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Competitive Risk Analysis of Thymic Carcinoma Based on the Surveillance, Epidemiology, and End Results Database

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Abstract: In general, we use the classical Cox proportional hazards model to derive factors that affect the prediction of patients diagnosed with thymic carcinoma (TC); however, when competing risks exist, the results can be biased. This study aimed to build a competing risk model for patients with TC to explore a more accurate method for assessing the relevant factors affecting patient prognosis. We obtained data on patients with TC who met the inclusion criteria between 2004 and 2016 (with additional treatment fields) in the Surveillance Epidemiology, and End Results database. The cumulative incidence function and Gray's test were used for univariate analysis, followed by the fine-Gray and Cox proportional hazards models for multivariate analysis. Of the 478 subjects with TC who were finally included, 284 (170 died from TC, and 114 died from other causes) (59.41%) died, and 194 (40.59%) patients were alive. Univariate Gray's test results indicated that age, marital status, tumor size, summary stage (localized, regional, or distant), chemotherapy status, and surgery status significantly affected the cumulative incidence of the target event ($P < 0.05$). Multivariate competing risk analyses indicated that tumor size, marital status, summary stage, and surgery status were independent risk factors for the prediction of subjects ($P < 0.05$). This study explored a more accurate method to assess the prognostic factors of patients with TC. Our findings can contribute to the clinical development of more scientific and accurate treatment methods, providing benefits to the majority of patients with TC.

Keywords: Thymic Carcinoma, Competing-Risks Model, SEER, Fine-Gray Model, Cause-Specific Model

1. Introduction

Thymic carcinoma (TC) is classified as a separate entity according to the World Health Organization histological classification, which is distinct from thymic neuroendocrine neoplasms and thymomas [1-3]. It is a rare high-grade malignant tumor that is highly metastatic and invasive. Its 5-year survival rate is only 28–67%, which results in significant burden to the patient and his/her family [4, 5].

The prevalence of thymoma is extremely rare (0.17/100,000), but the incidence rate of TC is even lower, accounting for 15–20% of all thymic epithelial neoplasms [6-8]. Surgical treatment is the first treatment of choice for resectable TC and is supplemented with adjuvant therapies, such as chemotherapy and radiotherapy. Nevertheless, for the majority of patients with advanced thymic cancer who have lost the opportunity for surgery, the effects of surgical intervention remain inconclusive [9, 10]. Multidisciplinary collaboration in combination with preoperative chemotherapy can be used as a treatment for patients with unresectable TC, but there is no consensus on the efficacy of this approach due to the low incidence rate of TC and insufficient clinical cases to be studied. In clinical practice, combined chemotherapy has been selected for patients with TC. However, these regimens do not work well, and patients' responses to chemotherapy vary widely [10-13].

In today's society, with rapid development and emphasis on accurate and personalized cancer treatment, accurately

determining the risk factors that have an effect on patient mortality will have a significant effect on clinical treatment and decision-making. In fact, only a portion of patients with TC eventually die from TC. The causes of death from other diseases, such as suicide, traffic accidents, and cardiovascular disease, are not usually reported separately [14, 15]. When analyzing the risk factors affecting the prognosis of patients with cancer, the non-cancer factors that contribute to patient mortality are generally considered competitive risk events. However, when there is a competitive risk event, multiple causes of death often coexist and compete to produce data with competing risks [16-18]. Therefore, the use of competitive risk models to exclude the influence of other causes of death will help us obtain more realistic and accurate results [19-21].

This study used data from the Surveillance Epidemiology, and End Results (SEER) database to perform a competitive risk analysis of subjects diagnosed with TC. Compared to the simple Cox proportional risk model, we can obtain more precise factors affecting the prognosis of subjects diagnosed with TC.

2. Materials and Methods

The SEER*Stat software (version 8.4.0) was used to extract TC patient data that met our requirements from the SEER database [22, 23]. The SEER database is an authoritative cancer diagnostic database in the United States that includes a large amount of accurate, factual data [24]. Cases diagnosed histologically were determined according to icD-O-3 specific codes: (I) primary sites, C37.9 (thymus) and (II) histological codes, 8586/3 (TC). We then extracted information on patients enrolled in the SEER database between 2004 and 2016, including demographics, marital status at diagnosis, Masaoka–Koga stage, grade, combined summary stage (localized, regional, or distant), tumor size (TS), surgery status, radiation recovery, and chemotherapy. Patients without information on the grade and Masaoka–Koga stage were excluded. The following nine factors were extracted from the SEER database: race, sex, age, marital status at diagnosis, combined summary stage, TS, surgery status, radiation dose, and chemotherapy (Figure 1).

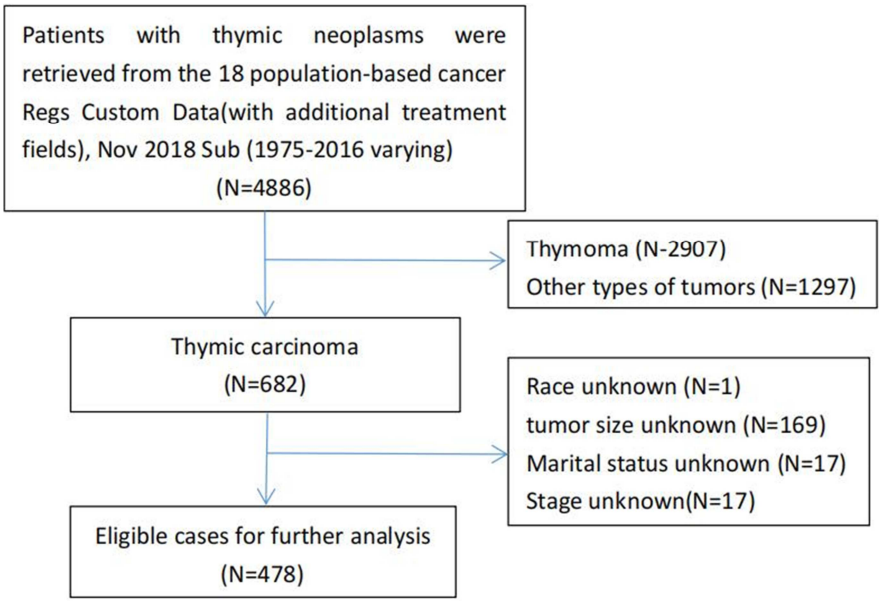


Figure 1. *Case inclusion process.*

All variables, except age, were classified as variables. Race was divided into white, black, and other races. TS was divided into three groups: TS I (largest dimension, or diameter ≤ 5 cm), TS II (largest dimension, or diameter > 5 cm and ≤ 10 cm), and TS III (largest dimension, or diameter > 10 cm). The summary stage was classified into three types: localized, regional, and distant. Marital status was classified into three types: married, unmarried, and others (separated/divorced/widowed [DSW]). The exclusion criteria were (1) age < 18 years, (2) no diagnosis, and (3) missing data, unknown outcomes, and uncertainty. A total of 478 patients met the inclusion and exclusion criteria.

Statistical Analyses

Categorical baseline data are expressed as frequencies and percentages. Continuous data are presented as mean ± standard deviation. Patient outcomes were divided into the following three categories: TC-specific death, other causes of death, and survival. The cumulative incidence function (CIF) [25] was used as a univariate analysis to calculate the probability of each event, the Nelson–Aalen cumulative risk curves of the incidence function for TC-specific death were calculated, and the differences between groups were analyzed using Gray's test [26]. The Fine–Gray model was used for multivariate analysis to identify the factors that influence the cumulative incidence of TC [16, 20, 27, 28]. Subsequently, the results of the multivariate analysis were compared with those of the traditional Cox proportional hazards model. All statistical analyses were performed using the IBM SPSS

software (version 27.0) and R software. All statistical tests were two-sided, with a probability value of $P < 0.05$ considered statistically significant. The SEER database was available free of charge, and informed consent from the included patients was not required for this study by the Institutional Research Committee of the First Affiliated Hospital of Jinan University.

3. Results

3.1. Patient Characteristics

Of the 478 patients with TC who were finally included, 284 (170 died from TC, and 114 died from other causes) (59.41%) died, and 194 (40.59%) patients were alive (Table 1).

Table 1. *General characteristics of the patient.*

Variable	All patients (%)	Die of TC (%)	Died of other causes (%)	alive (%)
N	478	170	114	194
Age	61.12 ± 13.66	58.92 ± 14.10	63.94 ± 14.68	61.39 ± 12.33
Sex				
male	300 (62.76)	105 (61.76)	73 (64.04)	122 (62.89)
female	178 (37.24)	65 (38.24)	41 (35.96)	72 (37.11)
Race				
white	337 (70.50)	120 (70.59)	79 (69.30)	138 (71.13)
black	67 (14.02)	26 (15.29)	21 (18.42)	20 (10.31)
other	74 (15.48)	24 (14.12)	14 (12.28)	36 (18.56)
Marital status				
I	286 (59.83)	91 (53.53)	70 (61.40)	125 (64.43)
II	84 (17.57)	35 (20.59)	17 (14.91)	32 (16.50)
III	108 (22.60)	44 (25.88)	27 (23.69)	37 (19.07)
Tumor size				
I	129 (26.99)	29 (17.06)	35 (30.70)	65 (33.50)
II	212 (44.35)	70 (41.18)	49 (42.98)	93 (47.94)
III	137 (28.66)	71 (41.76)	30 (26.32)	36 (18.56)
Stage				
I	77 (16.11)	10 (5.88)	20 (17.54)	47 (24.23)
II	222 (46.44)	70 (41.18)	53 (46.49)	99 (51.03)
III	179 (37.45)	90 (52.94)	41 (35.97)	48 (24.74)
radiation recode				
no	226 (47.28)	88 (51.76)	63 (55.26)	75 (38.66)
yes	252 (52.72)	82 (48.24)	51 (44.74)	119 (61.34)
chemotherapy				
no	202 (42.26)	53 (31.18)	58 (50.88)	91 (46.91)
yes	276 (57.74)	117 (68.82)	56 (49.12)	103 (53.09)
surgery status				
no	195 (40.79)	101 (59.41)	44 (38.60)	50 (25.77)
yes	283 (59.21)	69 (40.59)	70 (61.40)	144 (74.23)

Note: Marital status I, married; marital status II, unmarried; marital status III, other (separated/divorced/widowed); tumor size I (largest dimension, or diameter ≤ 5 cm); tumor size II (largest dimension, or diameter > 5 cm and ≤ 10 cm); tumor size III (largest dimension, or diameter > 10 cm); summary stage I, localized; summary stage II, regional; and summary stage III, distant.

Most of the subjects who died from TC were male (n = 105, 61.76%), were white (n = 120, 70.59%), had not received surgery (n = 101, 59.41%), did not receive radiation therapy (n = 88, 51.76%), received chemotherapy (n = 117, 68.82%), were married (n = 91, 53.53%), had distant metastasis (n = 90, 52.94%), and had a TS ≥ 10 cm (TS III) (n = 71, 41.76%).

3.2. Results of the Univariate Analysis

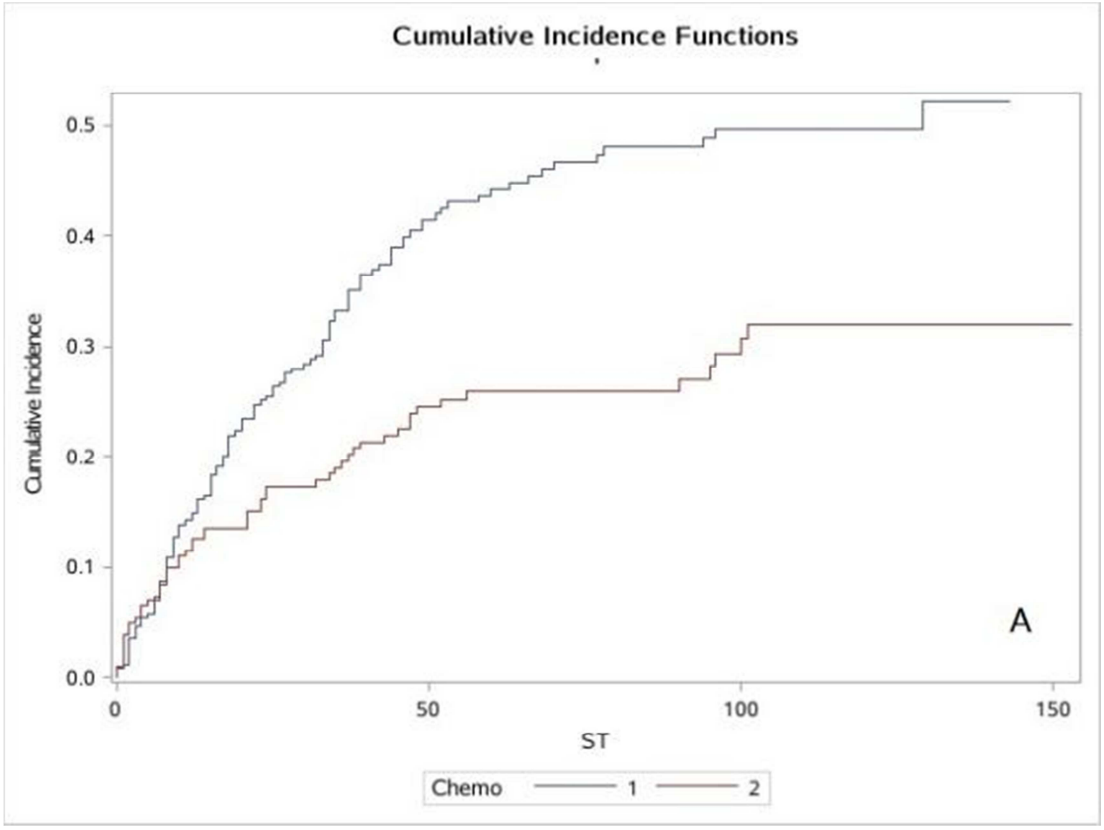
Gray's test indicated that age, TS, marital status, chemotherapy status, summary stage, and surgery status significantly affected the prediction of TC ($P < 0.05$). The Nelson–Aalen cumulative risk curves for variables in multiple categories are shown in Figure 2. The CIF for almost all variables increased over 1, 3, and 5 years and was higher for the subjects diagnosed with TC who were black, male, and unmarried, had a larger tumor, had distant metastasis, received chemotherapy, had not received radiotherapy, and had not received surgery. Additional information is provided in Table 2.

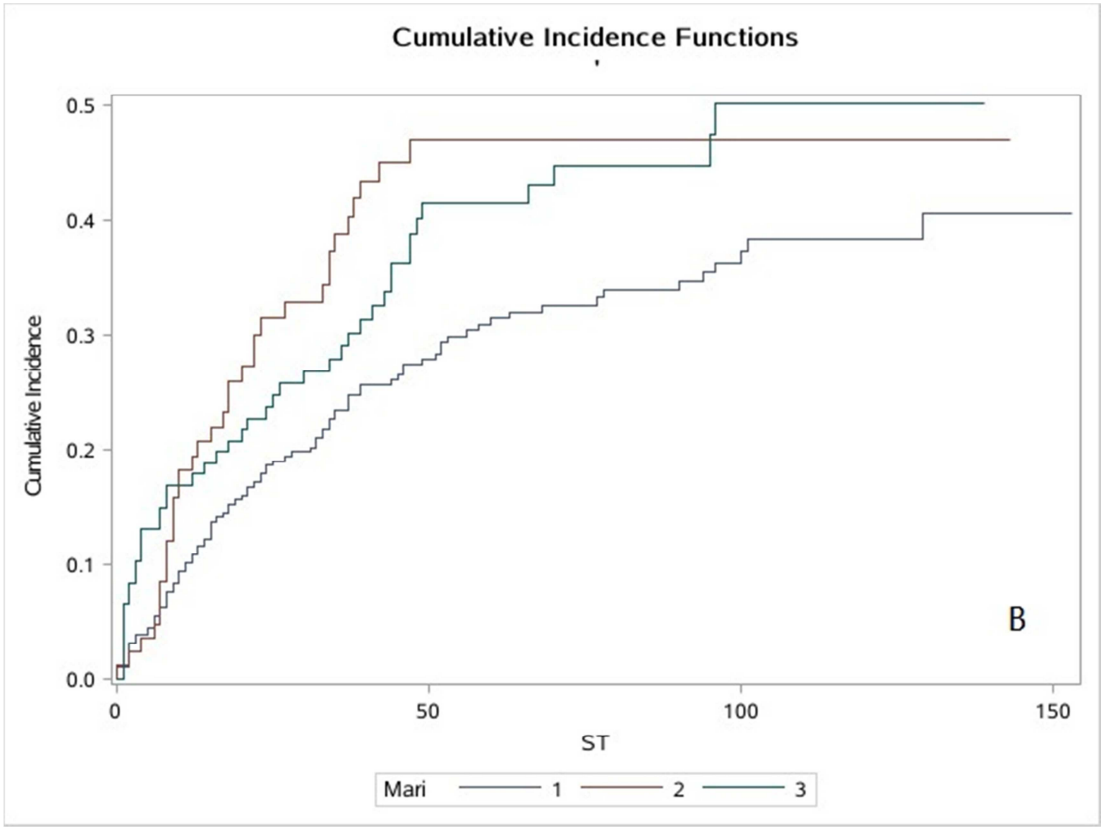
Table 2. *Univariate Analysis of Prognostic Factors in Patients With thymic Carcinoma.*

Variables	Gray's test	p-Value	Cumulative incidence function		
			12-months	36-months	60-months
Age	215.505	<.0001			
Gend	.008233359	0.9277			
male			0.14148	0.274747	0.36675
female			0.136027	0.27257	0.359596

Variables	Gray's test	p-Value	Cumulative incidence function		
			12-months	36-months	60-months
Race	0.61448	0.7355			
white			0.12591	0.25625	0.35431
black			0.209272	0.337748	0.415894
other			0.13708	0.295364	0.357616
Mari	6.52160	0.0384			
I			0.10887	0.234328	0.31473
II			0.19482	0.38806	0.470149
III			0.17870	0.29083	0.414925
Size	34.0943	<.0001			
I			0.04671	0.116418	0.232836
II			0.12396	0.238209	0.329552
III			0.25119	0.47970	0.53915
Stage	47.2579	<.0001			
I			0.02632	0.08494	0.15403
II			0.0895522	0.198806	0.297313
III			0.24899	0.453134	0.544478
Radia	2.75051	0.0972			
yes			0.10418	0.209091	0.33934
no			0.17888	0.34613	0.390909
Chemo	14.3986	0.0001			
yes			0.14972	0.332298	0.44264
no			0.12523	0.19582	0.259317
Surg	48.9561	<.0001			
yes			0.06088	0.154491	0.25281
no			0.25277	0.44867	0.526347

Note: TC: thymic Carcinoma; Marital status I: Married, Marital status II: Unmarried, Marital status III: other (separated/Divorced/Widowed-DSW); tumor size I (largest dimension, or diameter ≤ 5 cm); tumor size II (largest dimension, or diameter > 5 cm and ≤ 10 cm); tumor size III (largest dimension, or diameter > 10 cm); Stage I: localized, Stage II: regional, Stage III: distant.

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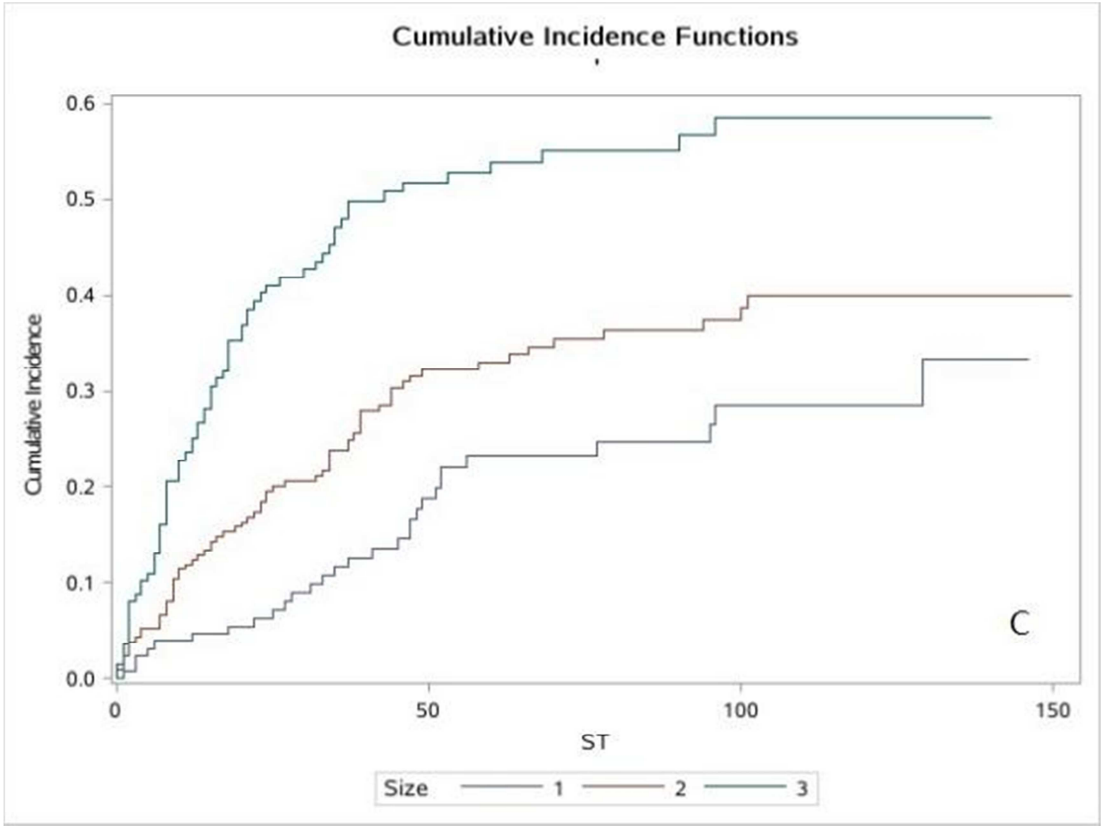
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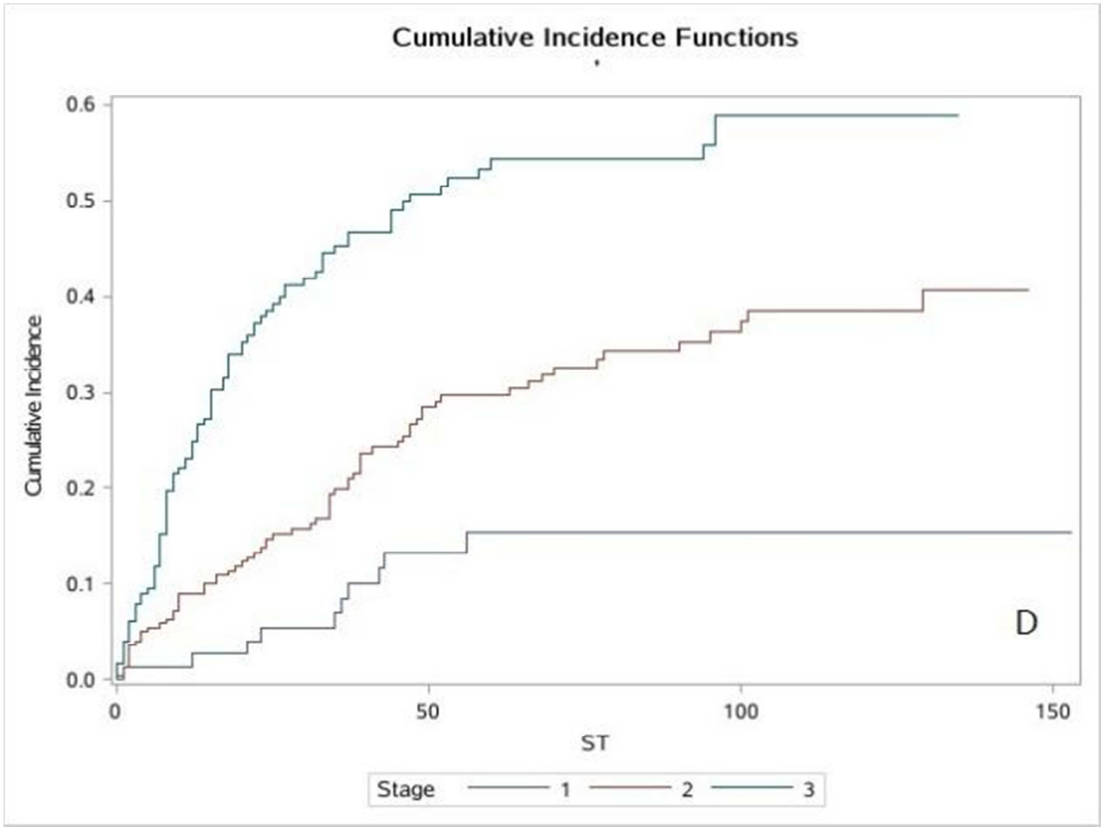

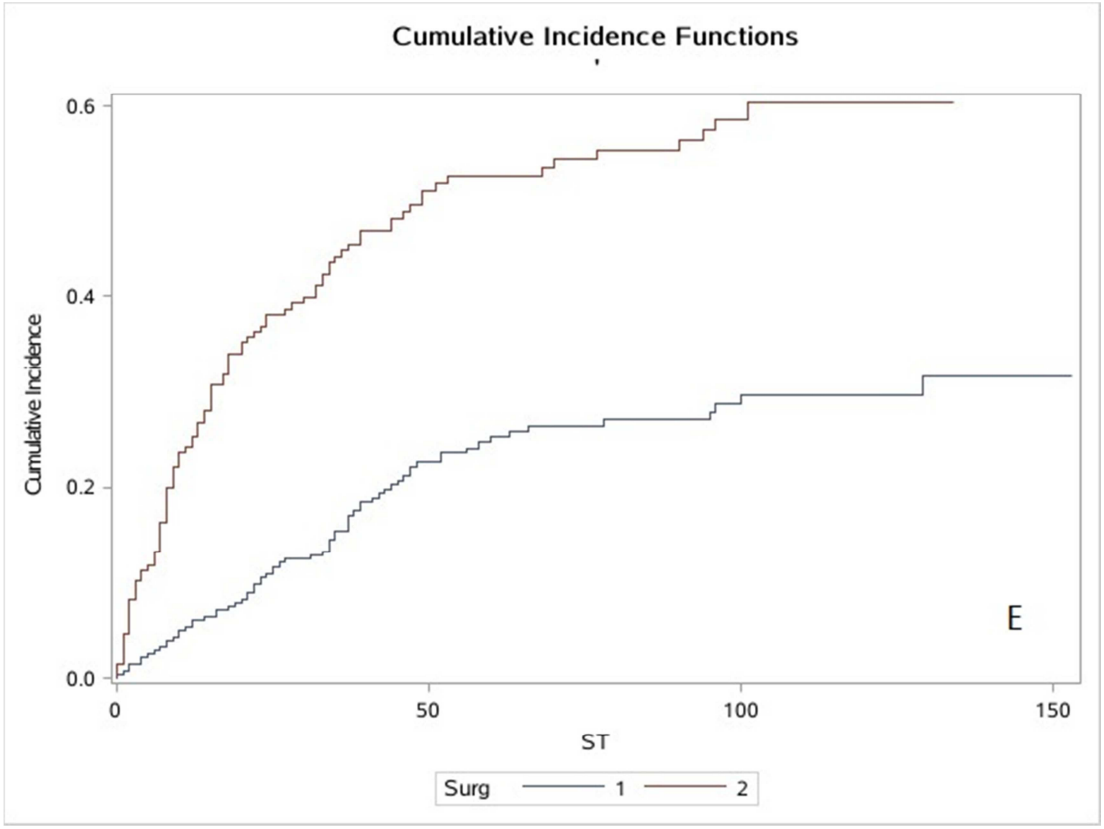

Figure 2. *(A) Cumulative incidence curves of cause-specific death according to chemotherapy. (B) Cumulative incidence curves of cause-specific death according to marital status. (C) Cumulative incidence curves of cause-specific death according to tumor size. (D) Cumulative incidence curves of cause-specific death according to summary stage. (E) Cumulative incidence curves of cause-specific death according to surgery status.*

3.3. Results of the Multivariate Analysis

A multivariate Cox regression model and a competitive risk model were used to analyze the results with statistical differences in the univariate analysis.

The results obtained from the Cox regression and Fine–Gray models indicated that the independent risk factors affecting the prediction of TC included TS, marital status, surgery status, and summary stage.

The results suggested that patients in the TS III group might have a worse prognosis (Cox model [vs. TS I: hazard ratio {HR} = 1.651, 95% confidence interval {CI} = 1.183–2.303, P = 0.0032] and Fine–Gray model [vs. TS I: HR = 1.949, 95% CI = 1.242–3.059, P = 0.0037]), but the TS II group had no significant statistical significance (P = 0.7151, 0.5266). Compared with married, others (DSW) had a worse prognosis (Cox model [vs. married: HR = 1.439, 95% CI = 1.076–1.924, P = 0.0142] and Fine–Gray model [vs. married HR = 1.567, 95% CI = 1.069–2.295, P = 0.0213]), but the unmarried had no significant statistical significance (P = 0.1000, 0.3518).

Patients with TC with higher summary stage had worse prognosis, and both statistical models drew similar conclusions, such as distant metastasis (Cox model [vs. localized metastasis: HR = 2.636, 95% CI = 1.684–4.126, P < 0.001] and Fine–Gray model [vs. localized metastasis: HR = 3.357, 95% CI = 1.693–6.653, P = 0.0005]) and regional metastasis (Cox model [vs. localized metastasis: HR = 1.527, 95% CI = 1.008–2.313, P = 0.0460] and Fine–Gray model [vs. localized metastasis: HR = 2.305, 95% CI = 1.175–4.520, P = 0.0151]).

For patients with TC, surgery was the most important treatment, and the results also showed that the operation was more beneficial in prognosis (Cox model [vs. no surgery: HR = 0.534, 95% CI = 0.406–0.701, P < 0.001] and Fine-Gray model [vs. no surgery: HR = 0.543, 95% CI = 0.384–0.768, P = 0.0006]). The results of both models suggested that chemotherapy had no statistically significant effect. Further details can be found in Table 3.

Table 3. *Multivariate Analysis of 2 Models of Prognostic Factors in Patients With thymic Carcinoma.*

Prognostic factors	Cox model			Fine-gray model		
	P	**HR**	**95%CI**	***P***	**HR**	**95%CI**
Age	0.9520	1.000	0.991 1.009	0.0615	0.989	0.977 1.001
Tumor size						
≤ 5 cm		Reference			Reference	
5-10cm	0.7151	1.060	0.774 1.454	0.5266	1.151	0.745 1.777
> 10 cm	0.0032	1.651	1.183 2.303	0.0037	1.949	1.242 3.059
Marital status						
Married		Reference			Reference	
Unmarried	0.1000	1.312	0.949 1.813	0.3518	1.220	0.803 1.854
DSW	0.0142	1.439	1.076 1.924	0.0213	1.567	1.069 2.295
Chemotherapy						
Yes		Reference			Reference	
No/unknown	0.3357	0.876	0.669 1.147	0.3848	1.176	0.815 1.697
Stage						
Localized		Reference			Reference	
Regional	0.0460	1.527	1.008 2.313	0.0151	2.305	1.175 4.520
Distant	<.0001	2.636	1.684 4.126	0.0005	3.357	1.693 6.653
Surgery						
No		Reference			Reference	
Yes	<.0001	0.534	0.406 0.701	0.0006	0.543	0.384 0.768

Note: DSW: (separated/Divorced/Widowed-DSW).

4. Discussion

Based on the SEER database data, this study adopted a competitive risk model to determine the accurate prognostic factors for TC patient-specific death. The results of this study found that having regional or distant metastases, not receiving surgical treatment, larger TS, and marital status III (DSW) were independent risk factors for TC-specific death.

Early surgery is the best treatment for patients with TC, followed by adjuvant chemotherapy and radiotherapy, but the prognostic effect of surgical intervention in patients with advanced TC remains unknown [5, 29, 30, 31]. There are conflicting conclusions regarding the effect of palliative chemotherapy on the prognosis of TC [32, 33, 34, 35]. In the era of personalized and precise cancer treatment, accurate analysis of risk factors affecting the survival and prognosis of patients with TC is of great significance. Because of the low incidence of TC, the existing literature reports mostly small-sample, single-center, retrospective studies [36]. Competing risk models for TC have not been studied to date, and the risk factors affecting its prognosis are unclear.

TC and other causes of death compete with each other because once the former occurs, the latter cannot occur. This model is not consistent with the basic assumptions of Cox regression, which considers only a single endpoint. When only a single cause of death is considered, the use of a single endpoint analysis approach will lead to bias in the estimated

probability of endpoint events when competing risk events are present. Therefore, the application of Cox regression may produce incorrect HR values or even lead to incorrect results of single factor influence [25, 37]. In this study, 114 of the 478 patients died for other reasons, accounting for 40.1% of the deaths, which would have been treated as censored data if ordinary survival analysis had been used, leading to erroneous conclusions. Using a competitive risk model analysis, such errors can be avoided, and it is more helpful to accurately judge the influencing factors affecting the prediction of subjects with TC. Therefore, this study used a competitive risk model to identify the risk factors that affect the prognosis of patients with TC. This model considers not only the death caused by TC but also the death and other events caused by other factors and their effects.

In this study, a fine Gray's proportional subdistribution risk model was used to evaluate the influence of dependent variables on CIF to identify the independent prognostic factors of TC. Although there was no significant difference between the risk factors determined by the Cox regression model and those determined by the competitive risk model in this study, their HR values were different. The Fine–Gray model indicated that stage II (HR = 2.305, 95% CI = 1.175–4.520, P = 0.0151) or stage III (HR = 3.357, 95% CI = 1.693–6.653, P = 0.0005) was a risk factor for death in patients with TC. Although this result is consistent with those of previous studies, the Cox model underestimated the risk of the transfer stage. Although this is only a numerical difference and no significant false-positive results were found, the results of the competing risks model were still more precise.

Both the Fine–Gray and CS models showed a higher cumulative risk of death in patients with larger tumors. The larger the tumor, the worse is the prognosis. Cox regression still underestimated this risk. A recent study of subjects with advanced TC using propensity score matching revealed that patients with tumors ≥ 7 cm in diameter were likely to have a worse prognosis. The larger the tumor, the worse is the prognosis, which is consistent with our findings [6]. Based on this, we suggest that the TS should be considered when formulating a treatment plan for patients with TC as a supplement to the pathological results.

Surgery is the primary treatment for TCs. In univariate and multivariate analyses, this study found that surgery was beneficial to patients with TC in terms of prognosis, and that complete TC resection had the best protective effect on survival (HR = 0.543, 95% CI = 0.384–0.768, P = 0.0006). The absence of surgery increases the risk of death in patients with TC. At present, chemotherapy and radiotherapy are used for patients with incompletely resected TC and for those with advanced TC who do not have access to surgery. However, this study showed that radiotherapy and chemotherapy have no benefit in prolonging the survival time of patients. Meanwhile, the HR of the Fine–Gray model was larger than that of the classical Cox regression analysis, indicating that Cox regression overestimated the protective effect of radiotherapy and chemotherapy on TC.

In addition, marital status was an independent risk factor for the death of patients with TC. Compared with married patients, DSW increased the probability of death in patients with TC (HR = 1.567, 95% CI = 1.069–2.295, P = 0.0213), and the Cox model results underestimated the risk of marital status (HR = 1.439, 95% CI = 1.076–1.924, P = 0.0142). Although this is only a point estimate difference, the competitive risk model is more precise. This survival advantage may be due to the increased emotional care and financial security that patients receive from their families.

Based on massive information and authoritative data from the SEER database, this study more accurately analyzed the independent risk factors affecting the prognosis of patients with TC. However, this study has some limitations. First, we only used the data from the SEER database from 2004 to 2016. A short follow-up period may affect the estimation of cumulative mortality. Second, this study was retrospective. Only the data of patients with TC in the United States were selected, and selection bias was inevitable. Third, the prognosis of patients with TC may be related to lifestyle, genes, environment, and other factors; however, this information cannot be obtained from the SEER database at present. Therefore, other factors need to be further investigated.

5. Conclusion

Using competing risk models, this study identifies more accurate independent risk factors affecting the prognosis of TC, including regional or distant metastases, failure to undergo surgical treatment, marital status III (DSW) and greater TS. we can use the results of this study to promote the reallocation of health care resources and prevent health care wastage if patients with several of these risk factors are given a tilt in favour of health care We should target patients for better treatment.

Conflict of Interest

All the authors do not have any possible conflicts of interest.

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