


# Prognostic value of tumor size in thymic epithelial tumors

## A systematic review and meta-analysis

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### Abstract

**Background:** Whether the size of thymic epithelial tumors (TETs) has an impact on prognosis has long been a controversial issue. Our study was designed to investigate the value of tumor size in the prognosis (overall survival (OS) and relapse-free survival) of patients with TETs.

**Methods:** We searched the databases such as PubMed, EMBASE, Web of Science, and clinical trials registration system for articles illustrating the impact of tumor size on survival data in TETs patients. We did a meta-analysis for OS and relapse-free survival.

**Results:** We recruited 9 studies in our meta-analysis. Our study illustrates that TETs patients with small tumor size had better relapse-free survival (hazard ratio = 1.66, 95% confidence interval 1.18–2.35,  $P = .004$ ) and OS (hazard ratio = 1.93, 95% confidence interval 1.30–2.80,  $P = .001$ ) in comparison to patients with large tumor size.

**Conclusions:** In conclusion, the results of our meta-analysis showed that TET size was significantly associated with overall and relapse-free survival of patients, with relatively small tumors tending to have a better prognosis.

**Abbreviations:** CI = confidence interval, HR = hazard ratio, OS = overall survival, RFS = relapse-free survival, TC = thymic carcinomas, TETs = thymic epithelial tumors, TNM = tumor node metastasis.

**Keywords:** prognosis, TETs, thymic carcinoma, thymic epithelial tumors, thymoma, tumor size

## 1. Introduction

Thymic epithelial tumors (TETs) are a relatively rare group of tumors usually located in the anterior mediastinum.<sup>[1]</sup> Based on the US Surveillance, Epidemiology and End Results Database, the incidence of TETs in North America is 2.14 per 1 million and 3.74 per 1 million in the Asian population.<sup>[2]</sup> TETs mainly consist of thymomas and thymic carcinomas (TCs). Unlike other tumors, the benign or malignant nature of TETs cannot be determined only by the characteristics of histology, but also by the surrounding invasion or dissemination to adjacent organs; the local recurrence after surgery is also inevitable in some TETs with invasive nature, based on the understanding so far, all TETs are currently considered to be potentially malignant.<sup>[3]</sup>

Currently, Masaoka–Koga staging<sup>[4,5]</sup> and tumor node metastasis (TNM) staging<sup>[4]</sup> are commonly used clinically to determine the extent and prognosis of TETs. In 1981, Masaoka et al<sup>[6]</sup> proposed a 4-stage Masaoka staging system after analyzing 93 patients. Koga et al<sup>[5]</sup> revised the Masaoka

staging after analyzing 79 patients and the revised staging system named Masaoka–Koga staging has been widely used. The TNM staging system for TETs was adopted by the Union for International Cancer Control in 2016. In 2017, the American Joint Committee on Cancer also released a new TNM staging system for TETs, and it was officially launched in 2018. The International Lung Cancer Association and International Thymic Malignancy Interest Group propose that the TNM staging system should be used alongside the Masaoka–Koga staging system for thymic tumors. Furthermore, all of classification and staging systems are relevant to the prognosis of patients with TETs.<sup>[7]</sup>

Neither the Masaoka–Koga staging system, nor the TNM staging system includes tumor size as a parameter. But it is debated whether the size of the tumor has an impact on the prognosis of patients with TETs.<sup>[8]</sup> The tumor size of TETs, as an indicator readily available in clinical practice through imaging or surgical specimens, is usually of greater concern to us in terms of its impact on surgical operations or radiotherapy procedures

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All data generated or analyzed during this study are included in this published article.

Meta-analysis does not require ethical statement.

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and is not routinely used to assess patient prognosis because of controversy. Some studies have shown a correlation between tumor size and patient overall survival (OS)<sup>[8–10]</sup> and relapse-free survival (RFS).<sup>[8,11–13]</sup> But other studies have shown no relationship between tumor size and OS<sup>[11,12,14–16]</sup> or RFS.<sup>[10,15]</sup> TETs are a relatively rare disease and previous studies have often suffered from an insufficient amount of data. There is also no meta-analysis to examine the effect of tumor size on patient prognosis (including OS and RFS) in TETs. So, we used a meta-analysis to investigate the value of tumor size in determining patient prognosis by summarizing data from previous studies.

## 2. Materials and methods

### 2.1. Literature search

Two researchers independently conducted systematic literature searches of the following databases: PubMed, EMBASE, Web of Science, and clinical trials registration system. Studies of TET size and patient prognosis published before 21 May 2022 were retrieved using the following search terms: TET, thymoma, TC, tumor, tumor size, neoplasm, RFS and OS. References from eligible studies were also perused for potential studies.

### 2.2. Inclusion criteria

Studies that meet the following criteria are considered eligible: Provide follow-up results for long-term survival: OS or RFS or sufficient data are provided to calculate these follow-up outcomes; studies directly include hazard ratios (HR) with 95% confidence intervals (CI) or these data can be derived from the original study; The type of tumor is consistent with a clear clinical diagnosis or pathological diagnosis; Tumor size is determined by imaging or surgical specimens.

### 2.3. Exclusion criteria

Studies with the following were excluded. No cutoff value was set for tumor size in the analysis of the relationship between tumor size and prognosis; Study of data duplication.

### 2.4. Extraction of study results

An independent study by 2 researchers based on the Cochrane Handbook for Systematic Reviews of Interventions Version 6.3, 2022 for data extraction. When the 2 researchers agree on what they have extracted from each other, the data are saved, and if there is disagreement, a third researcher steps in. The following data will be extracted; first author, country, year of publication, study design, duration of patients included, number of patients, age, gender composition, duration of follow-up, tumor type, treatment regimen, cutoff values for tumor size, and survival outcome. If both univariate and multivariate results are available, we prefer the results of the multivariate analysis.

### 2.5. Quality assessment

We used the Newcastle-Ottawa Scale<sup>[17]</sup> to rate the quality of all studies that could be included, and we considered a study to be of high quality when it had a score greater than 6.

### 2.6. Statistical analysis

We followed PRISMA guidelines to complete this study, and registered this meta-analysis in advance on the PROSPERO (CRD42022334366). Prognostic outcomes including OS and RFS were the primary endpoints of this meta-analysis. Pool HR values with 95% CIs to assess the value of tumor size in determining the prognosis (OS and RFS) of TETs patients. Fixed effects models were

used to analyze when the results of all studies combined were either low ( $I^2 < 25\%$ ) or moderate heterogeneity ( $I^2 = 25\% - 50\%$ ),<sup>[18]</sup> when significant heterogeneity ( $I^2 > 50\%$ ) was observed, a random-effects model was used to analyze.<sup>[19]</sup> We used Begg's test to quantify the presence of publication bias. If there is publication bias, we use the cut-and-patch method to verify that the conclusions are robust. In order to judge the robustness of our conclusions, we performed a sensitivity analysis by excluding each study on an item-by-item basis. All data analysis was carried out using STATA 12.0.

## 3. Results

### 3.1. Characteristics of eligible studies

After screening by our inclusion and exclusion criteria, a total of 9 studies<sup>[8–16]</sup> were selected for inclusion in our meta-analysis included 5246 patients (Fig. 1). The study characteristics of the 9 recruited articles are summarized in Table 1. HRs with 95% CIs regarding tumor size on OS could be obtained from 8 studies<sup>[8–12,14–16]</sup> directly and HRs with 95% CIs regarding tumor size on RFS could be obtained from 6 studies<sup>[8,10–13,15]</sup> directly. Of the 9 studies we included, the study by Liu et al<sup>[14]</sup> was only on TC, the study by Okumura et al<sup>[13]</sup> was only on thymoma, and the other 7 studies were on TETs (both thymoma and TC).

### 3.2. Prognostic impact of tumor size on OS

A total of 8 studies<sup>[8–12,14–16]</sup> explored the relationship between tumor size and patient OS included 3163 patients. Pooled results (Fig. 2) show that patients' relatively smaller tumor size is associated with better OS (HR = 1.93, 95% CI 1.30–2.80,  $P = .001$ ), with moderate heterogeneity ( $I^2 = 61.6\%$ ,  $P = .011$ ). Based on the results of the meta-analysis, we concluded that there was a significant association between tumor size and OS, with larger tumor size predicted to represent a worse OS. We performed a subgroup analysis (Table 2) of the relationship between tumor size and OS. We observed that in these studies with single centers or sample sizes of less than 180 samples, the pooled results were negative i.e. there was no relationship between tumor size and prognosis. And these single-center studies and studies with sample sizes less than 180 coincide with the same cohort of studies. It is possible that the small sample size and the single source of patients in these single-center studies led to negative results.

### 3.3. Prognostic impact of tumor size on RFS

A total of 6 studies<sup>[8,10–13,15]</sup> explored the relationship between tumor size and patient RFS included 3670 patients. Pooled result (Fig. 3) show that patients' relatively smaller tumor size is associated with better RFS (HR = 1.66, 95% CI 1.18–2.35,  $P = .004$ ), with moderate heterogeneity ( $I^2 = 82.7\%$ ,  $P = .000$ ). Based on the results of the meta-analysis we concluded that there was a significant association between tumor size and RFS, with larger tumor size predicted to represent a worse RFS. We performed a subgroup analysis of the relationship between tumor size and RFS. Due to only 6 studies that included RFS results, we only conducted subgroup analyses (Table 3) by sample size and tumor size cutoff value. When we pool the HRs of 4 studies with sample sizes less than 200, we obtained negative results, this result may be due to statistical bias caused by the small sample size of these studies. These 4 studies with sample sizes of less than 200 may also be an important source of heterogeneity. When we pool the HRs of 3 studies with tumor size cutoff value  $> 5$  cm, we also obtained negative results. This suggests that a cutoff value of  $\leq 5$  cm for tumor size may be reasonable when studying the relationship between tumor size and prognosis. This is consistent with the previous findings of Fukui et al<sup>[16]</sup> who observed in their study that RFS was most appropriate for the study patients when the cutoff value for tumor size was set at 3.5 cm.

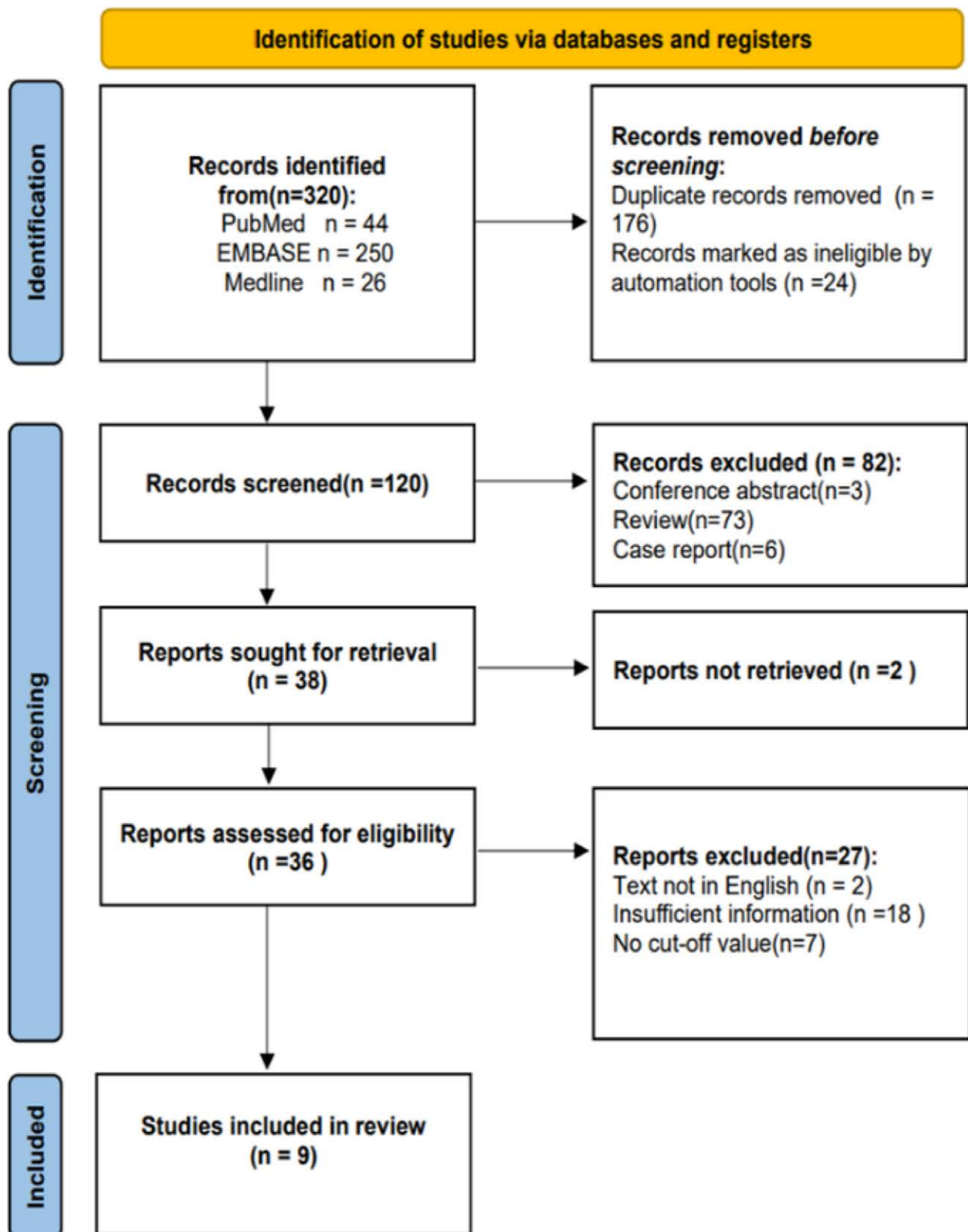


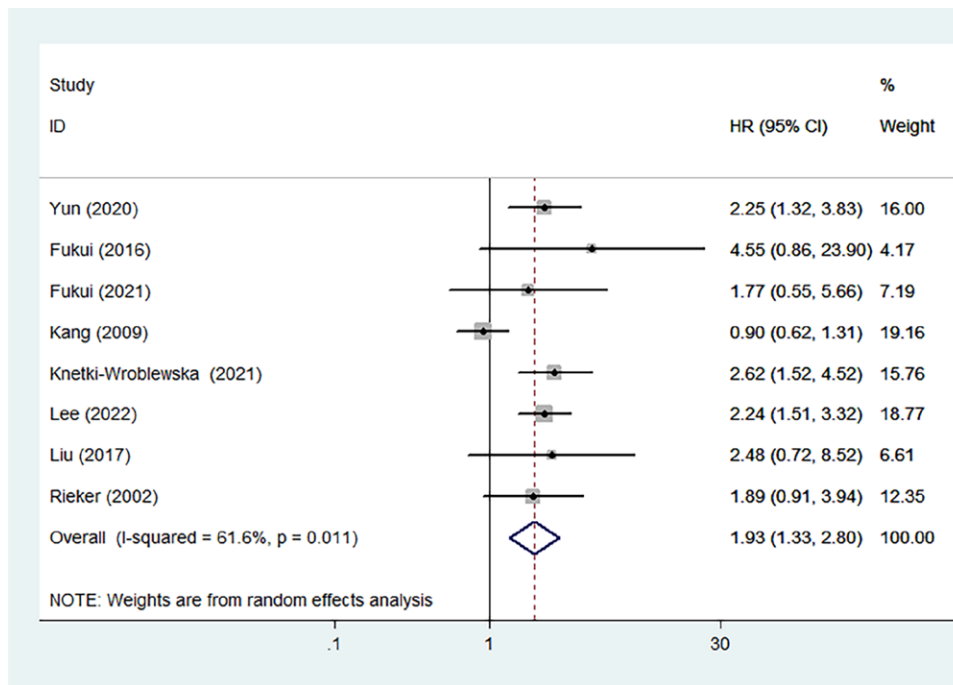
Figure 1. Flow diagram of literature review.

#### 3.4. Sensitivity analysis and publication bias

We performed a sensitivity analysis (Fig. 4) of the relationship between tumor size and OS and RFS, retrospectively. The results proved that our conclusions were robust. The results obtained were tested separately for publication bias using the Begg's test. No significant publication bias was found (all  $P > .05$ ).

#### 4. Discussion

Meta-analysis provides a way to increase statistical power and resolves inconsistencies. We have concluded by means of a meta-analysis that tumor size in TETs correlates with both OS and RFS. The results of our meta-analysis showed that TET size was significantly associated with overall and RFS of



**Figure 2.** Forest plots of comparison between large versus small tumor size in thymic epithelial tumors patients. In this illustration of statistical results, squares represent hazard ratio (HR). The overall impact of tumor size on overall survival (OS).

**Table 2**

**Subgroup analyses of the associations between tumor size and OS.**

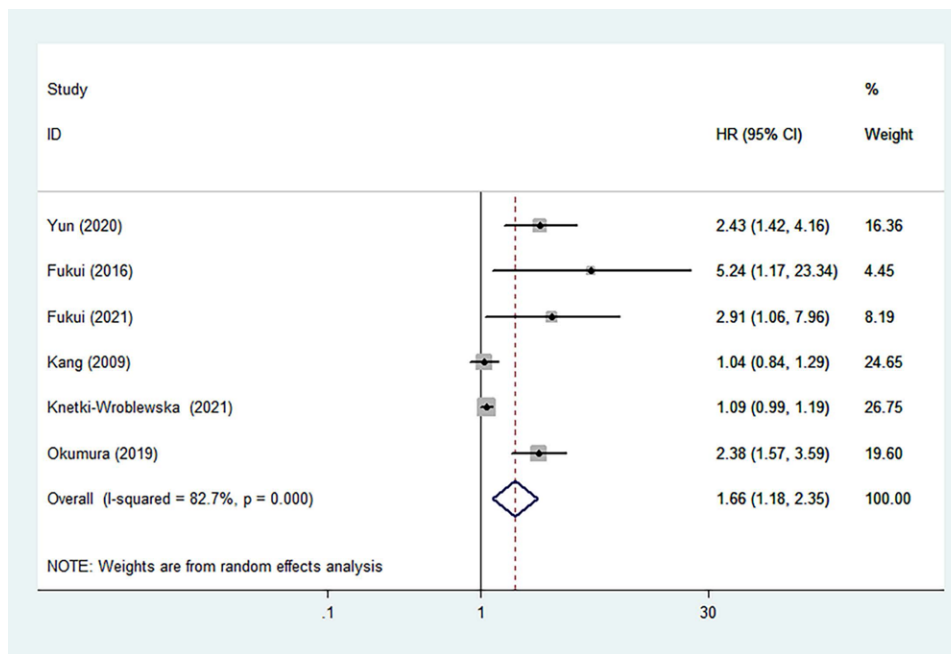
Subgroup	No. of studies	HR (95% CI)	P	Heterogeneity		Model
				I <sup>2</sup> (%)	Ph	
Aera						
Asian	6	1.84 (1.13–2.98)	.014	67.7	0.009	Random
Non-Asian	2	2.33 (1.51–3.62)	0	0	0.484	Fixed
Sample size						
>180	4	2.27 (1.76–2.94)	0	0	0.916	Fixed
<180	4	1.60 (0.78–3.32)	.201	51.8	0.101	Random
Tumor size cutoff						
>6 cm	4	1.74 (1.01–3.01)	.046	80.3	0.002	Random
<6 cm	4	2.31 (1.50–3.57)	0	0	0.834	Fixed
Study design						
Multicenter	4	2.27 (1.76–2.94)	0	0	0.916	Fixed
Single center	4	1.60 (0.78–3.32)	.201	51.8	0.101	Random

CI = confidence interval, HR = hazard ratio, OS = overall survival.

patients, with relatively small tumors tending to have a better prognosis.

The impact of tumor size on the prognosis of TETs has been controversial in previous studies. In 2014, Thymic Domain of the Staging and Prognostic Factors Committee used the International Thymic Malignancy Interest Group global database to examine the likelihood of tumor size as a factor in determining T classification, when data from 5796 patients were analyzed, other staging characteristics dominated the group by prognosis, with tumor size playing only a minor role, lagging far behind all other factors.<sup>[20]</sup> However, the current study and other retrospective studies challenge these findings and suggest that size can be used to predict OS and RFS.<sup>[8,11,21–23]</sup> And in 2019, the Japanese Association for Research of the Thymus used a compiled retrospective database of treated cases nationwide from 1991 to 2010 to examine the importance of tumor size on patient prognosis, this retrospective study, which included a sample of 2083 cases, ultimately concluded that tumor size

was an independent determinant of RFS and disease-specific survival.<sup>[13]</sup> Liou et al<sup>[22]</sup> retrospectively examined 1849 patients with Masaoka-stage I–III thymoma who underwent surgical resection in the US National Cancer Database from 2006 to 2013 and found that tumor size ≥ 8cm was associated with poor survival. Similarly, a Korean multicenter study of 1215 patients with TETs published in 2020 showed a significant effect of tumor size on overall survival and RFS in patients with limited stage (M-K stage I or II or TNM stage I).<sup>[8]</sup> In a multicenter study published in 2022, Safieddine et al retrospectively analyzed 1298 patients with TETs and showed that tumor size was associated with overall survival and freedom from recurrence in patients who have undergone R0 resection.<sup>[9]</sup> After 2014, these published clinical studies containing large samples have demonstrated that tumor size correlates with the prognosis of patients with TETs. So, we believe that the prognostic significance of tumor size in TET has not been fully assessed and we need more robust studies to explore the prognostic value of tumor size.

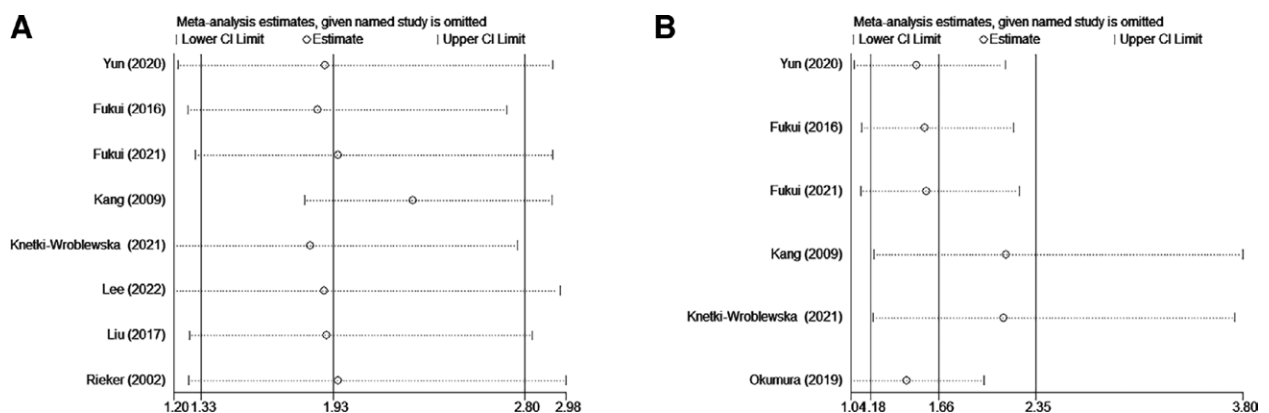


**Figure 3.** Forest plots of comparison between large versus small tumor size in thymic epithelial tumors patients. In this illustration of statistical results, squares represent hazard ratio (HR). The overall impact of tumor size on relapse-free survival (RFS).

**Table 3**  
**Subgroup analyses of the associations between tumor size and RFS.**

Subgroup	No. of studies	HR (95% CI)	P	Heterogeneity		Model
				I <sup>2</sup> (%)	Ph	
Sample size						
>200	2	2.40 (1.73–3.33)	0	0	0.951	Fixed
<200	4	1.19 (0.91–1.55)	.2	62.8	0.045	Random
Tumor size cutoff						
>5 cm	3	1.22 (0.93–1.61)	.147	76.8	0.013	Random
≤5 cm	3	2.57 (1.77–3.71)	0	0	0.587	Fixed

CI = confidence interval, HR = hazard ratio, RFS = relapse-free survival.



**Figure 4.** Sensitivity analysis for the association between tumor size and (A) overall survival (OS) and (B) relapse-free survival (RFS).

From a clinical practice perspective, size can also have a direct impact on surgical outcomes. Almost all reports on the surgical management of TETs indicate that complete resection is an independent prognostic factor for patients with TETs. Larger tumors, where a more difficult R0 resection may exist, are also an important factor contributing to poor prognosis.<sup>[14]</sup> Moreover, larger tumors tend to have higher blood loss during

surgery and an increased need for blood transfusions, which may contribute to worse tumor outcomes through transfusion-related immune modulation.<sup>[24]</sup> Larger sized tumors also usually imply a relatively delayed diagnosis and therefore a higher likelihood of association with other adverse factors and often a poorer prognosis.<sup>[25]</sup> From an oncological perspective, relatively large tumors, which tend to represent greater tumor

**Table 1**  
Study characteristics of studies investigating the prognostic relevance of tumor size.

Study	Year	Country	Duration	Study type	Study design	Sample size	Age	Gender (F/M)	Follow-up (mo)	Cancer type	Treatment	Tumor size cutoff (cm)	Survival outcome	Analysis	Newcastle-Ottawa Scale
Yun <sup>[8]</sup>	2020	Korea	2000–2013	Retrospective	Multicenter	1033	51.4 ± 13.0	582/633	Median 64.5 Mean 45	Thymic epithelial tumors	S + C + R	5.5	OS, RFS	M/M	9
Fukui <sup>[12]</sup>	2016	Japan	2001–2014	Retrospective	Single center	154	Median 61	70/84	Mean 45	thymic epithelial tumors	S	OS:5.5/ RFS:4.0	OS, RFS	M/M	8
Fukui <sup>[11]</sup>	2021	Japan	2001–2016	Retrospective	Single center	153	Median 62	69/84	Mean 58	Thymic epithelial tumors	S	5	OS, RFS	U/U	8
Kang <sup>[14]</sup>	2009	Korea	1995–2006	Retrospective	Single center	59	Mean 54	25/34	Mean 42	Thymic epithelial tumors	S + C + R	6.5	OS, RFS	M/M	8
Knetki-Wróblewska <sup>[10]</sup>	2021	Poland	1995–2015	Retrospective	Multicenter	188	Mean 54.3	96/92	132	Thymic epithelial tumors	S + C + R	11	OS, RFS	U/M	9
Lee <sup>[9]</sup>	2022	Korea	2000–2013	Retrospective	Multicenter	1298	Mean 51	671/681	Median 52.3	thymic epithelial tumors	S + C + R	6.5	OS	M/M	8
Liu <sup>[15]</sup>	2017	China	1996–2014	Retrospective	Single center	60	Median 50	19/41	Mean 73.3	Thymic carcinoma	S + C + R	5	OS	M/U	7
Okumura <sup>[3]</sup>	2019	Japan	1991–2010	Retrospective	Multicenter	2083	Mean 57	1130/951	NA	Thymoma	S + C + R	8	RFS	M/M	8
Rieker <sup>[16]</sup>	2002	Germany	1967–1998	Retrospective	Multicenter	218	Median 50	118/100	Mean 74	Thymic epithelial tumors	S + R	8	OS	M	7

C = Chemotherapy, CI = confidence interval, HR = hazard ratio, M = multivariate analysis, NA = not available, OS = overall survival, R = radiotherapy, RFS = relapse-free survival, S = Surgical treatments, U = univariate analysis.

aggressiveness and a higher tumor proliferation index, may have a more unfavorable tumor biological behavior.<sup>[26]</sup>

Tumor size is a readily available indicator and with advances in imaging technology, it can now be measured accurately with little variation in results between observers. In general, larger tumors in patients with malignancies are associated with poor prognosis and has been demonstrated in solid tumors such as lung, kidney, breast, and stomach cancers.<sup>[27–30]</sup> Thinking in terms of the biological behavior of tumors, the larger tumor size may reflect the potentially more aggressive biology of the tumor, Study have shown that tumor necrosis is positively correlated with tumor size, and tumor necrosis often represents a poorer prognosis.<sup>[31]</sup> Larger tumors are often associated with nerve invasion leading to impaired lung function, which is detrimental to the patient’s prognosis.<sup>[32]</sup> It has also been shown that phrenic nerve involvement increases the recurrence rate of TETs.<sup>[33]</sup> These factors may all contribute to the poorer prognosis of patients with larger tumors.

Currently, TET size also faces significant challenges in its clinical application as a prognostic parameter. In previous studies on tumor size and prognosis, as shown in Table 1, there is no relatively uniform cutoff value for size. Multiple cutoff values limit its clinical usefulness. And study have shown that different cutoff values should also be used for the determination of different prognostic indicators.<sup>[12]</sup> This suggests that in future studies, more precise cutoff values should be set for different prognostic indicators. It has also been argued that one-dimensional measurements do not objectively reflect tumor size and therefore the use of the tumor maximum area<sup>[34]</sup> or a better index has been proposed for evaluation.<sup>[35]</sup> This is really something we should work on, and with the development of imaging technology, we should try to use higher dimensional data in the future to give a more objective picture of tumor size. However, at present, most of our databases only have one-dimensional data, so they do not objectively reflect the size of the tumor and may cause some bias.

There are many limitations to our study: First, many of the original studies, which analyzed thymoma and TC under the broad category of TETs, were inherently heterogeneous. This is because limited-stage thymomas tend to progress slowly and have better survival rates, whereas TCs have poorer survival rates. Second, not all survival analyses used multivariate analysis. Therefore, there may be some confounding factors. Fourth, in our meta-analysis, the cutoff values for tumor size were relatively variable, which significantly increased clinical heterogeneity.

### 5. Conclusion

In conclusion, the results of our meta-analysis showed that TET size was significantly associated with overall and RFS of patients, with relatively small tumors tending to have a better prognosis. More well-designed studies are urgently needed to validate our findings.

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### Author contributions

Wei Liu designed the study, Yifeng Shao and Mingbo Tang collected the data, Linan Fang did the data analysis, and Yifeng Shao wrote the first version of the manuscript. All the other authors review the original draft.

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**Validation:** Linan Fang, Shixiong Wei.

**Writing – original draft:** Yifeng Shao.

**Writing – review & editing:** Mingbo Tang, Shixiong Wei, Xinliang Gao.

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