



# Development of a competing risk nomogram for the prediction of cause-specific mortality in patients with thymoma: a population-based analysis

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**Background:** This study was developed to assess the odds of cause-specific mortality and other types of mortality in thymoma patients. In addition, these analyses were leveraged to develop a comprehensive competing risk model-based nomogram capable of predicting cause-specific mortality as a result of thymoma.

**Methods:** Thymoma patients included within the Surveillance, Epidemiology, and End Results (SEER) database from 2004–2016 were identified, and the odds of cause-specific mortality due to thymoma and other forms of mortality for these patients were estimated. In addition, Fine and Gray's proportional subdistribution hazard model was constructed, and a competing risk nomogram was developed using this model that was capable of predicting the odds of 3-, 5-, and 10-year cause-specific mortality in thymoma patients.

**Results:** In total, 1,591 relevant cases in the SEER database were selected for analysis. In this patient cohort, the respective 5-year cumulative incidence rates for cause-specific mortality and mortality attributable to other causes were 12.4% and 8.2%. Variables significantly associated with cause-specific mortality included age, chemotherapy, surgery, and Masaoka stage. Additionally, the odds of other-cause-specific mortality rose with increasing patient age, and chemotherapy was correlated with other-cause-specific mortality. The competing risk nomogram that was developed exhibited good discriminative ability as a means of predicting cause-specific mortality, as evidenced by a concordance index (C-index) value of 0.84. Calibration curves further revealed excellent consistency between predicted and actual mortality when using this nomogram.

**Conclusions:** In summary, we herein assessed the odds of cause-specific and other-cause-specific mortality among thymoma patients, and we designed a novel nomogram capable of predicting cause-specific mortality for thymoma, providing a promising tool that may be of value in the context of individualized patient prognostic evaluation.

**Keywords:** Thymoma; competing risk analysis; cause-specific mortality; cumulative incidence; nomogram

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## Introduction

Thymoma is a relatively rare malignancy of thymic epithelial cells accounting for 0.2–1.5% of all malignancies (1). However, thymoma represents approximately 50% of all malignancies arising from anterior mediastinum (2). With relatively indolent behavior, thymoma presents substantial heterogeneity in prognosis. The most widely used staging systems for thymoma are Masaoka staging system and American Joint Commission on Cancer (AJCC) 8th Edition of TNM classification. The Masaoka staging system relies primarily on primary tumor extension and the degree of involvement beyond the thymus (3). The recently proposed AJCC 8th Edition of TNM classification is based on combination of primary tumor local invasion, nodal involvement and metastatic spread (4). However, both the Masaoka system and the TNM staging system are inadequate to explain the large heterogeneity in outcomes for patients with thymoma. Recent studies have reported that age, completeness of resection and histologic type were important prognostic factors supplementing stage (5–7). Therefore, the development of a technically feasible and clinically accessible predictive tool that incorporates patient-related, tumor-related, and treatment-related prognostic factors is needed.

With regard to age distribution, the incidence of thymoma increases with age into the eighth decade of life and then decreases (8). The mean age at diagnosis is 50–60 years old (2). Besides, thymoma is characterized by its indolent behavior and long natural history with 5-year overall survival of approximately 90% (8–10). As such, long-term survivors and elderly individuals often die of causes not specific to this particular form of malignancy. It is thus important to take such other causes of mortality into account when predicting thymoma patient prognosis. While several studies have assessed thymoma patient outcomes, a majority of these analyses have employed the Kaplan-Meier analytical approach, which is likely not appropriate given that it treats competing events as independent censoring, thereby potentially leading to an overestimation of cancer-specific death. A competing risk model is better suited to this analytical context, as it takes the type of censoring into consideration, thereby allowing for more reliable discrimination between the effects of particular risk factors on different outcome events (11).

Several recent studies have described the development of competing risk nomograms for the evaluation of patients with thyroid, breast, and renal cancer (12–14), but no such

nomograms have been developed to conduct a competing risk analysis of thymoma. This study selected all cases with thymoma registered in the Surveillance, Epidemiology, and End Results (SEER) database between 2004 and 2016 as well as performed a competing-risk analysis. We evaluated the probabilities for cause-specific mortality and other causes of mortality, and constructed a competing risk nomogram to predict cause-specific mortality for thymoma.

We present the following article in accordance with the TRIPOD reporting checklist (available at <https://dx.doi.org/10.21037/jtd-21-931>).

## Methods

### *Patients and data collection*

For the present study, patients in the SEER 18 registry maintained by the National Cancer Institute (1975–2016; dataset submitted November 2018) were analyzed, with thymoma patients being extracted with the SEER\*Stat software (v 8.3.9). All patients diagnosed with histologically confirmed thymoma from 2004–2016 were included in this analysis. No Institutional Review Board approval for this study was required owing to the anonymized and open-access nature of the SEER database.

The International Classification of Diseases for Oncology, third edition (ICD-O-3) criteria were used to classify tumor site and histology. Patients enrolled in this study were those with the ICD-O-3 site code C37.9 (thymus) and the ICD-O-3 histology codes 8580–8585. Patients were excluded if they met the following criteria: (I) patients <18 years old at the time of diagnosis; (II) patients diagnosed upon autopsy or by death certificate; (III) patients with other primary malignancies; (IV) patients for whom complete data pertaining to age at diagnosis, sex, ethnicity, stage, treatment, histology, vital status or survival month, or SEER cause of death records were not available; (V) patients with a recorded survival duration of <1 month. Variables for analysis were race, age, sex, histology, stage, surgery, radiotherapy and chemotherapy. Staging in the SEER database was grouped into the localized, regional, and distant disease categories, and we regrouped included thymoma patients into three groups based on corresponding Masaoka stages as follows: stage I/IIA (localized disease), stage IIB (regional disease), and stage III/IV (distant disease or any positive lymph nodes). The age at diagnosis was divided into four groups: <50, 50–59, 60–69 and ≥70 years. The histology was divided into four groups: A/AB, B1/B2,

B3 and not otherwise specified (NOS).

### Statistical analysis

Cause-specific and other-cause-specific mortality were treated as competing events in this study, with the probability of death being evaluated using a cumulative incidence function (CIF). Differences in cumulative incidence between groups were compared via Gray's test (15), and the combined effects of patient- and treatment-related characteristics on cause-specific and other-cause-specific mortality were assessed with a proportional subdistribution hazard model (16). Fine and Gray's model was used to develop a competing risk nomogram in order to predict cancer-specific mortality in thymoma patients (17). Concordance index (C-index) values and calibration plots were used to assess the performance of this nomogram. Calibration plots were generated via a bootstrap cross-validation approach with 1,000× resampling. R version 3.6.3 software (<http://www.r-project.org/>) was used for all statistical analyses. The 'rms', 'cmprsk', and 'mstate' R packages were used for model and nomogram construction, while model performance was assessed using the 'pec' package. A two-sided  $P < 0.05$  was the threshold of significance.

### Results

We identified 1,591 patients with histologically confirmed thymoma between 2004 and 2016 from SEER database. Patients' characteristics are shown in *Table 1*. The median age of these patients at diagnosis was 58 years, with 28.9%, 23.7%, 26.5%, and 20.9% of patients being <50, 50–59, 60–69, and  $\geq 70$  years old, respectively. Of the 1,591 patients, 50.3% were female. The majority of patients were white (66.6%). The proportions of patients with WHO histological classification A/AB, B1/B2, B3 and NOS were 26.7%, 28.9%, 17.9% and 26.5%, respectively. With respect to tumor stage distribution, 35.3%, 41.3% and 23.4% of patients presented with Masaoka stage I–IIA, IIB, and III–IV, respectively. A majority of patients (82.8%) underwent surgical treatment, while 45.7% and 28.6% of patients underwent radiotherapy and chemotherapy, respectively.

The median follow-up duration for patients included in this study was 65 months (interquartile range, 28–106 months). Up to the last follow up, a total of 1,241 patients (78.0%) had been censored, and 350 patients (22.0%) had died during follow up, including 195 deaths

(12.3%) from thymoma and 155 (9.7%) from other causes. The respective 5-year cumulative incidence rates for cause-specific mortality and other-cause-specific mortality were 12.4% and 8.2% (*Table 1*). In a competing risk analysis, older age, B3 histology, advanced stage, no surgical treatment, and chemotherapy treatment were significantly associated with cause-specific mortality ( $P < 0.001$ ). In addition, older age, no surgical treatment, and chemotherapy were significantly associated with a higher risk of other-cause-specific mortality. Corresponding CIF curves based upon these variables are shown in *Figure 1*.

Proportional subdistribution hazard models were utilized to assess the odds of cause-specific thymoma patient mortality (*Table 2*). In this analysis, age, surgical treatment, chemotherapy, and Masaoka stage were found to independently predict cause-specific patient mortality. Compared with Masaoka stage I/IIA disease, patients with stage IIB disease [subdistribution hazard ratio (SHR) = 1.95, 95% confidence interval (CI), 1.15–3.28,  $P = 0.013$ ] and stage III/IV disease (SHR = 3.18, 95% CI, 1.87–5.40,  $P < 0.001$ ) had higher risk of cause-specific death. Patients who did not receive surgery (SHR = 3.88, 95% CI, 2.74–5.48,  $P < 0.001$ ) experienced increased probability of mortality from thymoma. Decreased probability of cause-specific mortality was observed in patients without chemotherapy than those who underwent chemotherapy (SHR = 0.41, 95% CI, 0.29–0.59,  $P < 0.001$ ). After adjustment for various factors, histology was no longer predictive of cause-specific mortality. Age was significantly predictive of both cause specific death and other causes of death, with older patients carrying a higher risk of mortality. Besides, a higher cumulative incidence of other causes of mortality was observed in patients without chemotherapy (SHR = 2.13, 95% CI, 1.30–3.49,  $P = 0.003$ ).

Fine and Gray's model was used to develop a predictive nomogram capable of gauging the odds of 3-, 5-, and 10-year thymoma patient cause-specific survival based upon the sum of points corresponding to the included characteristics (*Figure 2*). This model exhibited good discriminative ability, with a C-index value of 0.84. Calibration plots exhibited good consistency between actual and predicted probability of cause-specific mortality in these patients (*Figure 3*).

### Discussion

Herein, we conducted an analysis of mortality rates among thymoma patients recorded in the SEER database from

**Table 1** Five-year cumulative incidences of mortality among patients with thymoma

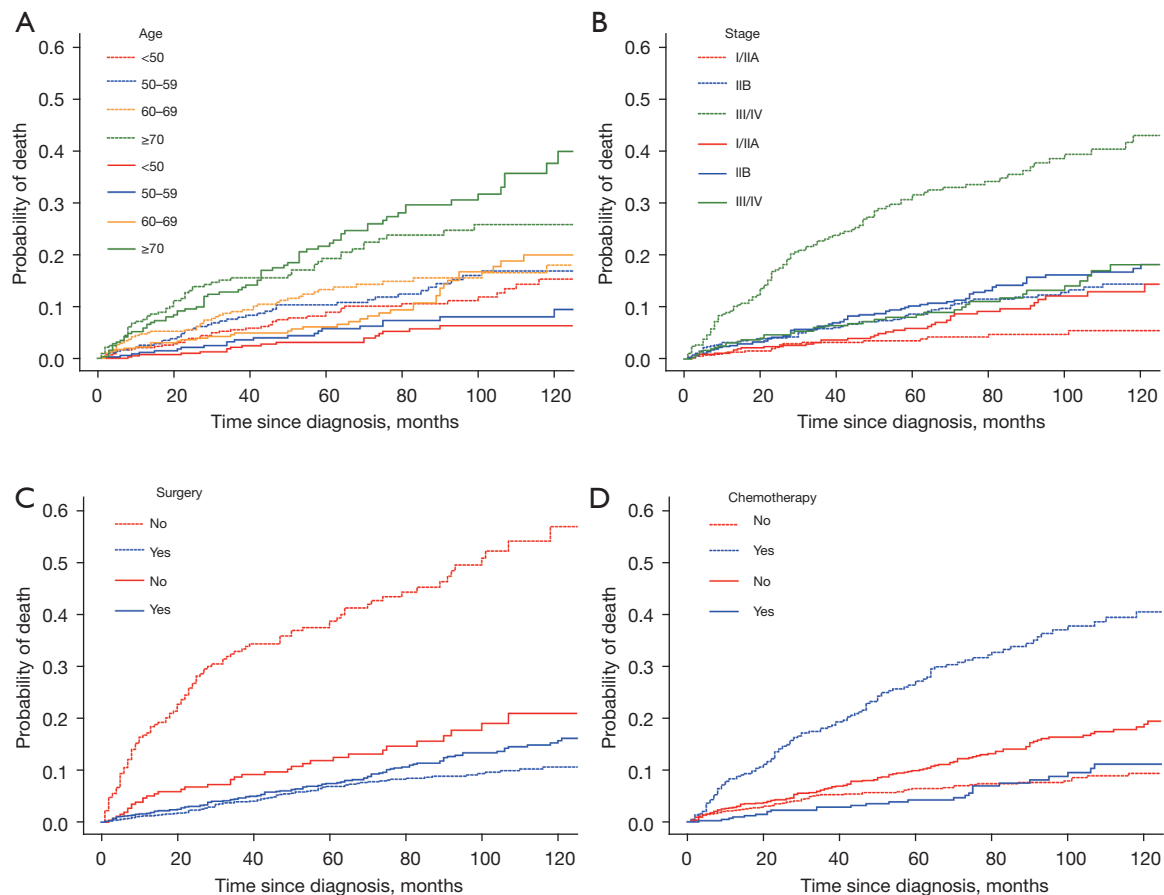
Characteristic	N (%)	Event (%)	Cause-specific mortality		Other causes of mortality	
			5-year (%)	P value	5-year (%)	P value
Age (years)				<0.001		<0.001
<50	460 (28.9)	61 (17.4)	8.9		3.1	
50–59	377 (23.7)	63 (18.0)	10.3		5.7	
60–69	422 (26.5)	91 (26.0)	13.2		6.0	
≥70	332 (20.9)	135 (38.6)	19.2		21.6	
Sex				0.150		0.465
Male	790 (49.7)	183 (52.3)	13.7		8.8	
Female	801 (50.3)	167 (47.7)	11.2		7.6	
Race				0.226		0.164
White	1,060 (66.6)	235 (67.1)	12.2		9.3	
Non-white	531 (33.4)	115 (32.9)	12.9		6.1	
Histology				<0.001		0.168
A/AB	425 (26.7)	69 (19.7)	6.8		9.7	
B1/B2	460 (28.9)	81 (23.1)	11.1		6.1	
B3	285 (17.9)	74 (21.1)	13.8		11.5	
NOS	421 (26.5)	126 (36.0)	17.8		7.0	
Masaoka stage				<0.001		0.183
I/IIA	562 (35.3)	62 (17.7)	3.5		5.9	
IIB	657 (41.3)	137 (39.1)	8.6		10.2	
III/IV	372 (23.4)	151 (43.1)	31.6		8.0	
Surgery				<0.001		0.034
Yes	1,318 (82.8)	206 (58.9)	6.9		7.4	
No	273 (17.2)	144 (41.1)	38.7		11.8	
Radiotherapy				0.364		0.177
Yes	727 (45.7)	156 (44.6)	12.4		7.0	
No	864 (54.3)	194 (55.4)	12.4		9.3	
Chemotherapy				<0.001		<0.001
Yes	455 (28.6)	150 (42.9)	27.1		4.2	
No	1,136 (71.4)	200 (57.1)	6.4		9.9	

NOS, not otherwise specified.

2004–2016. In this patient population, the respective 5-year cumulative incidence rates of cause-specific and other-cause-specific mortality were 12.4% and 8.2%. This study is the first to our knowledge to have explored the cumulative incidence of cause-specific mortality associated

with thymoma and to develop a competing risk nomogram model capable of predicting such mortality.

Identification of prognostic factors is critical in optimizing treatment for patients with cancer. The well recognized prognostic factors for thymoma include tumor



**Figure 1** Cumulative cause-specific and other-cause-specific mortality curves stratified according to patient (A) age; (B) Masaoka stage; (C) surgery; (D) chemotherapy. Cause-specific mortality is represented by a dotted line, while all other causes of mortality are represented by a solid line.

stage and resection status (6,7,18), which is consistent with our results that advanced stage predicted unfavorable cause-specific survival. Resection status has been considered as an important favorable prognostic factor and should be classified as complete resection (R0), microscopically incomplete resection (R1) and grossly incomplete resection (R2). Patients with R0 resection could have significantly superior survival than those with R1 or R2 resection (6,18). However, data regarding resection status was incomplete in SEER database.

Another potential prognostic factor is patient age. Rea *et al.* demonstrated that age had no effect on survival after adjusting for multivariates (19). Pediatric thymoma has been reported to present a more aggressive behavior and be associated with an increased risk of distant metastasis resulting in unfavorable survival compared with adults (20). However, our study excluded pediatric thymoma and

demonstrated that the risk of both cause-specific mortality and other causes of mortality increased with age, which is consistent with studies by Filosso and Ruffini (6,21). Elderly patients are associated with more comorbidities and poorer performance status which hinder them from receiving radical or aggressive treatment. The decrease in therapeutic intensity and comorbidities-related non-cancer death may result in the inferior prognosis in elderly.

According to the WHO histological classification, thymoma comprises a spectrum of unique tumors subdivided into type A, AB, B1, B2, and B3. The independent prognostic value of histologic type for thymoma is controversial. The worldwide retrospective study by International Thymic Malignancy Interest Group (ITMIG) reported that WHO histologic type seemed to correlate well with Masaoka stage. The majority of type A and AB tumors were Masaoka stage I or II, while the B

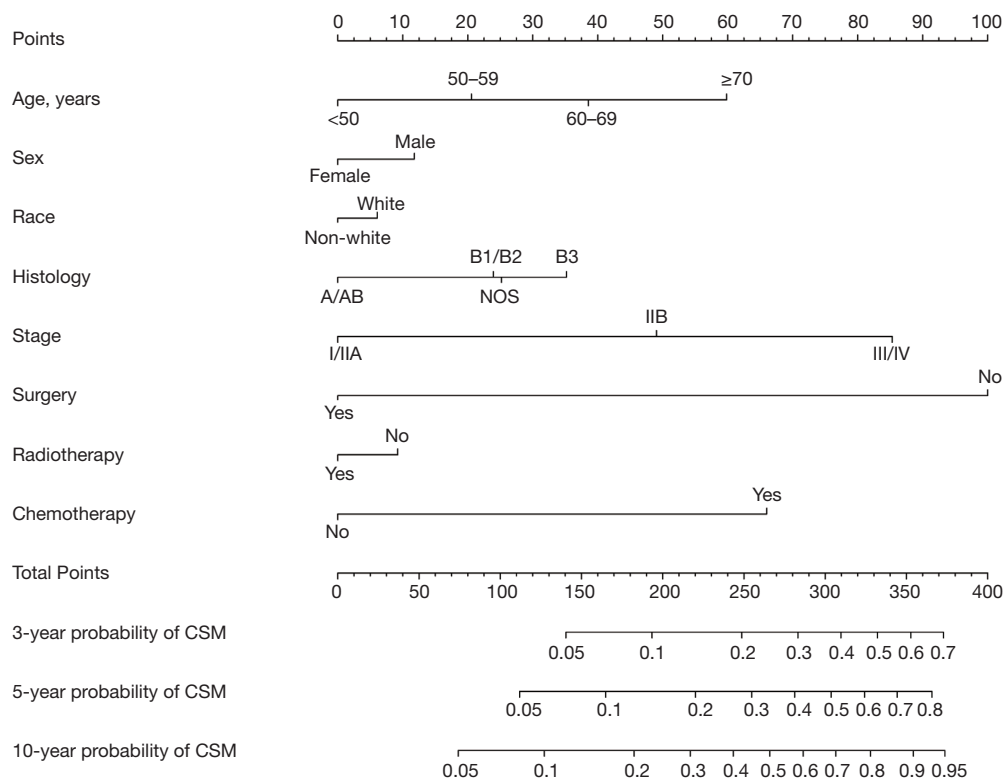
**Table 2** Proportional subdistribution hazard models of probabilities of mortality for patients with thymoma

Characteristic	Cause-specific mortality			Other causes of mortality		
	SHR	95% CI	P value	SHR	95% CI	P value
Age (years)						
<50	Ref			Ref		
50–59	1.32	0.87–1.99	0.190	1.50	0.80–2.84	0.210
60–69	1.69	1.12–2.54	0.013	2.68	1.54–4.66	<0.001
≥70	2.25	1.46–3.45	<0.001	6.30	3.69–10.77	<0.001
Sex						
Male	Ref		0.290	Ref		0.710
Female	0.85	0.64–1.14		0.94	0.68–1.30	
Race						
White	Ref		0.600	Ref		0.610
Non-white	0.92	0.68–1.25		0.91	0.64–1.30	
Histology						
A/AB	Ref			Ref		
B1/B2	1.38	0.85–2.26	0.190	1.00	0.63–1.60	1.000
B3	1.61	0.99–2.64	0.057	1.47	0.93–2.32	0.100
NOS	1.41	0.89–2.22	0.150	1.15	0.75–1.77	0.530
Masaoka stage						
I/IIA	Ref			Ref		
IIB	1.95	1.15–3.28	0.013	1.55	1.07–2.26	0.022
III/IV	3.18	1.87–5.40	<0.001	1.49	0.89–2.48	0.130
Surgery						
Yes	Ref		<0.001			0.310
No	3.88	2.74–5.48		1.29	0.79–2.13	
Radiotherapy						
Yes	Ref		0.42			0.320
No	1.13	0.84–1.54		1.18	0.85–1.62	
Chemotherapy						
Yes	Ref		<0.001			0.003
No	0.41	0.29–0.59		2.13	1.30–3.49	

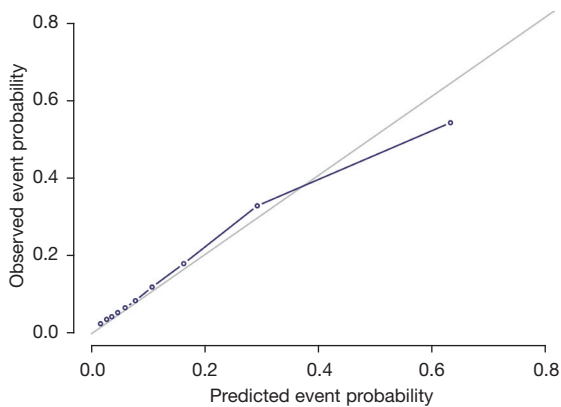
SHR, subdistribution hazard ratio; CI, confidence interval; NOS, not otherwise specified.

subtypes especially B3 subtype tended to present the higher Masaoka stages (7). Studies by Rea and Okumura suggested histologic type had independent prognostic value (19,22). Nevertheless, Weis *et al.* (7) suggested that the effect of

histologic type on recurrence was only observed in stage I/II thymoma, in type A and AB versus B1 to B3 thymoma. A multivariate study of the large database by European Society of Thoracic Surgeons (6) found no independent correlation



**Figure 2** Competing risk nomogram for the prediction of 3-, 5-, 10-year cause-specific mortality associated with thymoma. CSM, cause-specific mortality.



**Figure 3** Calibration plot for cause-specific mortality nomogram in thymoma. The x-axis and y-axis respectively correspond to the predicted odds of cause-specific survival and the actual observed incidence of cause-specific survival.

between histologic type and survival or recurrence, which is consistent with our results. In our study, histology was correlated with cause-specific mortality in univariate

analysis while failed to maintain its independent prognostic role after adjusting for various multivariates. In conclusion, the independent prognostic role of histologic type for thymoma has not been well defined.

Treatment modalities for thymoma include surgery, radiotherapy, chemotherapy and targeted therapy. Given the rarity of thymoma, the optimal utilization and sequencing of these treatment modalities have not been well defined through large randomized prospective studies. To date, complete surgical resection remains the mainstay treatment for thymoma. Complete resection is also a significant favorable prognostic factor. However, for locally advanced disease, complete tumor resection is often difficult to achieve. Research on the beneficial role of subtotal resection on survival for unresectable thymoma has shown inconsistent results. Some studies have reported better survival with debulking surgery combined with adjuvant radiotherapy (23,24) while others demonstrated no benefit from debulking surgery over biopsy alone (25,26). In 2015, a meta-analysis of retrospective studies demonstrated that debulking surgery for unresectable thymoma may

improve overall survival and be considered as an effective local treatment method for unresectable thymoma (27). However, the meta-analysis was limited by the existence of large heterogeneity between the included studies. In our study, surgery was associated with improved cause-specific survival, which is accordant with previous studies suggesting surgery as the cornerstone of a multimodal therapy for thymoma.

The role of radiotherapy in the management of thymoma remains somewhat controversial. For unresectable disease, definitive radiotherapy is recommended. To date, no randomized studies exist evaluating the role of adjuvant radiotherapy. Multiple retrospective studies have suggested that radiotherapy reduced recurrence rates and improved outcomes for incompletely resected thymoma (28-30). Adjuvant radiotherapy is not recommended for completely resected stage I thymoma (31). The role of adjuvant radiotherapy for completely resected stage II-III thymoma is debatable based on mixed results from several large-size dataset retrospective studies (30,32-34). Most retrospective data were subject to heterogeneity in resection status and histology type between radiotherapy and non-radiotherapy groups. The study by ITMIG represented the largest dataset focusing on completely resected stage II-III thymoma and demonstrated a beneficial role of adjuvant radiotherapy in this subgroup (34). However, radiotherapy was not associated with cause-specific survival in our study. Thymoma tumors are sensitive to chemotherapeutic treatment, with respective 1/3 and 2/3 complete and partial response rates. We found chemotherapy treatment to be a negative prognostic factor in thymoma patients. However, caution is warranted when interpreting this result owing to the potential for selection bias given that patients selected to undergo chemotherapy are more likely to have advanced staging, locoregional recurrence, or distant metastases.

Considering the increased incidence of thymoma with age and long-term survival rates for patients, competing non-cancer mortality represents a critical consideration when predicting prognosis for decision making. With the risk of competing other causes of mortality increases, and the benefit of increasing treatment intensity potentially diminishes. For the first time, we built a competing risk nomogram to predict cause-specific death for thymoma. This study has several strengths. The data are derived from a population-based cohort with relatively large sample size. Despite the rarity of thymoma, the SEER database provided a sufficiently large sample size to develop and validate the competing risk nomogram. In addition, the nomogram

has several clinical implications, such as helping clinicians improve outcome prediction and tailor individualized treatment. By combining a few predictors, the nomogram demonstrated good predictive ability and was also simple to use.

This study has several limitations that must be acknowledged. Data regarding some important prognostic factors such as margin status, tumor size and specific Masaoka stage were not available in SEER database. Masaoka stage was not specifically recorded, but was assigned based on recorded information instead. In addition, comorbidity score was reported to be significantly associated with other causes of mortality in other cancer types (35,36). However, this variable was not included in SEER database. Lastly, while internal bootstrapping-based validation was conducted to evaluate the performance of this nomogram and it performed well, external validation using a separate patient population will be essential to establish the relative accuracy of this model.

## Conclusions

In this analysis, the SEER database was leveraged to assess cause-specific and other-cause-specific mortality among thymoma patients. We additionally constructed a novel predictive nomogram capable of estimating 3-, 5-, and 10-year cause-specific mortality among thymoma patients. This nomogram exhibited relatively good performance, and may thus offer value as a reliable tool for individual prognostic analyses of thymoma patients. However, additional external validation of this model remains to be conducted.

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## Footnote

*Reporting Checklist:* The authors have completed the TRIPOD reporting checklist. Available at <https://dx.doi.org/10.21037/jtd-21-931>

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[org/10.21037/jtd-21-931](https://doi.org/10.21037/jtd-21-931)). The authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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