical importance [5].

Development and Validation of Nomograms

Nomograms to predict 1-year, 2-year and 3-year DFS and OS of patients with non-M3 AML are shown in Figure 1. The nomograms were constructed based on the 5 variables described above (Table 2 and Table 3). Total points, calculated from the sum of the allocated number of points for each variable in the nomograms, were corresponding to specific prognoses at 1 year, 2 years and 3 years. For example, a 45-year-old patient undergoing allo-HSCT, with an intermediate karyotype, a hemoglobin level of 94g/L and a serum albumin level of 33.9g/L, would have a total of 155 points(0 point for age, 41 points for hemoglobin<100g/L, 70 points for albumin<35g/L, 44 points for intermediate risk group, 0 point for allo-HSCT), for a predicted 1-year, 2-year and 3-year DFS of 59.3%, 45.1% and 37.5%, respectively (Figure 1A).

The discriminative abilities of the nomograms for DFS and OS were evaluated by C-index (0.715 for DFS and 0.731 for OS). To further evaluate the discriminative abilities, the Kaplan-Meier curves of DFS and OS were displayed in Figure 2. Patients with the lowest total points (quartile-4) had a worse DFS ($p < 0.001$; Figure 2A) and OS($p < 0.001$; Figure 2B), compared to quartile-1, -2 and -3. Specifically, the 3-year DFS proportion of quartile-1, -2, -3 and -4 was 57.1%(95%CI,46.3-70.5%), 34.3%(95%CI,26.1-44.9%), 19.4%(95%CI,11.3-33.4%) and 7.0%(95%CI,3.1-15.8%), respectively(Figure 2A). While the 3-year OS proportion of quartile-1, -2, -3 and -4 was 68.6%(95%CI,58.0-81.1%), 43.1%(95%CI,34.5-53.9%), 28.6%(95%CI,19.2-42.8%) and 10.14%(95%CI,4.8-21.2%), respectively. The accuracy of models was also evaluated by bootstrap validation with 350 resamplings. The 116-sample bootstrapped calibration curves for prediction of 3-year DFS and OS graphically showed good agreement (Figure 3).

Discussion

De novo non-M3 AML patients have a high overall mortality rate, ranging from 60% to 76% at 5-year.[7-10] Accurate prognostic models for individuals are needed, not only to select appropriate treatment regimens but also to inform patients regarding their long-term outcomes (which may aid them in their goals of care decisions). Mohamed *et al.* developed an AML composite model, to estimate the risk of death within 1 year after initial chemotherapy. However, models to predict the outcomes over a longer period currently do not exist. In this study, we constructed 2 nomograms that predict 1-year, 2-year and 3-year DFS and OS for AML patients after initial IA regimen. Moreover, these nomograms were validated with good discriminative ability indicated by a C-index of 0.715 for DFS and 0.731 for OS. According to Figure 3, the predicted probabilities of 3-year survival by the nomograms were similar to actual 3-year survival. Taken together, these results support that nomograms proposed in our study could predict the risk of relapse and survival for non-M3 AML patients.

In addition, nomograms proposed in our study incorporated previously reported variables found to be associated with prognosis of AML, including patient-specific and AML-specific features. A number of studies identified that increased age, poor-risk cytogenetics, anemia, hypoalbuminemia and treatment without allo-HSCT were correlated with inferior survival.[5, 8, 15, 26-30] Our findings corroborated with those results. WBC count proved as a predictor of death in newly diagnosed AML in some studies.[13, 31] However, we found that WBC count had a slight correlation with DFS($p = 0.065$; Table), likely due to widespread use of leukapheresis and hydroxyurea pre-induction chemotherapy in recent years.

While the cost and life expectancy of the AML varies with the baseline characteristics of the patient and available therapies [32-34], accurate prognostic model for patients with AML will be helpful to clinicians. For instance, as shown in Figure 1, allo-HSCT could increase 100 points for AML prediction, and correspondingly increase DFS and OS proportionally. Therefore, individualized prediction nomograms may play a role in choosing treatment regimen in the future.

Despite this, our study has some limitations. Firstly, the sample size was small due to the single-center nature of the study. There is a need to confirm the generalizability by conducting further multicenter

studies in the future. Additionally, retrospective nature of the study and use of electronic medical records for data collection are other potentially limitations. Finally, despite the internal validation by bootstrap validation, external validation remains to be seen.

Conclusions

In this study, we identified several independent prognostic variables, including age, Hb, albumin and cyto/molecular risk group at the time of diagnosis, and allo-HSCT treatment. Based on these associated factors, we developed nomograms to predict DFS and OS. Additionally, the nomograms displayed good calibration accuracy and discriminative ability on internal validation. Further studies are required to externally validated the nomograms for *de novo* non-M3 AML patients in the future which may serve as accurate prediction tools in this patient cohort.

List Of Abbreviations

AML, acute myeloid leukemia; OS, overall survival; DFS, disease-free survival; IQR, interquartile ranges; APL, acute promyelocytic leukemia; IDA, idarubicin; Ara-C, cytarabine; WBC, white blood cell; ELN, European Leukemia Net; NCCN, National Comprehensive Cancer Network; auto-SCT, autologous stem cell transplantation; Hb, hemoglobin; PLT, platelet; BM, bone marrow; PB, peripheral blood; allo-HSCT, allogeneic hematopoietic stem cell transplantation; CR, complete remission; ROC; receiver operating characteristic; C-index, concordance index.

Declarations

Ethics approval and consent to participate

This study was approved by institutional review board of the First Affiliated Hospital of Wenzhou Medical University. Consent was waived by the institutional review board due to retrospective nature of this study, yet confidentialities of patients were protected.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Na Wang performed the statistical analysis and was a major contributor in writing the manuscript. Kanchun Dai, Xianghong Jin and Bei Ge carried out the collection of data. Aakash Desai review the manuscript for clarity. Kang Yu participated in the design of the study. Weihong Lin and Haige Ye conceived of the study. And Haige Ye drafted the manuscript. All authors read and approved the final manuscript.

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Tables

Due to technical limitations, table 1,2,3 is only available as a download in the Supplemental Files section.

Figures

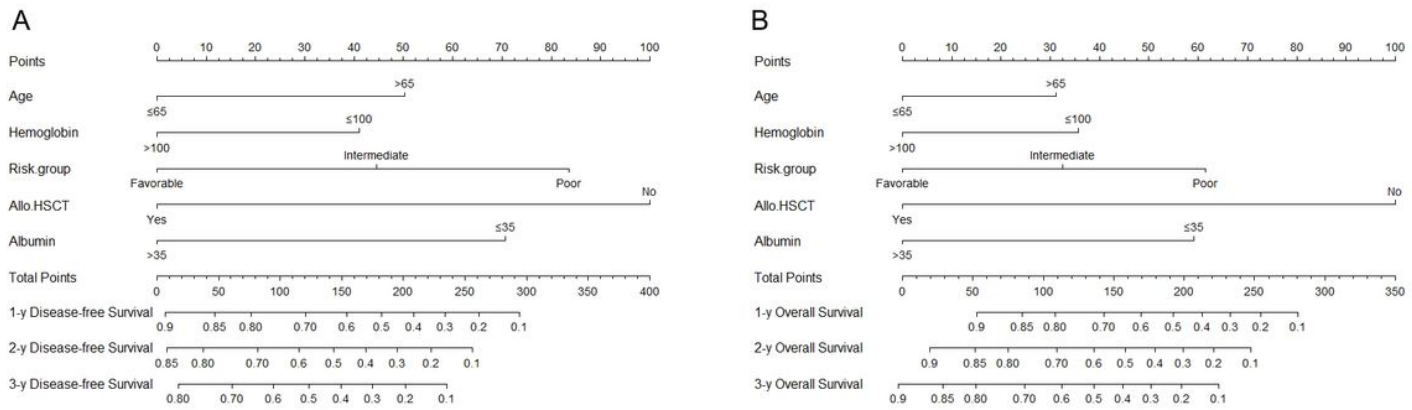

Figure 1

Nomograms predicting disease-free(A) and overall survival(B) in de novo non-M3 AML patients after IA regimen chemotherapy.

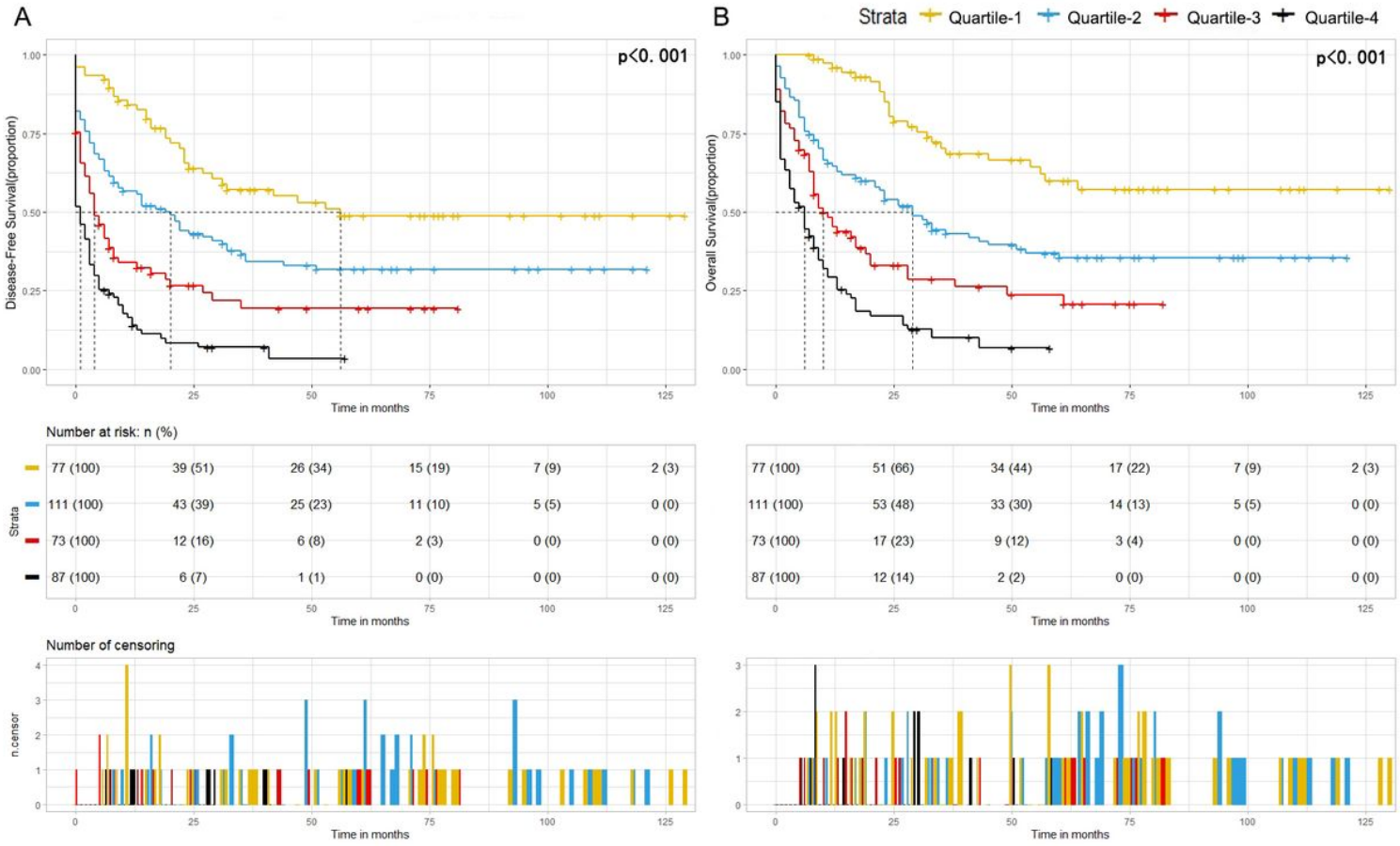

Figure 2

Kaplan–Meier curves of disease-free(A) and overall survival(B) in patients with non-M3 AML According to quartiles of total points calculated by nomograms. P-values were based on the log-rank test.

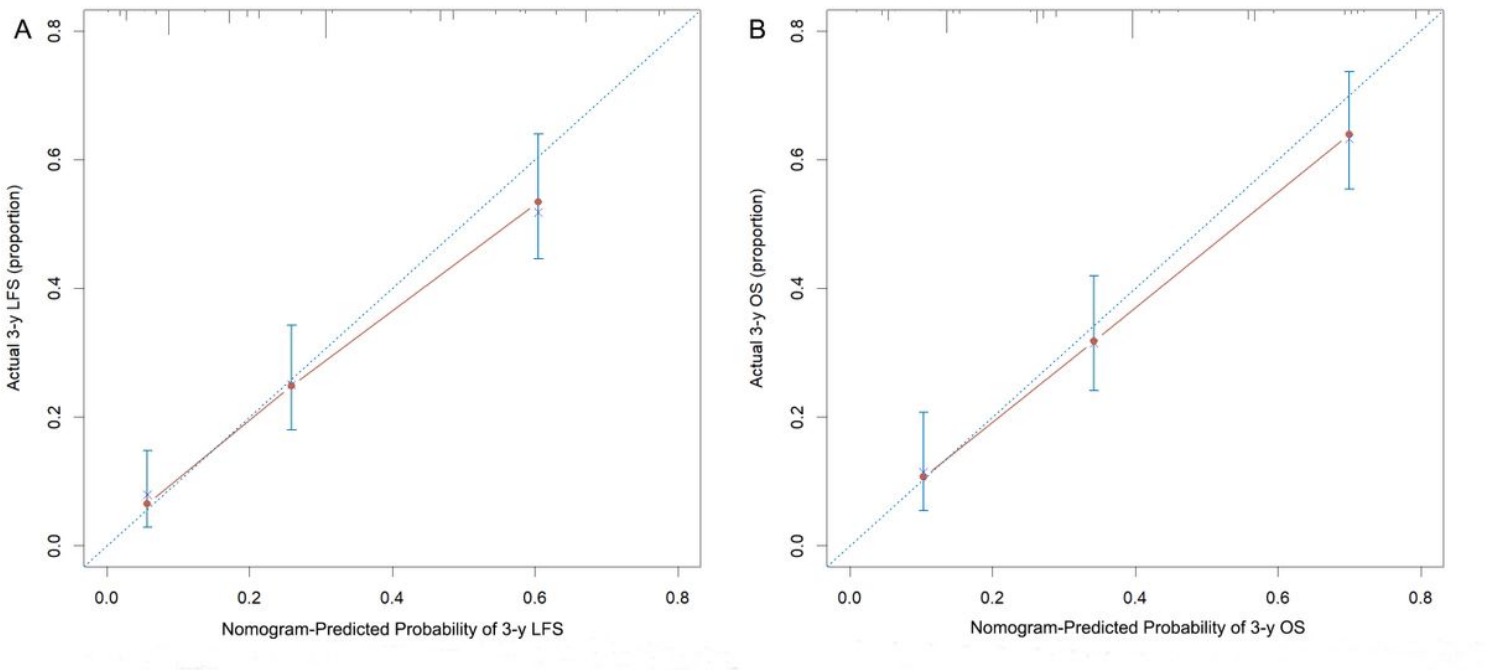

Figure 3

Calibration curve comparing predicted and actual 3-year disease-free(A) and overall survival proportion(B).

Supplementary Files

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- Table3.xlsx
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