Comparing the safety and efficacy of thoracoscopic surgery and thoracotomy for thymoma: a systematic review and meta-analysis

Ling Lv[1], Wenya Li[1], Wanfu Men[1], Zhenghua Liu[1], Chenggang Jiang[2]

[1]Department of Thoracic Surgery, The First Affiliated Hospital of China Medical University, Shenyang, China; [2]Department of Surgical Oncology and General Surgery, Key Laboratory of Precision Diagnosis and Treatment of Gastrointestinal Tumors, Ministry of Education, The First Affiliated Hospital of China Medical University, Shenyang, China

Contributions: (I) Conception and design: L Lv; (II) Administrative support: W Li; (III) Provision of study materials or patients: W Men; (IV) Collection and assembly of data: Z Liu; (V) Data analysis and interpretation: C Jiang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Chenggang Jiang. Department of Surgical Oncology and General Surgery, Key Laboratory of Precision Diagnosis and Treatment of Gastrointestinal Tumors, Ministry of Education, The First Affiliated Hospital of China Medical University, Shenyang 110001, China. Email: Jiangcg7516@163.com.

Background: To systematically evaluate the efficacy of thoracoscopic surgery compared to traditional thoracotomy for thymic tumors.

Methods: We performed a literature search on computer of the PubMed, Embase, Cochrane Library, Web of Science, China Biology Medicine (CBM), WanFang, and China national knowledge infrastructure (CNKI) databases from the date of establishment of the database to April 2021, and retrieved randomized controlled trials (RCTs) and cohort studies on thoracoscopic surgery and thoracotomy with conventional open thoracic surgery. After independent screening of the literature by two assessors, the relevant data was extracted and the risk of bias in the included studies was evaluated. RevMan 5.3 software was used to perform the analysis.

Results: Five RCTs and eight cohort studies were ultimately included, with a total of 1,093 patients. The results of meta-analysis showed that compared with traditional thoracoscopic surgery, thoracoscopy had shorter surgery duration (OR =22.2, 95% CI: –31.92, –12.52, P<0.00001), ICU stay (OR =0.29, 95% CI: 0.20, 0.42, P<0.00001), and hospitalization time (OR =0.531, 95% CI: 0.41, 0.69, P<0.00001) times, as well as reduced chest tube drainage time (OR =0.49, 95% CI: 0.33, 0.73, P=0.0004), less intraoperative bleeding (OR =43.27, 95% CI: –50.94, –35.60, P<0.00001), and a lower incidence of postoperative complications (OR =0.19, 95% CI: 0.11, 0.34, P<0.00001). However, the tumor recurrence rate was not significantly different between the two procedures (OR =0.69, 95% CI: 0.32, 1.48, P=0.34).

Discussion: The existing evidence suggests that thoracoscopic surgery has shorter surgery duration, ICU stay time, hospitalization time, reduced thoracic tube drainage, less intraoperative bleeding, and a lower incidence of postoperative complications compared with traditional thoracotomy surgery. However, due to the poor quality of the included research, more high-quality studies need to be conducted to verify the above conclusions.

Keywords: Thymoma; surgical treatment; retrospective study; curative effect; meta-analysis

Introduction

Thymoma is a common anterior mediastinal tumor originating in the thymic epithelium, accounting for approximately 20% of mediastinal tumors (1). National Cancer Institute statistics show a total population incidence of about 150/1,000, which is not statistically different between men and women. There are no special clinical symptoms in the early stage, and it is difficult for patients to perceive (2). They often observed during physical examination. In addition, thymoma often exists with paratumor syndrome, such as myasthenia gravis, erythrocyte aplastic anaemia alone, and hypopropyg lobulinemia, making the clinical disease more complex. As a potentially invasive tumor, treatment is preferred for thymoma, combined with postoperative radiotherapy or chemotherapy (3).

Thymomas are a group of mediastinal tumors derived from different thymic epithelial cells, with a total incidence of about 13/10 million. Despite its low overall incidence, it has exhibited a progressively increasing trend, and is the most common thoracic mediastinal tumor (4). At present, the most effective clinical treatment of thymoma is complete surgical resection. Traditional total thymectomy involves opening the sternum, resulting in considerable trauma and destruction of thoracic integrity as well as other postoperative complications. Meanwhile, thoracoscopic surgery [(video-assisted thoracoscopic surgery) VATS] offers reduced trauma and fewer complications; however, this procedure involves a limited intraoperative field, and resection of contralateral thymic and pericardial fat is not smooth (5).

With the continuous development of the thoracoscopic technique, thoracoscopic thymus dilatectomy has become one of the main surgical treatments for myasthenia gravis and thymoma (6). Compared with the traditional anterior median thoracotomy surgery, it has the characteristics of reduced surgical trauma, fast postoperative recovery, and less complications. At present, numerous surgical methods of thoracoscopic thoracectomy have been reported, including single and multiple operating holes through the right chest entrance, single and multiple operating holes through the left chest entrance, single and multiple operating holes through the sword protrusion, cervical chest double entry, robot surgery, etc. (7). However, there is no systematic evaluation method of myasthenia gravis surgery, and thus, the surgical approach and scope of thymectomy have become a particular research interest.

Gripp *et al.* (8) first reported improved symptoms following thymectomy in patients with myasthenia gravis. With the continuous development of surgical techniques, thymoma resection through the median sternum incision has become the standard surgical method for the thymus. Chao *et al.* (9) first performed thoracectomy, but the midmidmotomy was different from the right thoracic approach, and this operation could avoid opening the chest in patients with pleural adhesion or lung insufficiency, but only for benign lesions. In recent years, thoracoscopic right chest and transsword subthymic dilectomy has become a surgical treatment of myasthenia gravis, and is being gradually promoted. Compared with the traditional anterior median thoracotomy surgery, it has the characteristics of reduced trauma, faster postoperative recovery, and less postoperative complications (10). The surgical path of thymotomy is controversial, which is mainly reflected in laparoscopic surgery or thoracotomy. Some studies (10-12) have shown that there are differences in surgical effects in the treatment of malignant thymomas by surgical resection or lymph node dissection. Open heart surgery and thoracoscopy surgery is the surgical treatment of thymoma way, but how to choose operation method is to let the patients' families is difficult a problem, compared with the traditional open heart surgery, thoracoscope surgery is appearing in recent years, the rich clinical experience, though less open chest surgery, but thoracoscope surgery doesn't open chest, greatly reduce the patient's pain, Also can make the elderly and patients with increased tolerance of surgery in clinic is more popular than open heart surgery, but for patients with difficult to choose, especially in patients with malignant thymoma, experimenting with thoracoscope surgery, if it is found that the procedure is in violation of the principle of tumor therapy, should be timely to change professions open thoracic surgery, to remove the tumor cells.

The surgical path for thymectomy remains controversial. The classic traditional thymoma resection is median thoracectomy (TS transsternal thymectomy) (11). With the development of thoracoscopic technology in thoracic surgery, thoracoscopic surgery (VATS thymectomy) has been applied for resection. An increasing number of scholars in recent years have discussed the advantages and disadvantages of thymic thoracectomy and median thoracectomy; however, the results are inconsistent. Therefore, this study systematically evaluated the advantages and disadvantages of thoracoscopic surgery in thymomectomy in order to provide evidence for its clinical application. We present the following article in accordance

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with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/gs-21-786).

Methods

Inclusion and exclusion criteria

The inclusion criteria were as follows: (I) study type: randomized controlled trial (RCT) or cohort study; (II) patients clinically diagnosed with thyma (note: the nationality, race, and disease course of the study subjects was not limited); (III) intervention studies where the trial group underwent thoracoscopy and the control group received traditional thoracotomy surgery; (IV) studies with outcome indicators, including the operation time, time of stay, hospitalization time, amount of intraoperative bleeding, incidence of postoperative complications, and recurrence rate. The exclusion criteria were as follows: (I) non-Chinese/English literature; (II) repeatedly published documents; (III) studies with incomplete or missing analysis data

Search strategy

We performed a literature search of the PubMed, Embase, Cochrane Library, Web of Knowledge, CBM, WanFang, and CNKI databases from the date of establishment of the database to April 2021. We retrieved RCTs and cohort studies on thoracoscopic surgery and thoracotomy with traditional open thoracic surgery. In this study, Cochrane Library, PubMed, Web of Knowledge, Embase, CBM, CNKI, CQVIP and Wanfang were searched CECDB and other databases and related websites search. Subject words such as "Thoracoscopy", "VATS", "Thymus tumor" and so on. were retrieved as subject words and free words respectively. The literature retrieval scheme is shown in *Figure 1*.

Literature screening, data extraction, and risk of bias evaluation of included studies

Literature screening and data extraction were conducted and crosschecked independently by two evaluators. Differences between the two evaluators were resolved through discussion. Data extraction was performed using a predetermined data extraction table, which included the basic information of the included studies: study topic, author name, journal name, publication years, etc.; the basic characteristics of study subjects: cases, gender, age of each

group, specific details of intervention measures; the key factors of bias risk evaluation; and the outcome indicators and outcome measurement data of concern. The Cochrane risk of bias evaluation tool was used to evaluate the risk of bias of the included RCTs (8), while the risk of bias of the included cohort studies was evaluated using the Newcastle-Ottawa Scale (NOS).

Statistical analysis

Meta-analysis was performed using the RevMan 5.3 software (USA). The mean difference (MD) was used as the effect index, and odds ratio (OR) was used as the effect quantity. The point estimates and 95% CI are given for each effect quantity. The statistical heterogeneity between the study results (test level was $\alpha=0.1$) and the size of the heterogeneity was quantitatively determined combined with I^2. If there was no statistical heterogeneity between the studies, meta-analysis was performed using a fixed effects model. For significant clinical heterogeneity, meta-analysis was performed using a random effects model after excluding the sources of heterogeneity. If the results showed significant clinical heterogeneity, subgroup or sensitivity analyses were performed.

Heterogeneity analysis

Heterogeneity between studies was assessed using I^2 statistics, 25%, 50% and 75% representing low, medium and high heterogeneity, respectively, if $I^2<50\%$ and $P>0.1$ between studies using fixed effect models and if $I^2>50\%$ and $P<0.1$ from chi-square analysis showed study heterogeneity, Meta-analysis by random effects models and searched for possible heterogeneity by subgroup analysis source. The sensitivity analysis removed the included literature one by one to see whether the pooled effect values were stabled and reliabled.

Results

Results of the literature search

A total of 919 relevant documents were obtained in the preliminary search, including eight cohort studies, with a total of 1,093 patients (6-18). The CNKI, PubMed and Metetron databases were systematically searched from January 2010 to October 2021. Both Chinese and English search terms were used in the literature retrieval process.
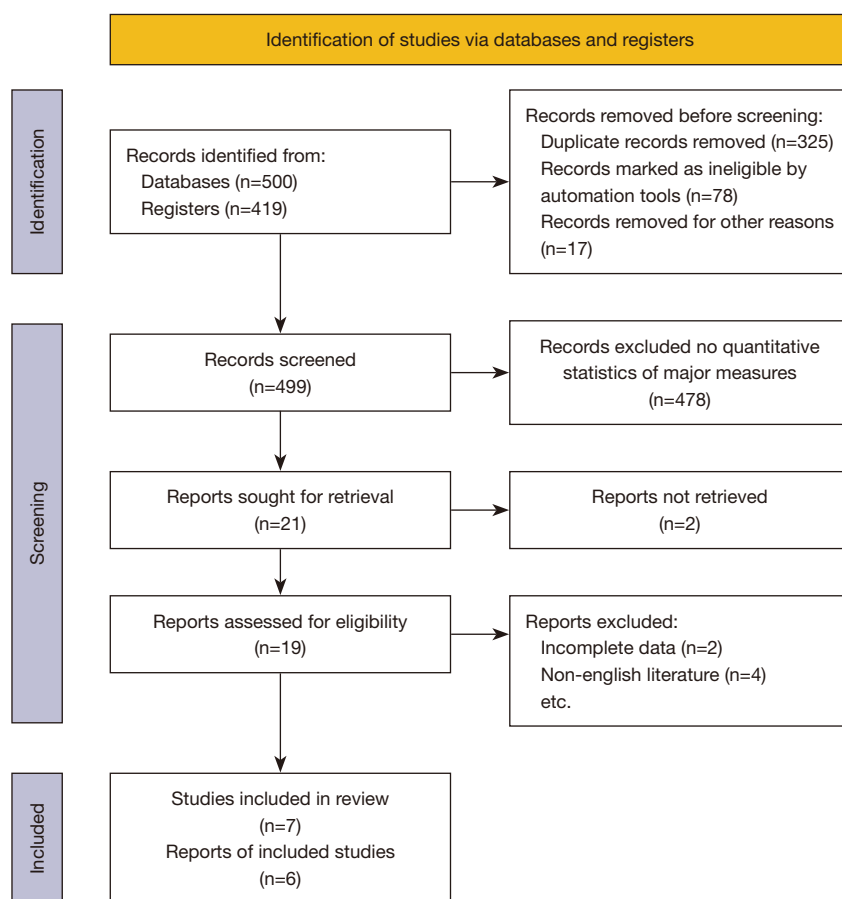
Figure 1 Literature screening process and results.

Literature retrieval was performed using a combination of subject and free words, and the references of relevant literature were manually searched after reading the full texts. The literature screening procedures and results are shown in *Figure 1*.

Basic characteristics of the included study and bias risk assessment results

Two researchers evaluated all of the included literature sequentially based on Cochran Literature Quality Evaluation Scale, and classified the bias risk level of each article as low risk, high risk, or uncertain risk. Data extraction included the following aspects: (I) general situation: author, group, gender, sample size, etc.; and (II) outcome index: operation time, estimated blood loss, days of hospitalization, transit chest opening rate, complications, etc. All of the studies we included were case-control studies;

therefore, for the risk of bias analysis, the NOS quality score was used, and all studies were found to be high-quality studies (NOS >7). Disagreements between the evaluators were resolved through discussion or no trilateral discussion settlement. The basic characteristics of the included studies are presented in *Table 1*.

Meta-analysis results

Operation time
All of the included studies reported on this outcome. Meta-analysis was performed using the random effects model, and the results showed that the operation time in the thoracoscopic group was significantly shorter than that in the open chest group, and the difference was statistically significant (OR =22.2, 95% CI: –31.92, –12.52, P<0.00001). The results of further subgroup analysis by study design showed that the operation time in the RCT subgroup was

Table 1 Basic characteristics of the included study

Study	Number (T/C)	Age (T/C, years)	Intervention		Outcome
			T	C	
Yanagiya 2019	41/41	53.32±5.14/54.63±6.64	Thoracoscopic surgery	Open chest surgery	a, b, c, d, e
Wright 2011	31/30	50.2±10.5/52.0±9.8	Thoracoscopic surgery	Open chest surgery	a, b, c, d, e
Gripp 1998	65/60	39±12	Thoracoscopic surgery	Open chest surgery	a, b, c, e
Chao 2015	46/46	67.52±4.43/68.63±7.64	Thoracoscopic surgery	Open chest surgery	a, b, c, d, e
Maniscalco 2015	62/62	37.78±3.06/38.24±2.12	Thoracoscopic surgery	Open chest surgery	a, b
Toker 2013	21/21	24.2±3.2/23.8±4.3	Thoracoscopic surgery	Open chest surgery	a, b, c, d, e
Weng 2020	62/58	38.4±9.2/39.2±8.1	Thoracoscopic surgery	Open chest surgery	a, b, c, d, e
Ma 2019	17/22	63.1±15.7/65.4 ±11.0	Thoracoscopic surgery	Open chest surgery	a, c, f
Liu 2021	22/18	51.9±14.2/51.1±13.2	Thoracoscopic surgery	Open chest surgery	a, c, f
Ried 2014	76/44	50.54±14.55/51.75±14.46	Thoracoscopic surgery	Open chest surgery	a, b, c
Ruffini 2011	15/12	51.4±16.0/50.9±15.0	Thoracoscopic surgery	Open chest surgery	a, b
Wang 2019	15/18	54.20 ±11.89/48.56±8.97	Thoracoscopic surgery	Open chest surgery	a, b, c, d, e, f
He 2013	49/44	51.3±13.4/50.9±14.8	Thoracoscopic surgery	Open chest surgery	c, d, f

T: test group; C: control group. a, Surgery time; b, Blood bleeding during; c, Length of hospital stay; d, Drainage time of the chest tube; e, Postoperative complications; f, ICU time.
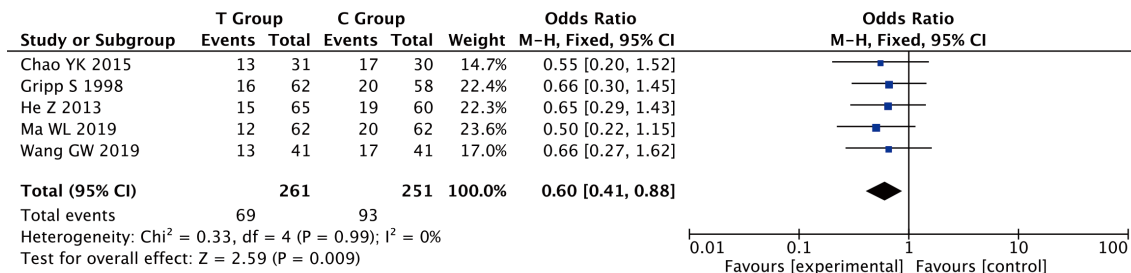
Figure 2 Meta-analysis of surgery time between thoracoscopy and thoracotomy groups.

significantly shorter than that in the thoracotomy group (OR =0.60, 95% CI: 0.41, 0.88, P=0.009) (*Figure 2*).

ICU time
Only eight cohort studies were included. Meta-analysis was performed using the fixed effects model, and the results showed that the ICU time in the thoracoscopic group was significantly shorter than that in the open chest group, and the difference was statistically significant (OR =0.29, 95% CI: 0.20, 0.42, P<0.00001) (*Figure 3*).

Hospital stay
Hospital stay was reported in 13 studies, including

four RCTs and seven cohort studies. Meta-analysis was performed using the random effects model, and the results showed that the hospital stay in the thoracoscopic group was significantly shorter than that in the thoracotomy group (OR =0.531, 95% CI: 0.41, 0.69, P<0.00001). The results of further subgroup analyses by study design showed that both the RCT and cohort study subgroups showed significantly shorter hospitalization in the thoracoscopy group than the open chest group, and the difference was statistically significant (*Figure 4*).

Chest tube drainage time
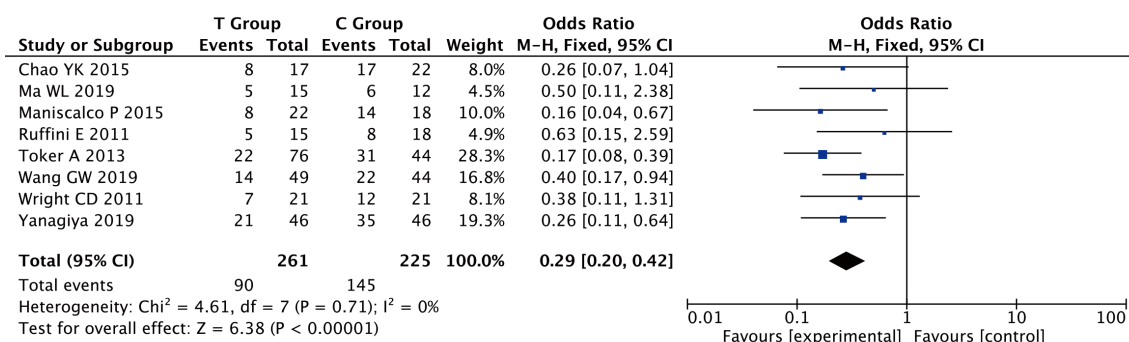A total of six studies reported on this aspect, including

Study or Subgroup	T Group Events	Total	C Group Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Chao YK 2015	8	17	17	22	8.0%	0.26 [0.07, 1.04]
Ma WL 2019	5	15	6	12	4.5%	0.50 [0.11, 2.38]
Maniscalco P 2015	8	22	14	18	10.0%	0.16 [0.04, 0.67]
Ruffini E 2011	5	15	8	18	4.9%	0.63 [0.15, 2.59]
Toker A 2013	22	76	31	44	28.3%	0.17 [0.08, 0.39]
Wang GW 2019	14	49	22	44	16.8%	0.40 [0.17, 0.94]
Wright CD 2011	7	21	12	21	8.1%	0.38 [0.11, 1.31]
Yanagiya 2019	21	46	35	46	19.3%	0.26 [0.11, 0.64]
Total (95% CI)		**261**		**225**	**100.0%**	**0.29 [0.20, 0.42]**
Total events	90		145			

Heterogeneity: Chi² = 4.61, df = 7 (P = 0.71); I² = 0%
Test for overall effect: Z = 6.38 (P < 0.00001)

Figure 3 Meta-analysis of the ICU times between the thoracoscopic and open chest groups.

Study or Subgroup	T Group Events	Total	C Group Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Chao YK 2015	15	41	18	41	8.6%	0.74 [0.30, 1.79]
Gripp S 1998	21	65	27	60	12.7%	0.58 [0.28, 1.21]
He Z 2013	15	46	19	46	9.3%	0.69 [0.29, 1.61]
Liu Z 2021	12	31	17	30	6.5%	0.48 [0.17, 1.34]
Ma WL 2019	5	15	8	18	3.3%	0.63 [0.15, 2.59]
Maniscalco P 2015	4	17	9	22	3.4%	0.44 [0.11, 1.81]
Ried M 2014	5	22	9	18	3.6%	0.29 [0.08, 1.15]
Ruffini E 2011	25	76	27	44	11.3%	0.31 [0.14, 0.67]
Toker A 2013	10	21	15	21	4.1%	0.36 [0.10, 1.30]
Wang GW 2019	16	49	18	44	9.4%	0.70 [0.30, 1.63]
Weng W 2020	22	62	32	58	12.5%	0.45 [0.21, 0.93]
Wright CD 2011	14	45	18	45	8.9%	0.68 [0.28, 1.61]
Yanagiya 2019	12	28	15	30	6.3%	0.75 [0.27, 2.11]
Total (95% CI)		**518**		**477**	**100.0%**	**0.53 [0.41, 0.69]**
Total events	176		232			

Heterogeneity: Tau² = 0.00; Chi² = 5.40, df = 12 (P = 0.94); I² = 0%
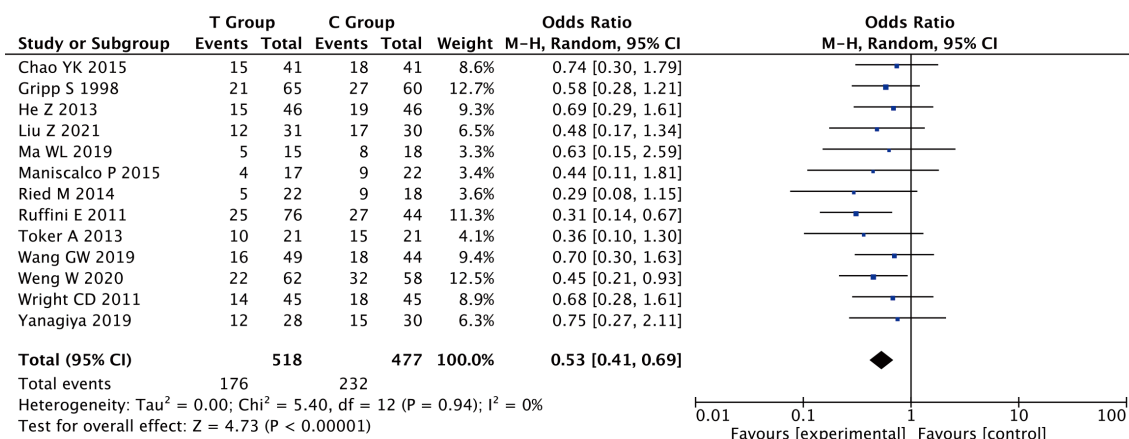Test for overall effect: Z = 4.73 (P < 0.00001)

Figure 4 Meta analysis of the duration of hospitalization between thoracoscopic and open-chest groups.

three RCTs and three cohort studies. Meta-analysis was performed using the random effects model, and the results showed that the chest tube drainage time in the thoracoscopic group was significantly shorter than in the open chest group, and the difference was statistically significant (OR =0.49, 95% CI: 0.33, 0.73, P=0.0004). The results of further subgroup analysis according to a different study design showed that the thoracic tube drainage time in both the RCT and cohort study subgroups was significantly shorter in the thoracoscopy group compared to the open chest group, and the differences were statistically significant (*Figure 5*).

Intraoperative bleeding

In total, seven studies reported on intraoperative bleeding, including three RCTs and four cohort studies. Meta-analysis was performed using the random effects model, and the results showed that there was significantly less bleeding

in the thoracoscopy group compared to the open chest group (OR =0.53, 95% CI: 0.36, 0.79, P=0.002). The results of further subgroup analyses performed by study design showed that the RCT and cohort in all subgroups of the study had significantly less bleeding in thoracoscopy group than open chest group (*Figure 6*).

Postoperative complications

A total of five studies reported on postoperative complication, including three RCTs and two cohort studies. Meta-analysis was performed using the fixed effects model, and the results showed that the incidence of postoperative complications was significantly lower in the thoracoscopy group compared to the hand-open chest group (OR =0.19, 95% CI: 0.11, 0.34, P<0.00001). Further results of subgroup analysis by study design revealed that the incidence of postoperative complications in the RCTs and cohort studies in all subgroups was markedly lower in the thoracoscopy
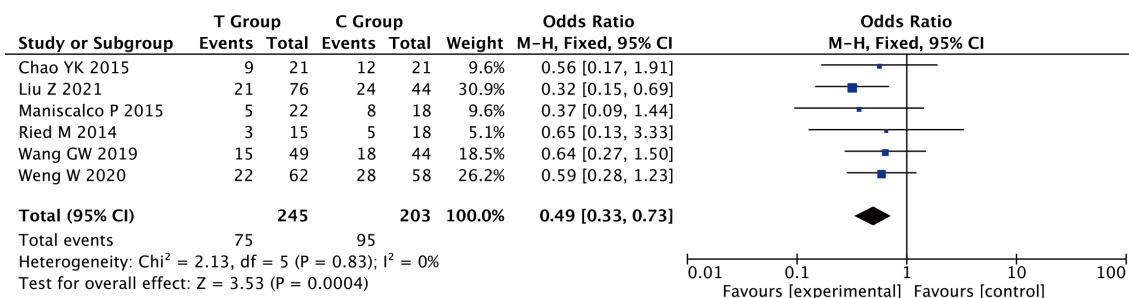
Figure 5 Meta-analysis of the thoracic tube drainage time in the thoracoscopic and open chest groups.
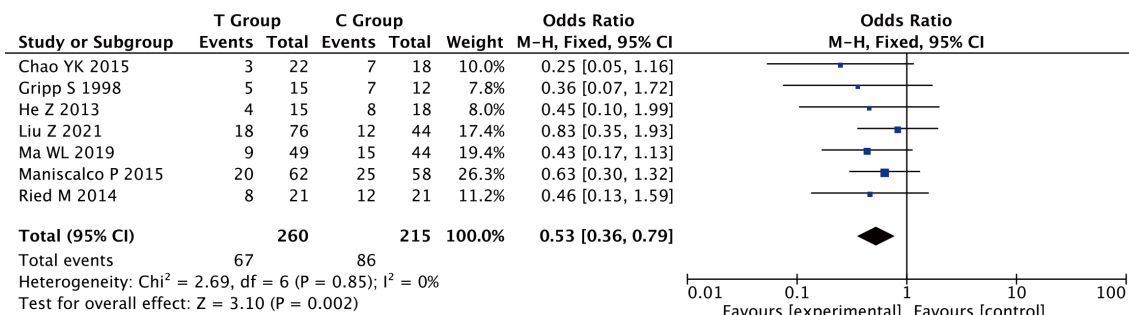

Figure 6 Meta analysis of intraoperative bleeding in the thoracoscopic and open chest groups.
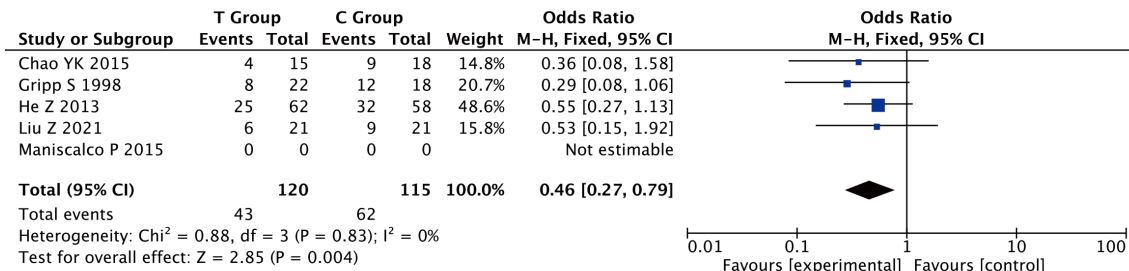

Figure 7 Meta-analysis of the incidence of postoperative complications in the thoracoscopic and open chest groups.

group than the hand-open chest group (RCT: OR =0.14, 95% CI: 0.06, 0.33, P<0.0001; cohort study: OR =0.46, 95% CI: 0.27, 0.79, P<0.004) (*Figure 7*).

Recurrence rate

A total of five studies reported on the recurrence rate, including three RCTs and two cohort studies. Meta-analysis was performed using the fixed effects model, and the results showed no significant difference in the recurrence rate between thoracoscopic surgery and open chest surgery. The results of further subgroup analysis according to the study design showed that the recurrence rates in both RCT and

cohort studies were not significantly different (OR =0.69, 95% CI: 0.32, 1.48), P=0.34) (*Figure 8*).

Bias analysis

Bias evaluation and sensitivity analysis were performed on the included research and outcome observation indicators, excluding the included literature one-by-one, and the fixed and random effects models were respectively adopted. The results were similar and showed good stability. In addition, the funnel map was analyzed, except for the operation time and intraoperative bleeding index, which indicating a large
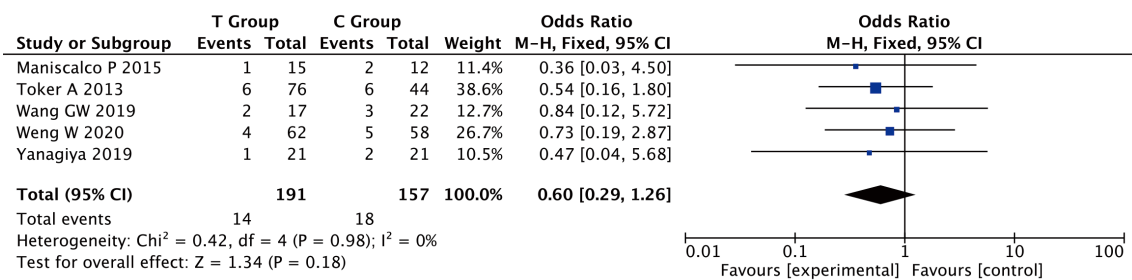
Figure 8 Meta-analysis of the tumor recurrence rates in the thoracoscopic and open-chest groups.
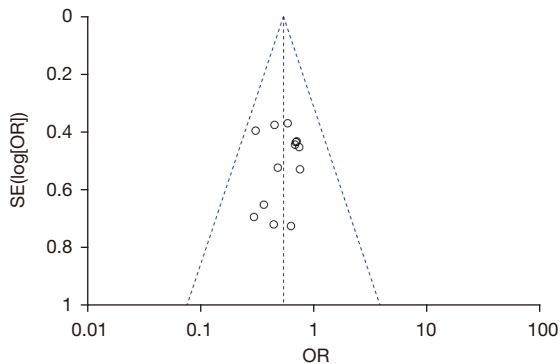

Figure 9 Funnel plot analysis of publication bias.

publication bias. However, the funnel map analysis of the remaining indicators was basically symmetrical, and the publication bias was small (*Figure 9*).

Discussion

Thymoma is a common mediastinal tumor with unclear etiology and pathology. Due to its potentially invasive nature and easy surrounding tissue involvement, surgical treatment is preferred after diagnosis (19). The commonly used surgical approach involves a neck incision, the posterior lateral chest incision, anterior lateral incision, and median thoracic incision (20-22). However, due to the considerable trauma of traditional open chest surgery, the damage to chest integrity, and the impact of diaphragm movement, it can easily cause serious complications, such as postoperative pulmonary lectasis, lung infection, and respiratory insufficiency. This will lead to slower patient recovery, extended hospitalization time, and increased costs (23). With the development of minimally invasive technology in the field of surgery, thoracoscopic surgery (VATS) has been increasingly applied to the surgical

resection of mediastinal tumors, which has the advantages of minimal trauma and a clear surgical field. However, it is a complex and difficult operation, and has high technical requirements for operators. Hence, its effect in thymus resection remains controversial (24-26).

The present study included five RCT and eight cohort studies (6-18), and the results showed that thoracoscopic surgery could shorten the surgical, ICU, hospitalization, and thoracic tube drainage times, as well as reduce the amount of intraoperative bleeding and the incidence of postoperative complications. However, no significant differences were observed between the procedures in terms of the tumor recurrence rate. At the same time, in terms of the operation time, only the RCT subgroup showed that the thoracoscopy group was significantly better than the traditional thoracotomy group, which may be associated with the fact that degree of operative surgical proficiency and patient tumor size were related, which accounts for the considerable differences in thoracoscopic surgery times (27-30). Compared with traditional thoracotomy surgery, thoracoscopic vision recognizes the anatomy more clearly and has minimal trauma and impact on the respiratory system, and therefore, a satisfactory effect can be achieved in the treatment of thymoma (31). However, careful selection of appropriate early patients is required clinically.

Many people believe that thoracoscopic minimally invasive surgery must be better than thoracotomy, as long as malignant thymoma requires minimally invasive surgery, which is also a misunderstanding of understanding. First of all, minimally invasive surgery refers to superficial incision and radical operation for malignant thymoma. Whether under thoracotomy or endoscopy, how much lung should be cut or how much lymph nodes should be removed or how much lymph nodes should be removed. In other words, the injury in the lung is not reduced because of minimally invasive surgery (32). In addition, endoscopic

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surgery is conditional, not all malignant thymomas can be used endoscopic. Thoracoscopy may not be appropriate for a number of patients (33). (I) From the disease itself, locally advanced tumors, T3 and T4, are not suitable for thoracoscopy. (II) Tumor growth location endoscopic surgery is especially suitable for peripheral malignant thymomas. For central malignant thymomas, if the tumor can be seen under the bronchoscope, thoracoscopy is generally not suitable (34). (III) Scope of lymph nodes. The scope of lymph node metastasis is wide, and thoracoscopy is not suitable. (IV) Thoracoscopy is not suitable for patients with tumor or lymph node invasion of blood vessels and bronchus, which increases the risk of surgery. (V) Patients with malignant thymoma who cannot tolerate single-lung ventilation and cannot undergo anesthesia. Endoscopic surgery has high requirements for doctors' skills and hospital equipment (35). Some patients may have some unexpected problems during the operation and change to thoracotomy, such as massive bleeding or difficulty in operation caused by tumor adhesion. In a word, whether the patient is suitable for endoscopic surgery and whether endoscopy can be used, the thoracic surgeon will complete all the examinations before surgery, fully evaluate, and formulate the most appropriate plan according to the specific condition (36).

There were some limitations in this study that should be noted. Firstly, only five RCTs (6-18) were included, all of which were Chinese studies. Therefore, a high risk of bias exists. Meanwhile, the included cohort studies were limited by study design, and the reliability of the meta-analysis is poor (37). Secondly, the tumor status (pathological grade, clinical stage) of each study, which may cause bias to the results. Thirdly, all of the included studies were not blinded when considering the clinical and functional results, and thus, observer bias is an important limitation.

Taken together, the current evidence shows that compared to traditional thoracotomy, thoracoscopic surgery shortens the surgical, ICU stay, hospitalization, and thoracic tube drainage times. In addition, it reduces intraoperative bleeding and the incidence of complications (38-40). However, the quality of the included studies was limited; thus, large sample, high-quality RCTs are needed to verify the above conclusions.

Acknowledgments

Footnote

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