Nomogram Predict Overall Survival of Patients with Thymic Epithelial Tumors After Surgery

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Abstract

Background: Hematological indicators and clinical characteristics play an important role in the evaluation of the progression and prognosis of thymic epithelial tumors. Therefore, we aimed to combine these potential indicators to establish a prognostic nomogram to determine the overall survival (OS) of patients with thymic epithelial tumors undergoing thymectomy.

Methods: This retrospective study was conducted on 167 patients who underwent thymectomy between May 2004 and August 2015. Cox regression analysis were performed to determine the potential indicators related to prognosis and combine these indicators to create a nomogram for visual prediction. The prognostic predictive ability of the nomogram was evaluated using the consistency index (C-index), receiver operating characteristic (ROC) curve, and risk stratification. Decision curve analysis was used to evaluate the net benefits of the model.

Results: Preoperative albumin levels, neutrophil-to-lymphocyte ratio (NLR), T stage, and underlying diseases (with hypertension and/or diabetes) were included in the nomogram. In the training cohort, the nomogram showed a stronger prognostic predictive ability than the T staging (C index: 0.886 vs 0.725). Calibration curves for the overall survival (OS) were in good agreement with the standard lines in cohorts. The net benefit of the nomogram was higher than that of the T staging model.

Conclusions: The nomogram showed better performance in predicting the prognosis and survival of this patient population than the T staging prediction model. And it has potential to identify high-risk patients at an early stage. This is a relatively novel approach for the prediction of OS in this patient population.

1 Background

Thymic epithelial tumors common occur in the anterior mediastinum and can be divided into thymoma and thymic carcinoma according to histology. [1, 2] The Masaoka-Koga staging system, which is based on the progression of the primary tumor and the degree of involvement of the surrounding organs, has been widely accepted for thymoma and thymic carcinoma. [3–5] However, Yanagiya et al. found that age and histological type were significant prognostic factors in their cohort, which were not observed or reported in the Masaoka-Koga staging system. [6] Similarly, the results of the study published by Fukui et al. revealed that the new classification showed a better prognostic effect for thymic tumors than the Masaoka-Koga classification. [7, 8] Moreover, compared with the staging systems for most other malignant tumors, the Masaoka-Koga system does not include the effect of lymph node or distant organ metastasis on prognosis as finely as the TNM staging.

At the same time, an increasing number of studies have used clinical factors such as history of hypertension, diabetes, [9] smoking, [10] and body mass index (BMI) [11] and hematological indicators including hemoglobin (Hb) [12], neutrophil-to-lymphocyte ratio (NLR) [13, 14], albumin (ALB) [15], and other such indicators to analyze the prognosis of various tumors. However, only few studies have comprehensively analyzed a combination of the two types of indicators to establish a prognostic model

for patients with thymic epithelial tumors after thymectomy. Currently, nomograms have been developed for most cancer types. [16–18] Compared with the traditional staging system for many cancers, the use of a nomogram has advantages in terms of prognostic prediction. Therefore, it has been proposed as an alternative method for cancer staging. [19–21]

Therefore, in this study, we aimed to use both preoperative hematological indicators and clinical factors to construct a prognostic predictive nomogram for patients with thymic epithelial tumors after thymectomy for a comprehensive evaluation. The nomogram results were also compared with those of the currently available T staging system to understand whether the nomogram can provide more accurate information for patient prognosis prediction, and use the nomogram score for risk stratification to identify high-risk patients.

2 Materials And Methods

Study population

This study was approved by the Medical Ethics Committee of Sun Yat-sen University Cancer Center (SYSUCC; Approval No. B2020-353-01) and complies with the Declaration of Helsinki.

This study retrospectively analyzed 167 patients with thymic epithelial tumors who underwent thymectomy at SYSUCC between May 2004 and August 2015. Most patients were included in the training group (n = 134), and the remaining patients were included in the verification group (n = 33). The inclusion criteria were as follows: (1) patients older than 18 years; (2) patients who underwent thymectomy at our center; (3) presence of histopathologically confirmed thymic epithelial tumors; (4) related laboratory examinations (blood routine, biochemical routine and so on) were completed within seven days before the operation. The exclusion criteria and the screening process are shown in Fig. 1.

Clinical data collection

Data were collected for the following clinical variables: hematological indicators (obtained within one week before the operation), neutrophil count(NE), lymphocyte count(LY), platelet count, hemoglobin levels, albumin levels, globulin levels as well as patients' sex, age, smoking history, drinking history(Drinking alcohol every day, and the specific amount of drinking is not limited and described), family history of tumor, underlying disease (hypertension and/or diabetes), tumor size, histological subtype, myasthenia gravis symptoms, body mass index, tumor capsule status(complete or incomplete), great vessel infiltration, Masaoka-Koga staging, and T staging. In addition, T staging and Masaoka staging were obtained by combining imaging data with intraoperative records and postoperative pathological information, we staged all patients according to the eighth edition of the TNM staging system and the modified Masaoka-Koga staging system.

Follow-Up

We followed up patients regularly. In the first two years, all patients were followed up every 6–12 months, every 12 months from the third to the fifth year, and then an annual follow-up was continued. The last follow-up date was August 22, 2020. The primary observational endpoint was OS. OS was defined as the time from surgery to death.

Statistical Analysis

Statistical analysis was performed using SPSS 25.0 (IBM, Chicago, Illinois, USA) and R software (version 4.0.3; <https://www.r-project.org/>). In addition to age and tumor size, each component was converted to binary according to the best cutoff value (using X-tile software; <http://www.tissuearray.org/rimmlab>) according to the best cutoff value defined by the minimum P value method variables. This method has also been applied in other studies. [22] In the training cohort, the Cox regression model was used to analyze risk factors through univariate and multivariate analyses. Univariate analysis was performed to determine important risk factors for OS. Variables with P values of less than 0.05 were further included in the multivariate Cox proportional hazard regression model. In the final multivariate analysis, P values of less than 0.05 were considered independent prognostic factors. Then, based on the results of the multivariate Cox analysis, we constructed a nomogram showing three-year and five-year survival rates.

The R statistical software packages "rms," "survival," "foreign," "survivalROC," and "rmda" were used to calculate the C index; to generate the calibration curve, receiver operating characteristic (ROC) curves, decision curve analysis (DCA) curve, and Kaplan-Meier (KM) curve; and to construct a nomogram. The nomogram was used to calculate the prognostic risk score for each patient; X-tile was used to divide the patient's score into different risk levels (low risk, medium risk, and high risk) and to show their stratification effect through the KM curve. [23] The C-index, DCA curve, and ROC curve were used to evaluate the predictive ability of the nomogram and T stage for prognosis. All statistical tests were two-sided, and P values of less than 0.05 were considered statistically significant.

3 Results

Basic Characteristics

A total of 167 patients participated in the study. Among them, 134 patients (Approximate 70%) were randomly assigned to the training group to build a nomogram, and the remaining 33 patients (Approximate 30%) were assigned to the verification group. Table 1 shows the data of the clinicopathological characteristics of the 167 patients. The three-year and five-year survival rates were 0.934 and 0.844, respectively. We found that 141 patients (84.4%) achieved a five-year survival time in all patients. These clinicopathological factors did not differ significantly between the training and validation cohorts.

Table 1
Patient, tumor, and treatment-related characteristics of thymic tumor (n = 167)

Characteristic	Training Cohort(n = 134)		Validation Cohort(n = 33)	
	N	%	N	%
Gender				
Male	71	53.0	20	60.6
Female	63	47.0	13	39.4
Age(years)				
≤ 60	104	77.6	28	84.8
>60	30	22.4	5	15.2
Smoking history				
Never	102	76.1	24	72.7
Ever	32	23.9	9	27.3
Drinking history				
No	116	86.6	30	90.0
Yes	18	13.4	3	9.1
Family history of tumor				
No	112	83.6	29	87.9
Yes	22	16.4	4	12.1
Underlying diseases				
No	103	76.9	23	69.7
Yes	31	23.1	10	30.3
Tumor size				
≤ 6	77	57.5	15	45.5
>6	57	42.5	18	54.5

NLR: neutrophil-to-lymphocyte ratio; Hb: hemoglobin; ALB: albumin; BMI: body mass index; NE: neutrophil count; LY: lymphocyte count; GLB: Globulin; SII: systemic immune-inflammation Index; PLT: platelet; PLR: platelet-lymphocyte ratio; pT stage: Pathological T stage.

Characteristic	Training Cohort(n = 134)		Validation Cohort(n = 33)	
pT stage				
T1	100	74.6	22	66.7
T2-3	25	18.7	9	27.3
T4	9	6.7	2	6.1
M stage				
M0	127	94.8	30	90.9
M1	7	5.2	3	9.1
Masaoka stage				
I	63	47.0	13	39.4
II-III	64	47.8	17	51.5
IV	7	5.2	3	9.1
WHO stage				
A-AB	52	38.8	11	33.3
B1-B3	71	53.0	14	42.4
C	11	8.2	8	24.2
Myasthenia gravis,				
No	123	91.8	31	93.9
Yes	11	8.2	2	6.1
BMI				
≤ 18.8	13	9.7	4	12.1
>18.8	121	90.3	29	87.9
tumor capsule status				
Incomplete	47	64.9	11	66.7
Complete	87	35.1	22	33.3

NLR: neutrophil-to-lymphocyte ratio; Hb: hemoglobin; ALB: albumin; BMI: body mass index; NE: neutrophil count; LY: lymphocyte count; GLB: Globulin; SII: systemic immune-inflammation Index; PLT: platelet; PLR: platelet-lymphocyte ratio; pT stage: Pathological T stage.

Characteristic	Training Cohort(n = 134)		Validation Cohort(n = 33)	
Invasion of great vessels				
No	102	76.1	25	75.8
Yes	32	23.9	8	24.2
ALB				
≤ 42.6	49	36.6	14	42.4
>42.6	85	63.4	19	57.6
GLB				
≤ 23.2	15	11.2	7	21.2
>23.2	119	88.8	26	78.8
A/G				
≤ 1.3	28	20.9	4	12.1
>1.3	106	79.1	29	87.9
Hb				
≤ 124	32	23.9	6	18.2
>124	102	76.1	27	81.8
NE				
≤ 5.6	116	86.6	28	84.8
>5.6	18	13.4	5	15.2
LY				
≤ 1.5	26	19.4	7	21.2
>1.5	108	80.6	26	78.8
NE/LY(NLR)				
≤ 3.1	119	88.8	29	87.9
>3.1	15	11.2	4	12.1

NLR: neutrophil-to-lymphocyte ratio; Hb: hemoglobin; ALB: albumin; BMI: body mass index; NE: neutrophil count; LY: lymphocyte count; GLB: Globulin; SII: systemic immune-inflammation Index; PLT: platelet; PLR: platelet-lymphocyte ratio; pT stage: Pathological T stage.

Characteristic	Training Cohort(n = 134)	Validation Cohort(n = 33)		
PLT				
≤ 314	121	90.3	29	87.9
>314	13	9.7	4	12.1
PLT/LY(PLR)				
≤ 145.7	105	78.4	28	84.8
>145.7	29	21.6	5	15.2
PLT/NE*LY(SII)				
≤ 688.5	116	86.6	24	72.7
>688.5	18	13.4	9	27.3
NLR: neutrophil-to-lymphocyte ratio; Hb: hemoglobin; ALB: albumin; BMI: body mass index; NE: neutrophil count; LY: lymphocyte count; GLB: Globulin; SII: systemic immune-inflammation Index; PLT: platelet; PLR: platelet-lymphocyte ratio; pT stage: Pathological T stage.				

Univariable and Multivariable Analyses in the Training Cohort

According to the results of univariate Cox regression analysis, there were nine variables related to OS: underlying disease, BMI, T stage, histology, ALB, Neutrophils(NE), NLR, systemic immune-inflammation Index (SII), and Globulin (GLB) (Table 2). In the multivariate Cox regression analysis, four parameters were defined as independent prognostic factors of OS: T stage (T1 vs. T2-3, hazard ratio, HR = 6.138, 95% confidence interval, CI [1.557–24.189], T1 vs. T4, HR = 6.892, 95% CI [1.752–27.109]), ALB (HR = 0.172, 95% CI [0.044–0.676]), underlying disease (HR = 12.584, 95% CI [3.067–51.634]), and NLR (HR = 13.215, 95% CI [3.074–56.817]) (Table 2).

Table 2
Univariate and multivariate analysis results in Training cohort(n = 134)

Variable	Univariate	Multivariate analysis		
	analysis			
	P	HR	95%CI	P
Gender				
Male vs Female	.275			
Age(years)				
≤ 60 vs >60	.694			
Smoking history				
Never vs Ever	.394			
Drinking history				
No vs Yes	.133			
Family history of tumor				
No vs Yes	.272			
Underlying diseases		Reference		
No vs Yes	.018	12.584	3.067–51.634	.000
Tumor size	.380			
≤ 6 vs >6				
pT stage		Reference	1.557–24.189	.010
T1 vs T2-3	.001	6.138	1.752–27.109	.006
T1 vs T4		6.892		
M stage				
M0 vs M1	.795			
Masaoka stage				
I vs II-III	.112			
I vs IV				

NLR: neutrophil-to-lymphocyte ratio; Hb: hemoglobin; ALB: albumin; BMI: body mass index; NE: neutrophil count; LY: lymphocyte count; GLB: Globulin; SII: systemic immune-inflammation Index; PLT: platelet; PLR: platelet-lymphocyte ratio; pT stage: Pathological T stage.

Variable	Univariate analysis	Multivariate analysis		
WHO stage				
A-AB vs B1-B3	.021			
A-AB vs C				
Myasthenia gravis,				
No vs Yes	.476			
BMI	.015			
≤ 18.8 vs ≥18.8				
tumor capsule status				
Incomplete vs Complete	.118			
Invasion of great vessels				
No vs Yes	.406			
ALB		Reference		
≤ 42.6 vs ≥42.6	.004	.172	.044-.676	.012
GLB				
≤ 23.2 vs ≥23.2	.009			
A/G				
≤ 1.3 vs ≥1.3	.193			
Hb				
≤ 124 vs ≥124	.344			
NE				
≤ 5.6 vs ≥5.6	.000			
LY				
≤ 1.5 vs ≥1.5	.154			
NE/LY(NLR)		Reference		
≤ 3.1 vs ≥3.1	.000	13.215	3.074–56.817	.001

NLR: neutrophil-to-lymphocyte ratio; Hb: hemoglobin; ALB: albumin; BMI: body mass index; NE: neutrophil count; LY: lymphocyte count; GLB: Globulin; SII: systemic immune-inflammation Index; PLT: platelet; PLR: platelet-lymphocyte ratio; pT stage: Pathological T stage.

Variable	Univariate analysis	Multivariate analysis
PLT ≤ 314 vs >314	.733	
PLT/LY(PLR) ≤ 145.7 vs >145.7	.065	
PLT/NE*LY(SII) ≤ 688.5 vs >688.5	.002	
NLR: neutrophil-to-lymphocyte ratio; Hb: hemoglobin; ALB: albumin; BMI: body mass index; NE: neutrophil count; LY: lymphocyte count; GLB: Globulin; SII: systemic immune-inflammation Index; PLT: platelet; PLR: platelet-lymphocyte ratio; pT stage: Pathological T stage.		

Establishment of the Nomogram

According to the results of the multivariate Cox regression analysis, T stage, ALB, underlying disease, and NLR were defined as independent prognostic factors, and these factors were integrated to form a nomogram (Fig. 2). In the training cohort, the C index was 0.886 (95% CI: 0.804–0.968), which was higher than that of the T staging prediction model (C index: 0.725, 95% CI: 0.602–0.848). Internal calibration curves for the three- and five-year OS closely matched those of the baseline in the training cohort (Fig. 3A and B).

Verification of the Nomogram

To better verify the actual predictive power of the nomogram, the above results were verified using the verification group data, showing that the C index was 0.741 (95% CI: 0.592–0.890), and the five-year and three-year external calibration curves met those of the standard baseline (Fig. 3C and D). We also used the ROC curve to verify the nomogram performance (Fig. 4). The AUC values of the training and validation groups at three and five years were both greater than 0.7 and by comparing the AUC values of the two groups, the nomogram model were significantly better than those of the T staging, showing better accuracy of the nomogram in predicting OS.

Decision Curve Analysis

Decision Curve Analysis (DCA) is a novel method for evaluating prognostic strategies that can evaluate the predictive power of prognostic models. Figure 5 shows the nomogram and DCA curve of T staging in

the training and validation cohorts. Compared with the T staging, the DCA of the nomogram has a higher net benefit, which indicates that the nomogram has a better net benefit. The clinical utility of the nomogram was better than that of the T staging.

Risk Stratification of OS

Based on the nomogram scores, patients were divided into low-risk (0–73 points), medium-risk (74–169 points), and high-risk (170 points or higher) subgroups. In the training cohort, there were 82 patients in the low-risk group, 43 patients in the intermediate-risk group, and 9 patients in the high-risk group. In the validation cohort, 16 patients were included in the low-risk group, 8 patients were included in the medium-risk group, and 9 patients were included in the high-risk group. There were significant differences in the incidence of OS among the subgroups, and the survival rate of the high-risk subgroup was lower than that of the other groups ($P < 0.05$) (Fig. 6).

4 Discussion

In this study, we obtained results from 167 patients at SYSUCC, and ALB, NLR, T stage, and underlying diseases were found to be independent prognostic factors of OS. We developed a nomogram that can effectively predict the OS rate of patients with thymic epithelial tumors at three and five years.

Slow disease progression and good prognosis have largely limited research on thymic epithelial tumors. At the same time, in the era of precision medicine, it is very important to analyze patient information as comprehensively as possible to screen factors affecting the prognosis for treatment decision-making. At present, the Masaoka-Koga staging system is still the gold standard for predicting the prognosis of thymic epithelial tumors. However, similar to the results of Fukui et al., [7] our results show that the T staging is better than the Masaoka-Koga staging in predicting prognosis. Therefore, the nomogram developed in this study was mainly compared with T staging model. The T staging prediction model does not contain other information related to prognosis, such as the patient's preoperative baseline disease status and hematological indicators. Based on this, the nomogram along with the patient's various clinical and hematological indicators was used to construct a prognostic model. The nomogram has the advantage of a multi-dimensional comprehensive prediction of prognosis.[24] Some studies have reported nomograms related to the prognosis of thymic epithelial tumors. However, they considered only the clinicopathological characteristics or treatment methods of patients and do not consider relevant hematological indicators. At the same time, many studies on hematological indicators have shown that Hb, NE, LY, platelet (PLT), NLR, ALB, GLB, ALB/GLB, platelet-lymphocyte ratio (PLR), NLR, and SII [12, 13, 15, 25] have potential to become prognostic hematological indicators for various tumors including thymic epithelial tumors.

Our nomogram is composed of several factors that affect prognosis, which are commonly used in clinical practice. The nomogram showed that a history of diabetes and hypertension was related to poor OS in patients with thymic epithelial tumors. This finding is consistent with the findings of other studies. [33] [9] In terms of T staging, lower T staging can result in a more satisfactory OS. In the studies of other researchers, the patient's preoperative clinical staging was a factor affecting the prognosis of thymic epithelial tumors. [26] At the same time, we found that elevated NLR was associated with poor prognosis in patients with thymic epithelial tumors. This is the same as other people's research results. [6, 27] In addition, a higher preoperative serum ALB level can often result in a more satisfactory prognosis, which is consistent with the findings of other studies reporting better prognosis in patients with thymic epithelial tumors with higher ALB levels. [15]

In predicting the prognosis of certain cancers, nomograms have been developed and proven to be more accurate than traditional staging systems. [28, 29] Therefore because thymectomy is an effective treatment for thymic epithelial tumors, [30–33] we constructed a prognostic nomogram for patients with thymic epithelial tumors after surgery. The nomogram performs well in predicting the survival rate. Its prediction is supported by the C index (0.886 and 0.741 for the training and verification cohorts, respectively), and the calibration curve was consistent with that of the baseline. Compared with other staging systems, the nomogram has higher accuracy in predicting survival, and the DCA curve also showed that the nomogram had better predictive ability than the T staging.

To the best of our knowledge, this is a relatively new attempt to develop a prognostic OS nomogram for patients with thymic epithelial tumors by combining hematological and clinical indicators. Although this nomogram did not include many hematological indicators in the end, it combines preoperative clinical indicators, hematological indicators, and other important clinical information to achieve the ultimate goal of integrating multi-dimensional data to jointly predict the prognosis of thymic epithelial tumors.

This study has several limitations. First, this was a retrospective study. Moreover, this was only a single-center study that included a small number of patients. Further research including more number of cases is still needed to verify our results. Second, tumor markers (CEA, SCC, AFP, etc.) and other potentially valuable hematological indicators were not included in this study. Third, the dynamic changes in hematological indicators considered in this study were not followed up after the operation.

5 Conclusions

In summary, by combining hematological and clinical indicators, we established and validated a nomogram for predicting the personalized survival rate of patients with thymic epithelial tumors. This convenient nomogram had better performance than the T staging to distinguish the prognosis and risk of patients. Our findings suggest that it may be a potentially easy-to-use tool for physicians and can aid in postoperative personalized prognosis assessment and early identification of high-risk patients. Although the nomogram appears useful for prognostication and identifying high-risk patients, further prospective studies are needed to validate the nomogram and confirm the contribution of each prognostic factor.

Abbreviations

NLR

neutrophil-to-lymphocyte ratio; Hb:hemoglobin; ALB:albumin; BMI:body mass index; NE:neutrophil count; LY:lymphocyte count; GLB:Globulin; SII:systemic immune-inflammation Index; PLT:platelet; PLR:platelet-lymphocyte ratio; pT stage:Pathological T stage; OS:overall survival; C-index:consistency index; ROC:receiver operating characteristic; DCA:decision curve analysis; KM:Kaplan-Meier.

Declarations

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2 Author Contributions

Conception and design of the work: MGW, HYY and WLL. Provision of study materials or patients: MGW. Acquisition of data: HYY, WLL and LX. Analysis of data: MGW, HYY and WLL. Interpretation of data: MGW, HYY. HYY and LSH drafted the manuscript; MGW and HYY substantially revised the manuscript. All authors read and approved the final manuscript.

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4 Availability of data and materials

Data from this study are available to any interested researchers upon reasonable request to the corresponding author.

Declarations

5 Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of Sun Yat-sen University Cancer Center (SYSUCC; Approval, No. B2020-353-01) and complies with the Declaration of Helsinki. At the same time, this study has obtained the exemption of informed consent application from the Ethics Committee of Sun Yat-sen University Cancer Center.

6 Consent for publication

All authors agreed to the publication.

7 Competing interests

The authors disclose no conflicts of interest.

8 Author details

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Figures

Figure 1
Flow chart of patient screening.

Figure 2

Nomogram predicting 3- and 5- survival after thymectomy for thymic epithelial tumors patients.

Figure 3

The calibration curves for predicting patient survival at (A, C) 3-y and (B, D) 5-y in the training and validation cohorts.

Figure 4

Receiver operating characteristic curve analysis for the sensitivity and specificity of the nomogram system and T staging system to predict 3-y survival (A, C) and 5-y survival (B, D) in training and validation cohorts. Nomogram system had higher accuracy compared with T staging system.

Figure 5

Decision curve analysis for the clinical benefit of the nomogram system and T staging system. Nomogram system behaved better than T staging system.

Figure 6

Survival analysis of patients after risk-stratification (A for training cohort; B for validation cohort)