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Effect of Age on the Clinicopathological Characteristics and Survival Outcomes of Thymoma Patients

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Abstract

Background: Age is an important prognostic factor for thymoma; however, few studies have specifically focused on age-related survival outcomes in thymoma patients. This study explored the effect of age on the clinicopathological features and survival outcomes of thymoma patients. **Methods:** We reviewed the clinical data of 1984 chest thymoma patients from the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute. In accordance with the World Health Organization age brackets, the patients were divided into young (group A, 0 - 44-year-old); middle-aged (group B, 45 - 59-year-old); old (group C, 60 - 74-year-old); and seniors (group D 75 - 84-year-old). Single-factor and multivariate analysis were performed using the Kaplan-Meier method, and a multivariate Cox regression model was generated to assess patient prognosis. **Results:** In total, 1984 patients were included. The median follow-up time was 156.0 months (range: 0 - 492 months). Group C (60 - 74-year-old) had the most patients (35.1%), and Group D had the fewest patients (12.3%). Among all age groups, the proportion of white people and men with thymoma increased with age, while the proportion of black people and women showed a downward trend. Univariate and multivariate analyses showed that the overall survival rate of thymoma patients was negatively correlated with age. The overall survival times of the four groups were significantly different ($p < 0.001$). Age, gender, race, surgery or not, and histological type were independent prognostic factors that affected overall survival. **Conclusion:** Age is an important prognostic factor for survival in thymoma patients, and younger patients have a survival advantage over older patients.

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Keywords

Age Group, Thymoma, SEER, Survival

1. Introduction

Although thymoma is a rare tumor, it accounts for 50% of all tumors in the anterior mediastinum. The Surveillance, Epidemiology, and End Results Program (SEER) database collects carcinoma incidence data from population-based cancer registries covering approximately 34.6% of the United State population. In this study, we used data from the SEER database mentioned above to identify the prognostic factors for overall survival among patients with Thymoma. Thymoma is a malignant tumor, and distant metastases and local recurrence are found in all stages of the disease, with local recurrence occurring as late as 5 years after surgery. Approximately 60% of patients die from causes unrelated to the tumor, making definitive prognostic statements difficult [1]. Moreover, after suffering from thymoma, the incidence of other malignant tumors such as non-Hodgkin lymphoma, malignant tumors of the digestive system, and soft tissue sarcoma is also increased [2] [3].

Histological classifications of thymomas are based on the incidence of non-malignant thymic epithelial cells and the proportion of lymphocytes (A, AB, B1, B2, B3, C), while the staging system involves localization of the lesion area. Surgery is the mainstay of treatment, and 10-year survival rates after R0 resection are 80%, 78%, 75%, and 42% for stages I, II, III, and IV, respectively [4]. Thus, surgical treatment remains the gold standard and must be performed whenever possible.

Currently, the most common surgical method is thoracoscopic thymoma resection, which is less invasive and has a better prognosis. In previous epidemiological studies, age, gender, race, grade, stage, surgery, and histological type were independent prognostic factors that affected overall survival (OS). The lack of precise details on age-stratified clinicopathological features for thymoma patients may lead physicians and patients to make erroneously informed decisions. Several previous studies have shown that younger thymoma patients have a better prognosis due to a higher incidence of early-stage, low-grade tumors compared with the elderly thymoma patient population [5].

Previous studies were mainly conducted on general epidemiological indicators, and few independently determined the effect of the age of thymoma patients on their clinicopathological characteristics and survival outcomes. Therefore, this study aimed to elucidate clinicopathological differences among thymoma patients stratified into the World Health Organization (WHO) age groups.

2. Materials and Methods

2.1. Patient Enrolment

This study was performed using the SEER 21-Registry database (1975-2018),

which covers approximately 30% of the US population [6]. We identified all patients between 1975 and 2018 whose primary site was labeled thymus (C37.9). Tumors were classified as thymoma according to the International Classification of Diseases codes (ICD-O-3) (8580-8585), with type C thymoma being heterogenous thymic carcinoma, type A thymoma being spindle cell or medullary thymoma, type AB thymoma being mixed thymoma, type B1 thymoma being organoid, lymphocyte-rich, lymphocytic, or predominantly cortical thymoma, type B2 thymoma being cortical thymoma, and type B3 thymoma being well-differentiated thymic carcinoma, epithelial thymoma, or squamoid thymoma.

2.2. Date Analysis Method

We collected demographic and clinicopathological characteristics of the patients, including age at diagnosis, gender, ethnicity, surgical information, survival time, and vital status. OS was defined as the time between the day of the first surgery and the last day of follow-up or death. Univariate and multivariate analyses were performed using Cox proportional hazards regression models to identify independent risk factors. Survival rates were calculated by the Kaplan-Meier method, and the log-rank test was used to compare survival rates between the two groups. The significance threshold was $P < 0.05$. All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

3. Results

Table 1 shows the clinicopathological characteristics of the 1984 patients included in the study. The median follow-up was 156.0 months (range: 0 - 492 months). The median age was 58-year-old (range: 6 - 84-year-old). Among the age groups, the proportion of patients in the elderly and middle-aged groups was the highest, accounting for 35.1% and 32.2% of the total population, respectively, and the proportion of patients in the elderly group was the lowest (12.3%). There was roughly the same proportion of male and female patients, surgical versus non-surgical or unknown patients. Regarding race, the majority of cases were among white people, accounting for 66.4% of the total; other races and black people accounted for 17.9% and 15.7% of the total population, respectively. Among histological types, C-type heterogeneous thymoma accounted for the majority of cases (56.0%); type A spindle cell or medullary thymoma accounted for the smallest proportion (5.7%); proportions of the other types were roughly similar.

Table 2 shows the distribution of clinicopathological characteristics in each age group. The proportion of female patients increased gradually from group A to group D, while the proportion of male patients gradually decreased. The difference between the genders was statistically significant ($P < 0.001$). White patients accounted for the highest proportion among the four groups, and the proportion increased with age. In contrast, black patients did not show these two

Table 1. Patient characteristics.

	n	%
Patients	1984	
Age, years		
Median (range)	58 (6 - 84)	
Age		
0 - 44	406	20.4%
45 - 59	638	32.2%
60 - 74	696	35.1%
75 - 84	244	12.3%
Sex		
Male	985	49.6%
Female	999	50.4%
Race		
Black	311	15.7%
White	1318	66.4%
Others	355	17.9%
Surgery		
Yes	979	49.3%
None/Unknown	1005	50.7%
Histology		
type C	1111	56.0%
type A	113	5.7%
type B	197	9.9%
type B1	187	9.4%
type B2	169	8.5%
type B3	207	10.4%

Note: type C thymoma, heterogenous thymic carcinoma; type A thymoma, spindle cell or medullary thymoma; type AB thymoma, mixed thymoma; type B1 thymoma, organoid, lymphocyte-rich, lymphocytic, or predominantly cortical thymoma; type B2 thymoma, cortical thymoma; type B3 thymoma, well-differentiated thymic carcinoma, epithelial thymoma, or squamoid thymoma.

trends; the difference between the two races was statistically significant ($P < 0.001$). There was no obvious difference in the proportion of patients with or without surgery. Among the histological classifications, type C thymoma had the highest proportion of cases and was approximately 10-fold higher than type A thymoma, which had the lowest proportion. Incidence decreased with age. First, we compared the prognosis of the four groups of patients. On the basis of Kaplan-Meier results, the 3-, 5-, and 10-year OS rates of group A were 82.1%, 77.2%,

Table 2. Clinicopathologic characteristics stratified by age.

	age 0 - 44 (group A)		age 45 - 59 (group B)		age 60 - 74 (group C)		age 75 - 84 (group D)		P value
	n = 406		*n* = 638		*n* = 696		*n* = 244		
	n	%	n	%	n	%	n	%	
Sex									
Male	219	53.9%	334	52.4%	335	48.1%	111	45.5%	<0.001
Female	187	46.1%	304	47.6%	361	51.9%	133	54.5%	
Race									
Black	83	20.4%	120	18.8%	92	13.2%	16	6.6%	
White	237	58.4%	414	64.9%	493	70.8%	174	71.3%	<0.001
Others	86	21.2%	104	16.3%	111	16.0%	54	22.1%	
Surgery									
Yes	185	45.6%	319	50.0%	361	51.9%	114	46.7%	<0.001
None/Unknown	221	54.4%	319	50.0%	335	48.1%	130	53.3%	
Histology									
type C	258	63.5%	361	56.5%	368	52.9%	124	50.8%	
type A	9	2.2%	21	3.2%	53	7.6%	30	12.3%	
type B	24	5.9%	68	10.6%	82	11.8%	23	9.4%	
type B1	40	9.9%	58	9.0%	60	8.6%	29	11.9%	<0.001
type B2	41	10.1%	64	10.3%	52	7.5%	12	4.9%	
type B3	34	8.4%	66	10.4%	81	11.6%	26	10.7%	

Note: Kaplan-Meier analysis of age groups as a factor, and other variables were stratified for comparison. Type C thymoma, heterogenous thymic carcinoma; type A thymoma, spindle cell or medullary thymoma; type AB thymoma, mixed thymoma; type B1 thymoma, organoid, lymphocyte-rich, lymphocytic, or predominantly cortical thymoma; type B2 thymoma, cortical thymoma; type B3 thymoma, well-differentiated thymic carcinoma, epithelial thymoma, or squamoid thymoma.

and 61.4%, respectively; those of group B were 85.3%, 78.1%, and 58.4%, respectively; those of group C were 76.4%, 66.3%, and 47.3%, respectively; and those of group D were 52.3%, 41.4%, and 19.8%, respectively. The median survival times for groups A to D were 170.0 months, 162.0 months, 111.0 months, and 43.0 months, respectively (Figure 1). The difference in OS between the two groups was statistically significant ($p < 0.001$). In univariate analysis, we observed an obvious difference between OS without surgery or unknown and surgery, 17.4% and 67.9%, respectively; the median survival times were 78.0 months and 174.0 months, respectively.

In multivariate analysis, surgery was identified as an important and independent prognostic factor for OS (hazard ration: 0.436, 95% confidence interval: 0.373 - 0.510, $P < 0.001$) (Figure 2). Age, gender, race, survival time, and vital status were also identified as prognostic factors associated with OS. To reduce selection bias and eliminate confounding factors, these categories were entered

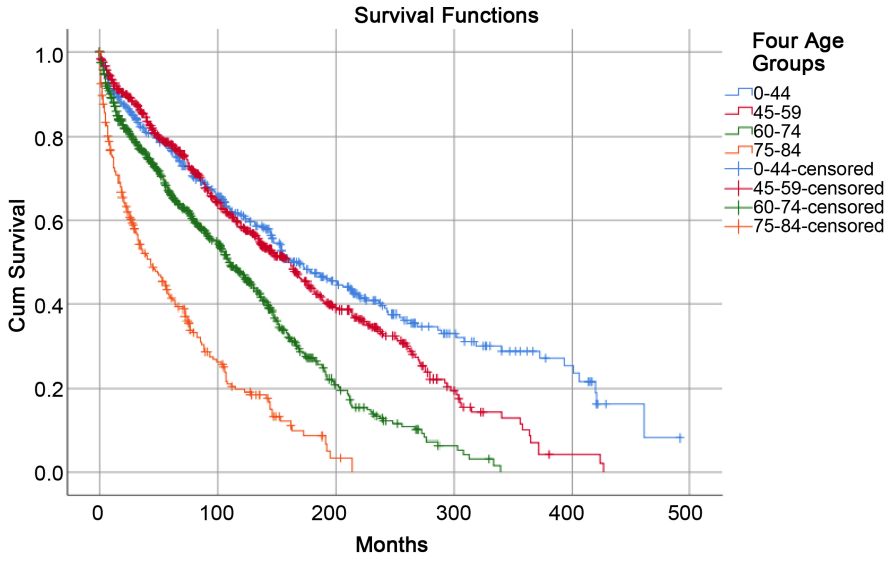

Figure 1. Estimated overall survival of thymoma patients stratified by age (group A, 0 - 44-year-old; group B, 45 - 59-year-old; group C, 60 - 74-year-old; and group D, 75 - 84-year-old) using Kaplan-Meier survival functions.

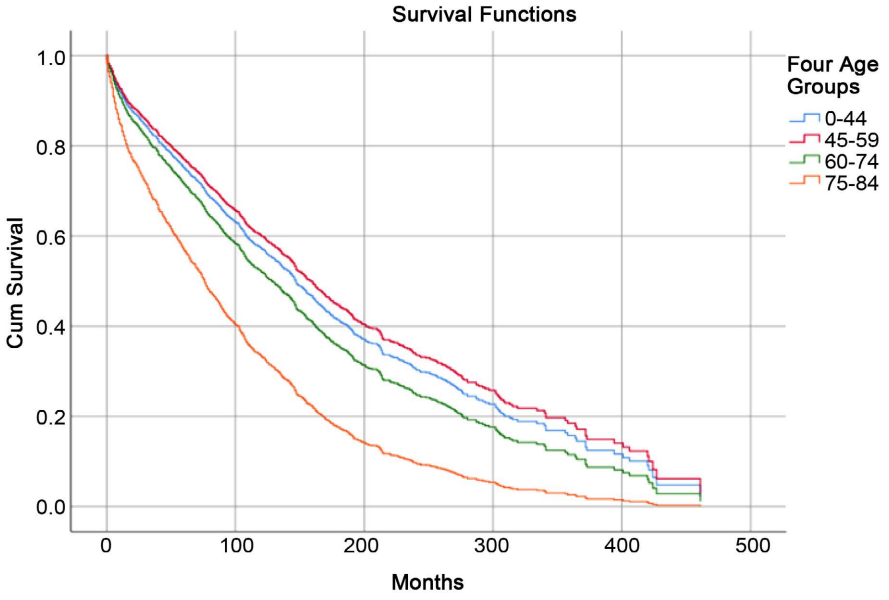

Figure 2. Estimated overall survival of thymoma patients stratified by age (group A, 0 - 44-year-old; group B, 45 - 59-year-old; group C, 60 - 74-year-old; and group D, 75 - 84-year-old). COX survival functions.

into the multivariate OS analysis system by Cox proportional hazards regression models. Age, gender, ethnicity, surgical information, survival time, and vital status at diagnosis were statistically significant as prognostic signatures for OS (Table 3).

4. Discussion

In this study, we analyzed the clinicopathological characteristics and survival

Table 3. Uni- and multivariate analyses of clinicopathologic parameters in relation to overall survival in thymomacancer patients.

	Univariate		Multivariate	
	HR (95% CI)	p value	HR (95% CI)	p value
Age				
0 - 44	1		1	
45 - 59	1.226 (1.029 - 1.460)	0.023	0.915 (0.700 - 1.196)	0.516
60 - 74	1.919 (1.616 - 2.279)	<0.001	1.167 (0.777 - 1.753)	0.456
75 - 84	3.932 (3.200 - 4.832)	<0.001	1.972 (1.125 - 3.454)	0.018
Sex				
Male	1		1	
Female	0.941 (0.837 - 1.056)	0.301	0.877 (0.780 - 0.986)	0.028
Race				
White	1		1	
Others	0.838 (0.713 - 0.985)	0.032	0.838 (0.713 - 0.986)	0.033
Black	1.086 (0.922 - 1.278)	0.324	1.207 (1.024 - 1.424)	0.025
Surgery				
None/Unknown	1		1	
Yes	0.433 (0.379 - 0.494)	<0.001	0.436 (0.373 - 0.510)	<0.001
Histology				
type C	1		1	
type A	0.662 (0.476 - 0.921)	0.014	0.792 (0.560 - 1.120)	0.187
type B	0.463 (0.350 - 0.611)	<0.001	0.722 (0.537 - 0.972)	0.032
type B1	0.661 (0.520 - 0.841)	0.001	0.916 (0.712 - 1.177)	0.492
type B2	0.512 (0.381 - 0.688)	<0.001	0.869 (0.638 - 1.183)	0.371
type B3	0.769 (0.620 - 0.954)	0.017	1.095 (0.870 - 1.379)	0.439

Type C thymoma, heterogenous thymic carcinoma; type A thymoma, spindle cell or medullary thymoma; type AB thymoma, mixed thymoma; type B1 thymoma, organoid, lymphocyte-rich, lymphocytic, or predominantly cortical thymoma; type B2 thymoma, cortical thymoma; type B3 thymoma; well-differentiated thymic carcinoma, epithelial thymoma, or squamoid thymoma.

outcomes of 1984 thymoma patients from the SEER database. Overall, there was a decreased survival rate with increased age in group A to group D. In terms of survival time and survival rate, the younger group of patients has a better advantage. This does show that age is one of the major factors influencing the prognosis of patients with thymoma. Younger patients have significantly better prognoses than older patients. However, we found that the survival rate of group A was lower than that of group B (69.0% vs. 69.1%) before 87 months, and then group A gradually surpassed group B, which may be related to T cell and thymus development [7] [8] [9] and remains to be further studied.

We also found significant differences in clinicopathological characteristics stratified by age among the four groups, with relatively older age, non-surgery, black race, and male sex being significantly associated with lower OS among thymoma patients. The median OS time was 174.0 months after surgical resection and 78.0 months without surgery or unknown, indicating that only the former had a significant effect on OS. There is no doubt that surgery remains the best treatment choice for thymoma.

In terms of age-stratified pathological types, groups C, A, and B1 were in line with the trend of decreased survival rates with increased age; however, there was no such trend for AB, B2, B3, or squamous thymoma. But there is no doubt that the survival rate of the elderly group (group D) was the lowest among the six histological categories, representing the worst prognosis; similar results have been reported in previous studies [10] [11].

Currently, the commonly used international staging systems for thymoma are the TNM and Masaoka-Koga staging systems [12]. Histopathological classifications of thymoma are associated with prognosis but are usually not independent predictors of prognosis. Modified Masaoka staging is an independent prognostic parameter of thymoma that is superior to histopathological classification [13]. Throughout the epidemiological literature and reports on thymoma, age is indeed an important factor that affects the survival and prognosis of thymoma [5] [14]. Because the thymus is where T lymphocytes mature, thymoma patients often develop immune-related diseases, such as myasthenia gravis [15], which still have a great impact on patient prognosis. The occurrence of thymoma requires further monitoring and analysis of the relevant immune markers in patients [16].

The strengths of this study are primarily based on its relatively large sample size and a central pathological review of histology. However, the current study is inconclusive, because the data are derived from the SEER database, and patient information is relatively incomplete, with several limitations, including different follow-up periods, and different treatment options for different types of surgeries over the years. Furthermore, the multivariate analysis may not have adequately minimized the effects of confounders because some of the variables analyzed in this study were collinear among themselves. In this case, we merely propose the hypothesis that younger patients with suspected thymoma may have a better prognosis than older patients. Larger patient populations in other countries and regions are needed to analyze the prognosis.

5. Conclusion

Thymoma is a rare tumor type, and surgery should be considered the best first-line treatment option. Nevertheless, age was an independent prognostic factor associated with OS. Further studies are needed to confirm its impact on treatment and prognosis to better find better treatment strategies for different age groups of thymoma patients. We hope that our findings will help to identify

more appropriate and practical approaches to treating thymoma.

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Data Availability Statement

The datasets generated and analysed during the current study are available in the SEER repository, https://seer.cancer.gov/.

Ethical Approval

All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflicts of Interest

The authors have no conflict of interest to declare.

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