Article

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Prognostic Correlation between Tumor Volume and Complete Resection of Thymoma at Different Masaoka-Koga Stages

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Objective: Thymoma is a slow-growing epithelial tumor of thymus gland. Its size is associated with its prognosis. The aim of this study was to analyze the prognostic correlation of tumor volume and complete resection of thymoma at different Masaoka-Koga stages.

Methods: A retrospective study was carried out, using the data of 502 patients who underwent complete resection of thymectomy at Zhongshan Hospital, Fudan University, in Shanghai, China, from February 2009 to February 2016. The characteristics of the patients were collected. Using Masaoka-Koga staging system, patients were divided into four different subcohorts: Stage I, stage II, stage III and stage IVa/IVb. The relationship between tumor volume and postoperative recurrence was analyzed for each subcohort, using receiver operating curves, cutoff values were obtained, and patients were grouped according to the cutoff values. Survival analysis was performed with the help of Kaplan–Meier method, and the difference between the two survival curves was compared using log-rank test. Whether tumor volume could be used as an independent risk factor for thymoma prognosis was analyzed, using a univariate Cox proportional hazards model.

Results: The area under the curve was 0.718, 0.740, 0.798, and 0.804 for the stage I, II, III, and IVa/IVb subcohorts, respectively, and the cutoff values of tumor volume for predicting recurrence were 47.90 cm^3, 53.70 cm^3, 76.35 cm^3, and 89.05 cm^3, respectively. Patients with tumor volumes greater than the cutoff values had significantly shorter recurrence-free survival than those with tumor volumes less than the cutoff values ($p < 0.001$). The results of the univariate Cox proportional hazards model indicated that tumor volume was an independent risk factor for thymoma prognosis and for postoperative prognosis of thymoma in Masaoka-Koga stage I ($p < 0.001$).

Conclusions: Tumor volume is significantly correlated with the postoperative prognosis of thymoma in Masaoka-Koga stage I and can serve as an independent risk factor for predicting postoperative tumor recurrence.

Keywords: thymoma; tumor volume; Masaoka-Koga staging; postoperative recurrence; risk factors

Introduction

Thymoma is a slowly-growing epithelial tumor of thymus gland and also the most common tumor of the anterior mediastinum [1]. According to the RARE-CARE project definition [2], thymoma is a rare tumor accounting for 0.2% to 1.5% of all malignant tumors [3]. The treatment of thymoma varies depending on the size and malignancy of the tumor, the patient's age and physical condition. Typically, total thymectomy is the most effective treatment [4]. Traditional open surgery, video-assisted thoracic surgery (VATS) and robot-assisted thoracic surgery (RATS) are the main operational styles [5].

After appropriate surgical treatment, more than 95% of patients with benign thymoma as well as 30% to 50% for patients with malignant thymomas would have a survival rate of more than 5 years [6]. It is reported that about 17% of patients with thymoma would suffer from recurrence after total thymectomy, with the majority of first recurrences occurring within 2–5 years after the surgery [4]. The long-term survival rate in patients with recurrence is much lower than in those without recurrence [7]. Thymoma recurrence is one of the major risk factors affecting the survival of patients. Therefore, it is helpful to accurately predict the risk of thymoma recurrence and detected it at an early stage, so as to target additional adjuvant therapy for patients with high risk of recurrence and improve their survival rates and quality of life.

Based on the Masaoka-Koga staging system and the Primary tumor, Regional lymph nodes, distant metastasis (TNM) staging system recognized by the International Association for the Study of Lung Cancer (IASLC)/the International Thymic Malignancies Interest Group (ITMIG) [8], the staging of thymoma is mainly determined by the

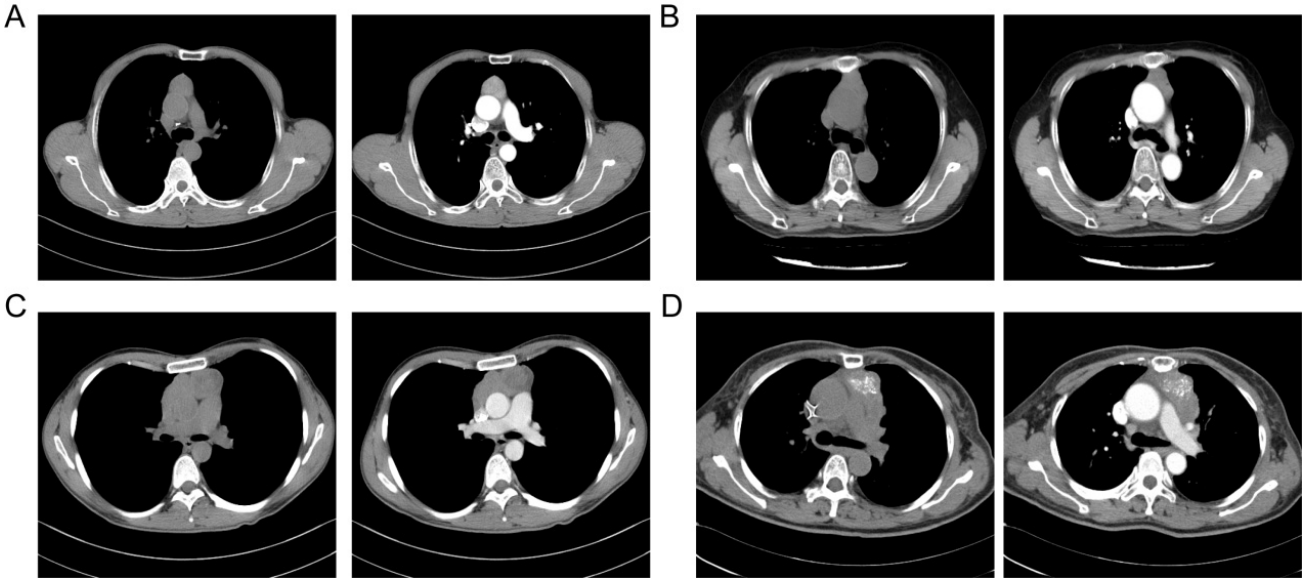

Fig. 1. Images of computed tomography (CT). (A) Masaoka-Koga Stage I of thymoma. (B) Masaoka-Koga Stage II of thymoma. (C) Masaoka-Koga Stage III of thymoma. (D) Masaoka-Koga Stage IV of thymoma.

degree of invasion of surrounding organs and the occurrence of distant metastases [9]. Previous studies found that the two staging systems have good guiding significance in judging whether patients with thymoma require adjuvant treatments, such as chemotherapy and radiotherapy, before and after surgery [10,11]. However, controversy exists over their ability to accurately forecast the risk of thymoma recurrence after total thymectomy is controversial [12,13]. Tumor size was reportedly not been taken into account, as a judgment factor by either the Masaoka-Koga staging system or the TNM staging system [14]. In fact, an important association was found between thymoma size and the prognosis and recurrence of the disease [15,16].

Therefore, the hypothesis behind this study was that thymoma size may be an independent risk factor for the prognosis and recurrence of thymoma. The aim of this study was to explore the association between thymoma size and the prognosis and recurrence of the disease.

Materials and Methods

Included Patients

In this clinical retrospective study, 502 patients with thymoma who underwent total thymectomy in the Department of Cardiothoracic Surgery at Zhongshan Hospital, Fudan University (Shanghai, China) from February 2009 to February 2016 were included.

The inclusion criteria were:

(1) Patients with thymoma who underwent total thymectomy and received pathological examination to confirm the diagnosis of thymoma;

(2) Patients underwent complete preoperative examination without surgical contraindications;

(3) Patients with complete clinical data.

The exclusion criteria were:

(1) Patients with history of thoracic surgery;

(2) Patients with malignant tumors of other systems;

(3) Patients with neurological and psychiatric diseases who could not cooperate with the follow-up examination.

Data Collection

The following information was collected from the medical records: Gender, age, operational style, World Health Organization (WHO) stage of thymoma, Masaoka-Koga stage of thymoma, tumor volume, adjuvant treatment modality, having myasthenia gravis, and follow-up duration. All patients underwent a computerized tomography (CT) prior to any adjuvant treatment and surgery (Fig. 1). The tumor volume was calculated through analyzing the acquired CT images, using the modified "Watchin GGO" software (https://ssl.lisit.jp/images/WatchinGGO20141026.pdf, LISIT, Co., Ltd., Tokyo, Japan) [17]. In addition, thymoma was staged based on the Masaoka-Koga staging system [18] and thymoma was classified into five subtypes: A, AB, B1, B2, and B3 following the WHO criteria [19,20]. According to the guidelines proposed by the International Thymic Malignancy Interest Group [21], the recurrence of thymoma during follow-up was determined by the results of radiological imaging. The recurrence rate of thymoma during the follow-up period was recorded.

Statistical Analysis

Statistical Package for the Social Sciences version 26.0 software (IBM Corporation, Armonk, NY, USA) was used for data analysis. Categorical data were expressed as number of cases (%). Continuous data were checked for

normality of distribution, using Shapiro-Wilk test. Normally distributed continuous data described as mean ± standard deviation (SD). Continuous data that did not fit a normal distribution were described as median [interquartile range]. Levene's test or the Bartlett's test was used to test for equal variance. The relationship between tumor volume and recurrence was analyzed using the receiver operating characteristic (ROC) curve. The area under the curve (AUC) with was used as an indicator of the value of tumor volume in predicting postoperative recurrence, the sensitivity, specificity, positive and negative predictive values were calculated. The point on the ROC curve with the largest Youden index was taken as the volume cutoff value of the thymoma at that Masaoka-Koga stage. A p value < 0.05 was considered statistically significant.

Recurrence-free survival (RFS) was defined as the time from the time the patient underwent radical total thymectomy to the first postoperative recurrence. In each subcohort, patients were artificially grouped depending on the tumor volume cutoff values. With the help of Kaplan–Meier survival curves, the survival rates were calculated. The log-rank test was carried out to compare the difference between the two survival curves. If the log-rank test results revealed a significant difference between the two curves, a univariate Cox proportional hazards model was further applied to determine whether tumor volume could be used as an independent risk factor related to prognosis of thymoma.

Results

Baseline Characteristics

As shown in Table 1, a total of 502 patients with thymoma were included in this study. Among them, 259 (51.6%) were men and 243 (48.4%) were women. They aged from 18 to 83 years, with a median [interquartile range] of 55 [46–62] years.

According to World Health Organization (WHO) staging criteria, 14 (2.8%) patients were type A, 99 (19.7%) were type AB, 161 (32.1%) were type B1, 156 (31.1%) were type B2, and 72 (14.3%) were type B3. On the basis of Masaoka-Koga staging system, 314 (62.5%) patients were at stage I, 85 (16.9%) at stage II, 43 (8.6%) at stage III, and 60 (12.0%) at stage IVa/IVb. Totally 118 patients received adjuvant therapies other than surgery, of which 39 (32.2%) received adjuvant radiotherapy, 28 (23.1%) received adjuvant radiotherapy and chemotherapy, and 54 (44.6%) patients received neoadjuvant radiotherapy. There were 53 (10.6%) patients of total 502 patients developed myasthenia gravis. The survival time after total thymectomy ranged from 27.7 to 136.2 months, with a median [interquartile range] of 88.45 [73.50–101.80] months.

Table 1. Clinical characteristics of patients.

Indicators	Values
Age (years)	
Range	18–83
Median [interquartile range]	55 [46–62]
Gender (%)	
Male	259 (51.6%)
Female	243 (48.4%)
WHO stages (%)	
A	14 (2.8%)
AB	99 (19.7%)
B1	161 (32.1%)
B2	156 (31.1%)
B3	72 (14.3%)
Masaoka-Koga stages (%)	
I	314 (62.5%)
II	85 (16.9%)
III	43 (8.6%)
IVa/IVb	60 (12.0%)
Tumor volume (cm^3)	
Range	0.5–776.4
Median [interquartile range]	34.8 [20.8–58.0]
Therapy methods (%)	
Adjuvant radiotherapy	39 (32.2%)
Adjuvant radiotherapy and chemotherapy	28 (23.1%)
Neoadjuvant radiotherapy	54 (44.6%)
Myasthenia gravis (%)	
No	449 (89.4%)
Yes	53 (10.6%)
Survival time (months)	
Range	27.7–136.2
Median [interquartile range]	88.45 [73.50–101.80]

Relationship between Tumor Volume and Recurrence

The effect of tumor volume on thymoma recurrence at different Masaoka-Koga stages was explored using ROC curves (Fig. 2). For thymoma at stage I, the AUC was 0.718 (95% confidence interval [CI]: 0.590–0.846, $p = 0.001$), the optimal cutoff value for tumor recurrence was 47.9 cm^3, and the sensitivity and specificity were 54.5% and 89.7%, respectively; For stage II, the AUC was 0.740 (95% confidence interval [CI]: 0.541–0.939, $p = 0.014$), the optimal cutoff value for tumor recurrence was 53.7 cm^3, and the sensitivity and specificity were 80.0% and 73.7%, respectively; For stage III, the AUC was 0.798 (95% confidence interval [CI]: 0.635–0.960, $p = 0.014$), the optimal cutoff value for tumor recurrence was 76.35 cm^3, and the sensitivity and specificity were 85.7% and 80.6%, respectively; As for stage IVa/IVb, the AUC was 0.804 (95% confidence interval [CI]: 0.637–1.000, $p = 0.015$), and the optimal cutoff value for tumor recurrence was 89.05 cm^3, with a sensitivity and specificity of 83.3% and 77.8%, respectively. In total, the AUC was 0.743 (95% confidence interval [CI]: 0.657–0.828, $p < 0.001$), the optimal cutoff value for tumor recurrence was 53.7 cm^3, and the sensitivity and specificity were 68.9% and 76.6%, respectively (Table 2).

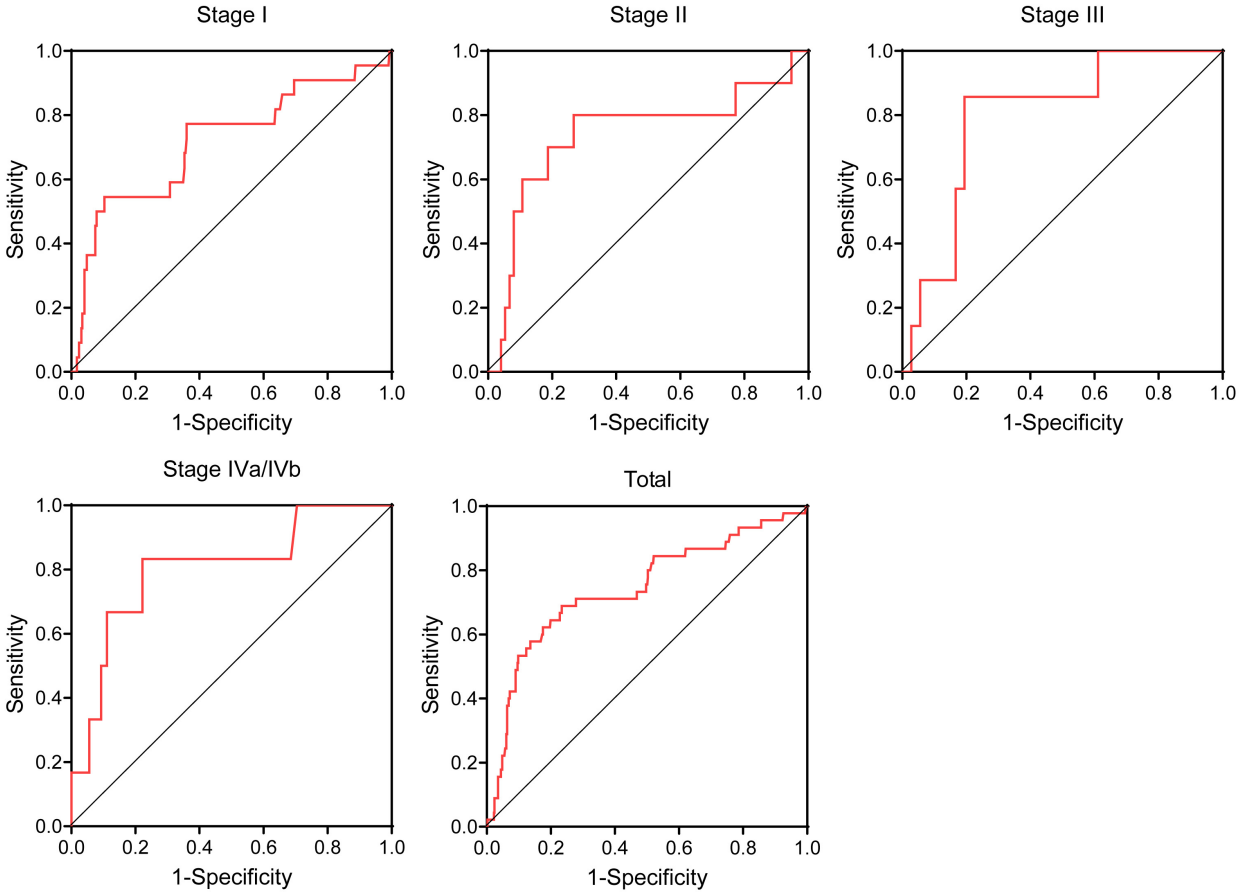

Fig. 2. ROC curves to analyze the relationship between tumor volume and recurrence of thymoma at different Masaoka-Koga stages. ROC, receiver operating characteristic.

Table 2. Results of ROC curve analysis.

	AUC	95% CI	*p*	Sensitivity (%)	Specificity (%)	Optimal cutoff value
I	0.718	0.590–0.846	0.001	54.5	89.7	47.90
II	0.740	0.541–0.939	0.014	80.0	73.7	53.70
III	0.798	0.635–0.960	0.014	85.7	80.6	76.35
IVa/IVb	0.804	0.637–1.000	0.015	83.3	77.8	89.05
Total	0.743	0.657–0.828	0.000	68.9	76.6	53.70

Abbreviations: ROC, receiver operating characteristic; AUC, the area under the curve; CI, confidence interval.

Survival and Recurrence of Thymoma Patients during the Follow-Up Period

As shown in Table 3, 22 deaths were reported during the follow-up period. The 3-year, 5-year and 10-year overall survival rates were 99.6%, 98.5% and 82.9%, respectively. During the follow-up period, 45 cases were recurrent, of which 12 were localized mediastinal recurrences. Because of the disease recurrence, 15 patients underwent re-excision of tumor, of which 6 had pleural metastases and 9 had mediastinal disease. Notably, there were 4 patients with recurrence underwent more than one re-excision, and one of them underwent pneumonectomy.

Survival Curves and Univariate Cox Proportional Hazards Model Analysis for Two Groups of Patients in Each Subcohort

As shown in Fig. 3, the patients in each subcort were grouped depending on the tumor volume cutoff values obtained from ROC curve analysis (stage I: 47.90; Stage II: 53.70; Stage III: 76.35; stage IVa/IVb: 89.05). Kaplan–Meier survival curves enabled obtaining the survival rates were obtained. Statistically significant differences in survival were found between the tumor volume greater than the cutoff value and that less than the cutoff value in the stage I ($p < 0.001$), stage II ($p < 0.001$), stage III ($p < 0.001$), and stage IVa/IVb ($p < 0.001$) subcohorts. As shown in Table 4,

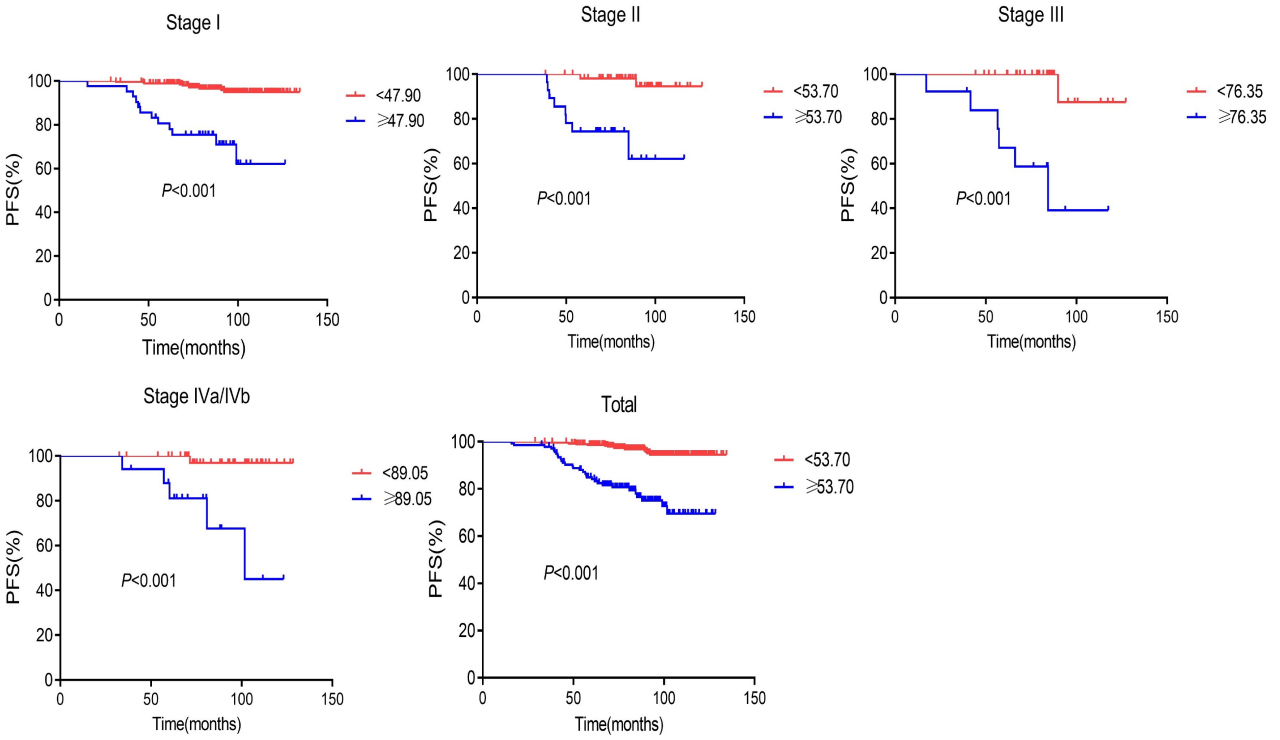

Fig. 3. Postoperative recurrence-free survival in two groups of each subcohort grouped by tumor volume.

Table 3. Patient survival and recurrence during the follow-up period.

Included patients	502
Overall survival rates	
Deaths	22
3-year (%)	99.6%
5-year (%)	98.5%
10-year (%)	82.9%
Recurrence	
Cases	45
Localized mediastinal recurrence	12
Re-excision	15
Pleural metastasis	6
Mediastinal disease	9
Multiple re-excision	4
Pneumonectomy	1

Table 4. Results of the univariate Cox proportional hazards model analysis for tumor volume.

	p value	Hazard ratio	95% CI
Stage I	< 0.001	11.620	3.082–43.820
Stage II	0.055	8.719	0.953–79.751
Stage III	0.065	7.961	0.882–71.844
Stage IVa/IVb	0.358	298.859	0.002–56935315.140
Total	< 0.001	6.981	2.729–17.857

Abbreviations: CI, confidence interval.

a univariate Cox proportional hazards model was applied for tumor volume. The hazard ratio (HR) was 11.620 (95% confidence interval [CI]: 3.082–43.820, $p < 0.001$) in the stage I, 8.719 (95% confidence interval [CI]: 0.953–79.751, $p = 0.055$) in the stage II, 7.961 (95% confidence interval [CI]: 0.882–71.844, $p = 0.065$) in the stage III, and 298.859 (95% confidence interval [CI]: 0.002–56935315.140, $p = 0.358$) in the stage IVa/IVb. In terms of the whole cohort, the HR was 6.981 (95% confidence interval [CI]: 2.729–17.857, $p < 0.001$). These results suggest that tumor volume is significantly associated with the prognosis of patients with thymoma undergoing total thymectomy and may serve as an independent risk factor for predicting postoperative recurrence.

Discussion

Thymoma is a relatively rare tumor with low prevalence. So far, there are fewer clinical studies related to thymoma compared with other common tumors. A focused investigation of risk variables linked to thymoma prognosis and recurrence would be of considerable value to enhance the clinical assessment system for thymoma and improve the outcome of thymoma patients. The present study adopted a measurement method proposed earlier, in which the tumor volume was semi-automatically measured using a modified version of the "Watchin GGO" software by tracing the contour around the outer edge of the tumor on CT images, and the tumor volume reflected the size of the thy-

moma [17]. Prior research estimated the size of thymoma mainly by measuring the maximum diameter on CT or magnetic resonance imaging (MRI) 2D images. Unfortunately, the maximal diameter alone may not be accurate, because thymomas can vary greatly in shape [22]. Compared with previous studies, the study can assess the size of thymoma more accurately and largely avoid the impact of measurement errors on the results.

To further explore the association between the thymoma size and the prognosis of thymoma, the entire cohort was divided into four subcohorts (stage I, II, III, and IVa/IVb cohorts) according to the Masaoka-Koga staging system, and patients in each subcohort were artificially divided into two groups (tumor volume greater than the cutoff value and tumor volume less than the cutoff value) based on the cutoff value obtained from the ROC curve analysis. Moreover, the difference in survival between each two groups was examined. The study showed that in the whole cohort, the recurrence rate during the follow-up period was much higher in thymoma patients with tumor volume greater than 53.7 cm^3 than in those with tumor volume less than 53.7 cm^3. In each subcohort, the thymoma volume was significantly associated with the recurrence rate of thymoma at Masaoka-Koga stage I, which was also an independent risk factor for the prognosis of thymoma at Masaoka-Koga stage I.

The present study is, to the authors' knowledge, the first study to do so. Another study [14] also concluded that tumor volume was an independent risk factor for predicting prognosis in thymoma by survival curve analysis, but it plotted survival curves depending on tumor stage (i.e., one group for stage I and II and another group for stage III and IV). By comparison, it was found that the method tried in this study could better avoid the effect of confounding factors (e.g., the degree of invasion of peripheral organs and the occurrence of distant metastases) other than tumor volume on survival, suggesting this study was more accurate in predicting the prognosis.

The clinical significance of this study lies in the identification of four cutoff values (stage I: 47.90 cm^3, stage II: 53.70 cm^3, stage III: 76.35 cm^3, and stage IVa/IVb: 89.05 cm^3) that can be used to guide clinical practice. Based on the results of this study, clinicians could pay attention to their stages and types when treating patients with thymoma in addition to whether their tumor volume exceeds these cutoff values. If this threshold is exceeded, they must be very aware of the likelihood of tumor recurrence following total thymectomy, and other patient factors must be considered when deciding whether to administer adjuvant therapy in advance to stop tumor recurrence.

In the entire cohort, the study found that the tumor volume greater than 53.70 cm^3 was significantly linked to thymoma recurrence. This value was generally consistent with the 4.0 cm and 5.0 cm cutoff values proposed in two previous studies [15,16], as projected by the uniform spherical volume formula. Hence, the findings of this study have a high degree of reliability. This study does have certain restrictions, though. This study is a single-center retrospective study. Therefore, future validation of the findings may require a prospective cohort study including several centers.

Conclusions

This retrospective analysis revealed a correlation between thymoma volume and risk of recurrence of thymoma patients after total thymectomy. Cutoff values for tumor volume at different stages were obtained. These findings may contribute to thymoma clinical evaluation system improvement and offer a fresh viewpoint for predicting the prognosis of thymoma patients, subject to further prospective multi-center studies.

Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding author upon request.

Author Contributions

GC and HY—contributions to conception and design; HY and GC—been involved in drafting the manuscript and revising it critically for important intellectual content; LZ, YT and JD—made substantial contributions to acquisition of data; LZ, YT and JD—analysis and interpretation of data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Zhongshan hospital, Fudan University (B2022-156).

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Conflict of Interest

The authors declare no conflict of interest.

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