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How can the rate of nontherapeutic thymectomy be reduced?

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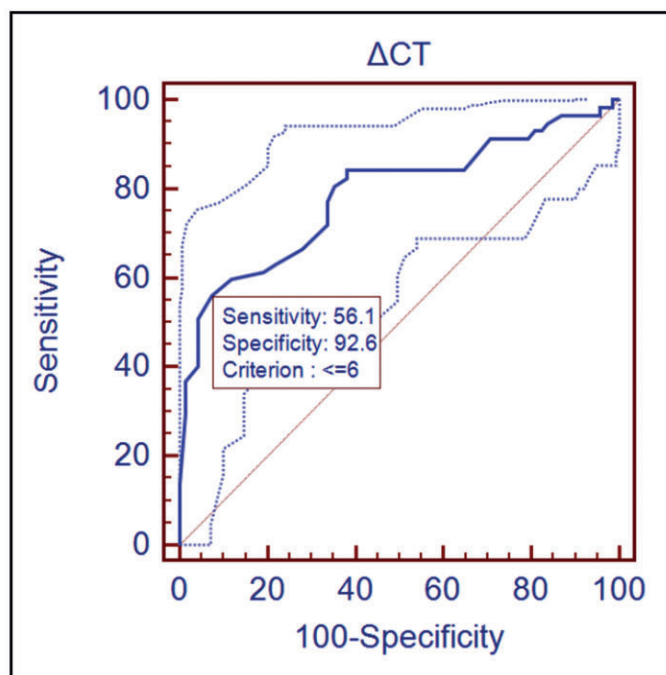
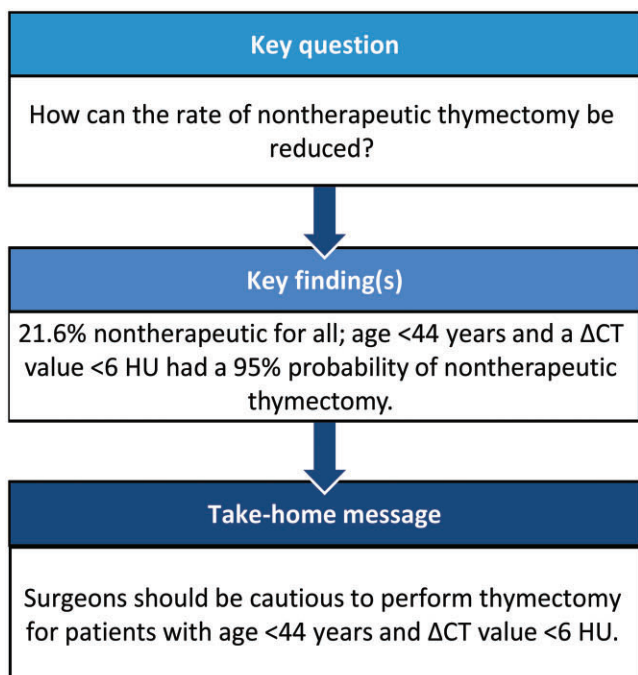
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Abstract

OBJECTIVES: The aim of this study was to determine the prevalence of nontherapeutic thymectomy and define a clinical standard to reduce it.

METHODS: From 2016 to 2020, consecutive patients who underwent thymectomy were retrospectively reviewed. Univariable and multivariable analyses were used to identify the correlation factors of nontherapeutic thymectomy. A receiver operating characteristic curve was analysed to assess the cut-off threshold of factors correlated with nontherapeutic thymectomy.

RESULTS: A total of 1039 patients were included in this study. Overall, 78.4% ($n=814$) of thymectomies were therapeutic and 21.6% ($n=225$) were nontherapeutic. Thymoma (57.9%, $n=602$) was the most common diagnosis in therapeutic thymectomy. Among those of nontherapeutic thymectomy, thymic cysts (11.9%, $n=124$) were the most common lesion. Compared with therapeutic thymectomy, patients with nontherapeutic thymectomy were more likely to be younger (median age 50.1 vs 55.6 years, $P<0.001$) with a smaller

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precontrast and postcontrast computed tomography (CT) value ($P < 0.001$, $P < 0.001$), as well as Δ CT value [10.7 vs 23.5 Hounsfield units (HU), $P < 0.001$]. Multivariable analysis indicated that only age and Δ CT value were significantly different between therapeutic and nontherapeutic thymectomy groups. Receiver operating characteristic curve analysis showed that cut-off values of age and Δ CT value were 44 years and 6 HU, respectively. Patients with age ≤ 44 years and a Δ CT value ≤ 6 HU had a 95% probability of nontherapeutic thymectomy.

CONCLUSIONS: Surgeons should be cautious to perform thymectomy for patients with age ≤ 44 years and Δ CT value ≤ 6 HU. This simple clinical standard is helpful to reduce the rate of nontherapeutic thymectomy.

Keywords: Nontherapeutic thymectomy • Thymic cyst • Lymphoma • Thymoma • CT attenuation

ABBREVIATIONS

CT	Computed tomography
FDG	Fluorodeoxyglucose
HU	Hounsfield units
IL-8	Interleukin-8
MG	Myasthenia gravis
ROC	Receiver operating characteristic

INTRODUCTION

The evaluation of thymic masses can be challenging due to their broad differential diagnosis [1]. Although imaging methods have made great progress, there is still a significant overlap of findings between benign and malignant conditions [2]. Thymectomy, which requires the removal of the whole thymus and the lesion, is the most prevalent treatment for thymic epithelial tumours [3]. However, this procedure is usually based on computed tomography (CT) scan findings, while the final diagnosis may be a condition such as thymic hyperplasia or thymic cyst, for which surgery is not the best option while the follow-up by imaging is more appropriate and thymectomy is not therapeutic [4, 5]. Nontherapeutic thymectomy has been defined as the removal of the thymus without therapeutic benefit for the diagnoses of lymphoma, thymic hyperplasia [in the absence of myasthenia gravis (MG)], thymic cyst, ectopic thymus or other benign diseases of the thymus [6]. But conditions combined with infection, bleeding, compression or any other symptoms reflecting a progressive disease were not included. Nontherapeutic thymectomy rates were ranged from 22% to 68% based on previous studies [6]. A survey from members of the European Society of Thoracic Surgeons reported that 91% of centres recommended thymectomy without biopsy if thymoma was suspected [7], although they only obtained chest CT scan features but no evidence from additional imaging modalities. Although thymectomy can achieve minimally invasive and low mortality through modified sternal retractors under the xiphoid process and video-assisted thoracoscopic techniques [8], a nontherapeutic thymectomy is associated with the potential postoperative morbidity and increased consumption of health care resources [9]. This invasive procedure brings little therapeutic benefit.

Several studies had explored the cause of nontherapeutic thymectomies and contrasted the image features of those entities in a single institution cohort of consecutive thymectomy patients [2, 6, 10]. Researchers have reported the prevalence of nontherapeutic thymectomy, but no exact criterion has been developed to define under what circumstances thymectomy is nontherapeutic. The aim of our study was to determine the incidence of nontherapeutic thymectomy and clarify a specific clinical criterion to lower the nontherapeutic thymectomy rate.

PATIENTS AND METHODS

Ethics statement

This study was approved by the Research Ethics Committee of Zhongshan Hospital, Fudan University (B2021-703R). The formal consent was obtained.

Patient selection and clinical data

We selected patients who underwent thymectomy between January 2016 and January 2020 in Zhongshan Hospital, Fudan University. After the review of consecutive patients, we developed inclusion and exclusion criteria based on whether the primary pathology involved the thymus and whether the purpose of the surgery was to target the thymus. Fulfilment of these inclusion criteria was determined through a review of electronic medical records (clinical and operative notes, physical examination, imaging reports, laboratory studies and pathology reports). On the basis of these criteria, the following types of cases were excluded: thymectomy for management of MG [11]; cervical or other ectopic thymic tissue removed during the process of neck dissection or other dissection procedures and incidental thymectomy for cardiac surgery, tracheal anomalies, thyroidectomy or parathyroidectomy; data were not provided regarding baseline characteristics of patients; clinical information was incomplete; pathology diagnosis was unclear. Patients without enhanced chest CT scanning prior to neoadjuvant therapy were excluded, if these patients received neoadjuvant therapy. We also excluded patients without enhanced chest CT examinations before surgery, if these patients did not receive neoadjuvant therapy. Patients diagnosed with the following diseases were classified into the nontherapeutic thymectomy group for the unclear benefit of thymectomy: thymic cyst, thymic hyperplasia or remnant, lymphoma, Castleman disease, granuloma, thymic fibrosis, other inflammatory lesions and thymic hypertrophy. For patients diagnosed with thymoma, thymic carcinoma, mesenchymal tumours or metastatic cancers, thymectomy has clear therapeutic benefit and is classified into the therapeutic thymectomy group. Medical records and laboratory data were collected in accordance with the recommendation of the International Thymic Malignancy Interest Group standard definitions and policies.

Computed tomography protocol and image interpretation

All chest CT examinations were performed on inspiration with the following CT scanner in Zhongshan Hospital of Fudan University: a 128-slice CT scanner (SOMATOM Definition AS, Siemens Healthineers, Germany). All patients were asked to fast for at least 4 h before the CT scan. The field of the scan was performed from the apex to the base of the lung. Mediastinal, lung,

and bone window images were evaluated on the monitors. Contrast-enhanced CT images were acquired after intravenous injection of 100 ml non-ionic contrast agent (300 mg I/ml; Ultravist, Bayer Schering Pharma, Berlin, Germany), using an automated injector at a rate of 3 ml/s. The arterial CT phases were acquired by scanning the images for 30–35 s. CT scan parameters were as follows: tube voltage of 120 kVp; tube current of 160 mAs; rotation time of 0.5 s; pitch of 0.9, detector collimation of 32×1.2 mm; field of view of $387 \text{ mm} \times 387 \text{ mm}$; matrix size of 512×512 ; slice thickness of 1.5 mm and slice interval of 1.5 mm.

All CT scanning data were transferred to the picture archiving and communications system, using the DICOM reader software Centricity DICOM Viewer 3.1 (GE Healthcare, Chicago, IL). Image analysis was performed by thoracic fellowship-trained radiologists. Two radiologists (Junzhen Liu and Shihai Zhao) who were blinded to the pathological results analysed the CT images independently. A third radiologist (Junzhen Liu) was asked to review the images and make the final diagnosis if there was a controversy between the two younger observers. CT imaging features were analysed, including lesion location, size, lesion morphology and shape, attenuation or density, region of interest measurement of attenuation, presence of pleural or pericardial effusion and presence of satellitic focus. The shape was described as round, oval or plaque. The contour of the lesions was described as smooth, lobulated or irregular. Homogeneity versus heterogeneity of density was assessed. For the purpose of statistical analysis. Attenuation in Hounsfield units (HU) was assessed for data analyses, avoiding streak artefact and image noise. The HU values of the individual case obtained by radiologists were averaged for statistical analysis. Attenuation before and after the contrast injection was calculated in HU, and the degree of enhancement (Δ CT) was defined as post-contrast HU minus pre-contrast HU.

Statistical analysis

The study sample size was large and data normality was confirmed by plotting the frequency distribution map. According to statistical and data reporting guidelines [12, 13], univariable and multivariable statistical analyses were performed by SPSS Version 20.0 (For Windows; Chicago, IL, USA) to determine the significant differences in various characteristics between the therapeutic thymectomy and nontherapeutic thymectomy groups. To identify the best cut-off value and evaluate the efficiency of predicting nontherapeutic thymectomy, receiver operating characteristic (ROC) curve analysis was conducted by MedCalc program version 15.2 (MedCalc Software, Ostend, Belgium). A nomogram was built through the rms package in R version 3.3.1 (<http://www.r-project.org/>). The maximum score of each variable was set as 100. The performance of the nomogram was measured based on the Harrel concordance index (C-index). Bootstraps of 1000 resamples were set, and calibration curves were calculated by the regression analysis. A *P*-value of 0.05 or less was considered statistically significant.

RESULTS

Patient characteristics

A total of 1388 patients who underwent total thymectomy were identified from January 2016 to January 2020. According to the

inclusion and exclusion criteria, 1039 patients were included in this study. The case selection steps were summarized in Fig. 1. In this study, the preoperative diagnosis of patients with neoadjuvant therapy was pathological confirmation. All those patients received therapeutic thymectomy. The median age was 55 years (range, 18–82 years), and the average postoperative hospital stay was 3.9 days. Thymectomy was considered therapeutic in 78.4% ($n=814$) of cases and nontherapeutic in 21.6% ($n=225$) of cases (Table 1). The most common diagnoses were thymoma (57.9%, $n=602$) and thymic carcinoma (13.7%, $n=142$) in the therapeutic group; and thymic cyst (11.9%, $n=124$) and thymic hyperplasia (2.8%, $n=29$) in the nontherapeutic group, respectively. For thymoma patients, type AB (21.5%, $n=223$) was the most common, followed by type B2 (11.4%, $n=118$). For thymic carcinoma patients, squamous cell carcinoma (9.3%, $n=97$) was the most common pathological type (Table 2). Of all included patients, 18 (1.7%) cases were robotic-assisted thoracoscopic surgery and were all in the therapeutic thymectomy group; 833 (80.2%) cases were video-assisted thoracoscopic surgery and 188 (18.1%) cases were routine open thoracotomy.

Univariable analysis of the correlation factors of nontherapeutic thymectomy

Patients in the nontherapeutic group were significantly younger (median age, 50.1 vs 55.6) than those in the therapeutic group and more likely to be female (56.0% vs 45.2%) (Table 3). To our surprise, no significant differences in lesion size, location, effusion, shape or density were found ($P > 0.05$). However, the CT attenuation value of the nontherapeutic group was lower than that of the therapeutic group in terms of the precontrast (28.7 vs 39.8), postcontrast (39.4 vs 63.3) and Δ CT values (10.7 vs 23.5). Univariable and multivariable logistic regression analyses were used to investigate the association of preoperative clinical factors with nontherapeutic thymectomy. Preoperative variables entered in the univariable logistic regression analysis included age, gender, pleural or pericardial effusion, size, location, shape, contour, density, satellitic focus and CT attenuation of lesions. Univariable logistic regression analysis indicated age ($P < 0.001$), gender ($P = 0.004$), precontrast CT value ($P < 0.001$), postcontrast CT value ($P < 0.001$) and Δ CT value ($P < 0.001$) were correlated to nontherapeutic thymectomy. However, size ($P = 0.206$), location ($P = 0.062$), pleural or pericardial effusion ($P = 0.081$), shape ($P = 0.082$), contour ($P = 0.075$), density ($P = 0.055$) and satellitic focus ($P = 0.944$) did not reach the statistical significance. Only variables with *P*-value < 0.05 were entered into the multivariable logistic regression analysis. Multivariable logistic regression analysis was performed using forced entry. Multivariable analyses showed that only age ($P < 0.001$) and Δ CT value ($P < 0.001$) were independent correlation factors of nontherapeutic thymectomy.

Receiver operating characteristic analysis of the significant correlation factors of nontherapeutic thymectomy

Based on ROC analyses of prejudgement for nontherapeutic thymectomy (Fig. 2), the threshold values of age and Δ CT value were 44 years and 6 HU with both maximum sensitivity and specificity. The area under the ROC curve (AUC) of age and Δ CT value in differentiating therapeutic thymectomy and nontherapeutic thymectomy

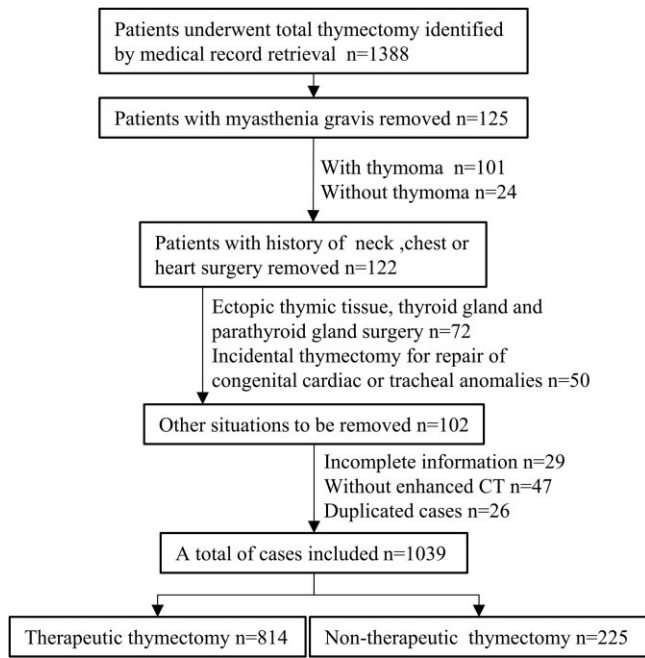


Figure 1: Study diagram of patient selection process.

Table 1: Diseases classifications of patients with therapeutic or nontherapeutic thymectomy

Variables (1039 cases)	Cases	Percentage
Therapeutic thymectomy (814, 78.4%)		
Thymoma	602	57.9
Thymic carcinoma	142	13.7
Mesenchymal tumours	54	5.2
Metastatic cancer	16	1.5
Non-therapeutic thymectomy (225, 21.6%)		
Thymic cyst	124	11.9
Thymic hyperplasia or remnant	29	2.8
Lymphoma	28	2.7
Castleman disease	9	0.9
Granuloma	23	2.2
Thymic fibrosis	6	0.6
Other inflammatory lesions	5	0.5
Thymic hypertrophy	2	0.2

were 0.586 (95% confidence interval: 0.495–0.673, sensitivity: 33.3%, specificity: 86.8%) and 0.786 (95% confidence interval: 0.704–0.854, sensitivity: 56.1%, specificity: 92.6%), respectively. When combining the optimal cut-off value of age and Δ CT, we found that 95% of patients with Δ CT value ≤ 6 and age ≤ 44 received nontherapeutic thymectomy (Chi-square= 6.089, $P = 0.013$) (Supplementary Material, Table S1).

Predictive nomogram

The nomogram was constructed based on the multivariate model. To calculate the probability of nontherapeutic thymectomy, we first identify each factor based on the points scale at the top of the nomogram and then sum the points of each factor. Finally, the probability of nontherapeutic thymectomy was obtained based on the bottom point scale of the nomogram

Table 2: Pathological diagnoses of patients with therapeutic or nontherapeutic thymectomy

Variables (1039 cases)	Cases	Percentage
Thymoma		
A	42	4.0
AB	223	21.5
B1	72	6.9
B2	118	11.4
B3	54	5.2
B2 + B3	36	3.5
Metaplastic	11	1.1
Micronodule	21	2.0
Undefined	25	2.4
Thymic carcinoma		
Squamous	97	9.3
Adenocarcinoma	13	1.3
Carcinoid	9	0.9
Small cell	5	0.5
Large cell	6	0.6
Lymphoepithelioid	1	0.1
Mucoepidermoid	1	0.1
Undifferentiated	10	1.0
Mesenchymal tumours		
Angioma	15	1.4
Sarcoma	8	0.8
Lipoma	5	0.5
Fibroma	10	1.0
Spindle cell tumour	4	0.4
Leiomyoma	3	0.3
Other	9	0.9
Metastatic cancer	16	1.5
Thymic cyst	124	11.9
Thymic hyperplasia or remnant	29	2.8
Lymphoma	28	2.7
Castleman disease	9	0.9
Granuloma	23	2.2
Thymic fibrosis	6	0.6
Inflammatory lesions	5	0.5
Thymic hypertrophy	2	0.2

(Fig. 3). The calibration plots based on bootstrap resampling validation demonstrated that the nomogram is in good agreement with the actual observation for the probability of nontherapeutic thymectomy. The C-index was 0.769.

DISCUSSION

It is a consensus from the guideline that for any suspected thymoma, all patients should be managed by a multidisciplinary team with experience and surgical resection is the standard of care if possible. For locally advanced or unresectable cases, tissue biopsy is recommended. But most early-stage thymomas are resectable through image evaluation and can be performed with very low morbidity and very long-term symptom-free survival. Therefore, doctors are usually not willing to take risks of infection or seeding of pleural space to do tissue biopsy preoperatively, which means a thymectomy is typically undertaken on the clinical and radiographic suspicion of thymoma. However, the post-operative pathological diagnosis may be a benign lesion and the thymectomy is not therapeutic.

We included 1039 thymectomy patients in this study and found age and Δ CT value were significant correlation factors of nontherapeutic thymectomy. By ROC analyses, we first

Table 3: Clinical data and preoperative enhanced computed tomography features of patients with therapeutic or nontherapeutic thymectomy

Variables	Nontherapeutic	Therapeutic	P-Value
Age (years, interquartile range)	50.1 (42.0–60.0)	55.6 (47.8–62.3)	<0.001
Sex			
Female	126	368	0.004
Male	99	446	
POD (days)			
>3	47	455	<0.001
<3	178	359	
Size			
>3 cm	130	508	0.206
<3 cm	95	306	
Location			
Left	65	259	0.062
Right	68	290	
Middle	92	265	
Pleural or pericardial effusion			
Absent	199	750	0.081
Present	26	64	
Shape			
Round	69	218	0.082
Oval	76	239	
Plaque	80	357	
Contour			
Smooth	82	266	0.075
Lobulated	55	263	
Irregular	88	284	
Density			
Heterogeneous	73	321	0.055
Homogeneous	152	493	
Satellitic focus			
Absent	207	750	0.944
Present	18	64	
CT attenuation (HU, interquartile range)			
Pre-contrast	28.7 (17.1–40.2)	39.8 (34.8–46.0)	<0.001
Post-contrast	39.4 (22.3–50.5)	63.3 (54.5–74.3)	<0.001
Δ CT value	10.7 (4.6–13.8)	23.5 (10.7–32.3)	<0.001

CT: computed tomography; HU: Hounsfield units; POD: postoperative hospital stay.

developed a clinical criterion of patient evaluation who had the potential for nontherapeutic thymectomy based on two cost-effective correlation factors. Considering that the probability of nontherapeutic thymectomy was 95%, total thymectomy is not recommended as the first choice for those patients with age ≤ 44 years and Δ CT ≤ 6 HU.

Our study has clinical implications specifically because it was based on large-scale imaging and pathological data from adult patients who underwent total thymectomy. The data proved the high rate of nontherapeutic thymectomy again in clinical practice and will arouse thoracic surgeons' awareness of it significantly. What is more, we attempted to find a way to change the situation and the criterion we advanced will assist in the creation of differential diagnosis when such patients are encountered in clinics before any surgical intervention or pathology results. The information from this criterion will not only facilitate the development of differential diagnoses of mediastinal lesions but aid in clinicians to logically choose different imaging modalities and avoid some invasive inspections.

Given the potential risk of infection, bleeding or seeding of pleura by transthoracic needle biopsy, the diagnosis of anterior mediastinal masses at present mainly relies on clinical manifestations and imaging examinations such as CT and magnetic resonance imaging (MRI) [4, 5, 15, 16]. On CT images, intrathymic cysts have more homogenous density, more smoothly contour, less satellite focus and

lower CT value than thymoma, researchers pointed out that CT can reveal the location, size, density, shape and contour of a lesion [5]. Thoracic CT scan is now the imaging modality of choice for thymic tumours due to its high spatial and temporal resolution and convenience [17]. However, small thymoma and intrathymic cysts have overlapping clinical and radiological features, and interpretation variability between observers and even within the same observer makes it difficult to reach an accurate diagnosis. Even worse, evidence also showed benign mediastinal cysts including thymic cysts could be misinterpreted as solid on CT when they are of soft-tissue attenuation on account of proteinaceous or haemorrhagic content caused by bleeding and inflammation [4, 18, 19]. According to NCCN Guidelines Version 1.2021, when assessing a mediastinal mass, detection of thymic malignancy versus thymic cyst can be better discriminated with chest MRI compared to chest CT [20]. MRI has specific benefits in certain scenarios though it is not routinely used in the evaluation of thymic tumours, such as to distinguish solid from cystic lesions, to evaluate necrotic components, to evaluate enhancing septum within cystic lesions and to evaluate for areas of subtle local invasion [21]. What is more, chemical shift imaging can be utilized to detect microscopic or intravoxel fat and therefore to differentiate thymic hyperplasia and thymoma [15]. Unfortunately, a recent research based on Multi-Institutional, International, Radiology Databases [22] revealed that the use of MRI for chest evaluation has been lagging behind in other parts of the

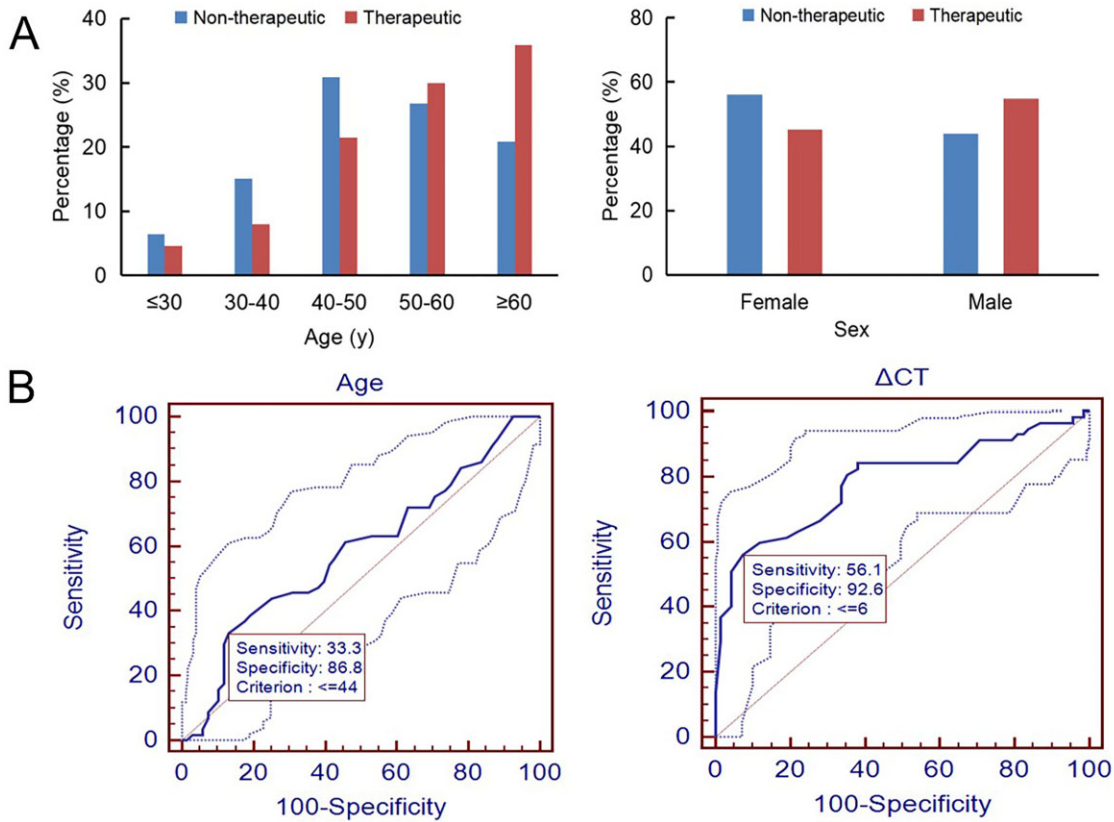


Figure 2: Distribution difference of age and sex between therapeutic and nontherapeutic thymectomy groups (A). Receiver operating characteristics curve analysis of age and Δ CT value for patients undergoing therapeutic and nontherapeutic thymectomy.

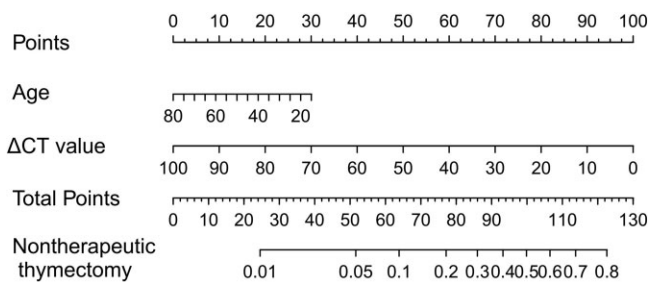


Figure 3: The nomogram for predicting probability of nontherapeutic thymectomy.

body. Fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT has incompletely defined roles in the evaluation of thymic masses. On the one hand, the role of PET/CT is clear in thymic carcinoma and occult metastasis, due to its high sensitivity and the higher overall FDG uptake value (SUV max) than lower grade thymic tumours [23, 24]. However, FDG can be taken by infection, thymic hyperplasia, fibrosing mediastinitis, and other non-neoplastic processes, which cause false-positive results. On the other hand, the lack of increased FDG uptake is seen in some histological types of thymic malignancy, and there is a lack of standardization in techniques which can result in quantitative variability and controversy between studies [25]. In addition, PET/CT and MRI are generally not the preferred examination modalities for the vast majority of patients due to financial burden and accessibility. Therefore, reaching clinical decisions by CT image alone can result in misinterpretation of thymic cysts, thymic hyperplasia, and lymphoma, which has caused many nontherapeutic thymectomies [2]. Besides, from our

clinical experience, thoracic surgeons tend to take total thymectomy surgery when thymic malignancies are suspected, even though they got only image evidence; reasons include: it is a consensus that early thymomas should be removed; patients are concerned about the potential malignancies and require surgery.

In summary, the high rate of nontherapeutic thymectomy seems inevitable. However, many researchers have been trying to find solutions based on present evidence, they analysed the clinical data of patients with nontherapeutic thymectomy and found that age, sex, enhanced CT value, tumour size, location, mediastinal lymph node enlargement, Δ CT value, lobulated contour, mediastinal pleura invasion, and PET-CT SUV-max had significant differences between therapeutic and nontherapeutic group [16–20], although there were also some conflicting results. Some studies further combined age, sex, imaging examination and other clinical features to establish a presumed diagnostic structure to guide further examination and treatment [26]. Li *et al.* [5] evaluated the CT values of 30 patients and revealed that the best CT threshold for distinguishing thymoma and thymic cysts was 31.2 HU. Lee *et al.* [27] believed that the CT values of benign cysts were slightly higher than 10 HU, which was significantly lower than 41.5 HU for solid tumours. Although these attempts have led to certain improvements, the rate of nontherapeutic thymectomy is still high.

To lower the rate of nontherapeutic thymectomy, we built the clinical criterion for the evaluation of thymic lesions for the first time. These two factors, age and Δ CT value, have also been proven to be very important for judging whether thymectomy is necessary in the previous studies [5, 16, 19]. But the results of previous studies differed greatly. In this study, we analysed clinicopathologic data of 1039 cases, which had the maximum sample size up to now.

Through ROC analyses, we also found the optimal cut-off values of age and Δ CT value. Our findings offer surgeons a clear reference for determining whether to offer total thymectomy. Based on this criterion, for imaging-suggested benign conditions such as thymic cysts and thymic hyperplasia, or unclear diagnosis of well-circumscribed mediastinal lesions, surgery should not be first recommended, instead, the policy of 'wait and see' by imaging is a better choice. Most benign diseases remain stable for a long period of time; however, once any malignant potential, infection, bleeding or compression symptoms occur, surgery can be taken into account and thymectomy at that time is therapeutic.

Perhaps accurate diagnosis is the best way to avoid nontherapeutic thymectomy. In the absence of biopsy or molecular biological diagnostic indicators, the patient's clinical features, imaging and other auxiliary examinations are not enough to completely distinguish thymoma from other thymic diseases or mediastinal masses. Our recent research revealed that interleukin-8 (IL-8) is a candidate biomarker for thymoma [28], and we found significantly elevated IL-8 levels in naive T cells in patients with thymoma compared to those with other thymic lesions, such as thymic cysts. After surgical resection, the IL-8 levels in naive T cells are significantly decreased and increase again when thymoma recurs. Combining CT/MRI and IL-8 detection can significantly reduce the misdiagnosis rate between thymoma and other mediastinal masses to lower the nontherapeutic thymectomy rate. Combining imaging evidence and biomarker tests such as IL-8 detection is a promising future strategy.

At present, CT remains the imaging modality of options for mediastinal masses evaluation. MRI and PET are useful adjuncts. As recommended by the NCCN guideline, MRI can be used to differentiate malignant and benign diseases of the mediastinum, but its diagnostic value has not been fully clarified. Regarding FDG-PET, it is merely an auxiliary diagnostic modality for anterior mediastinal cysts. It means more medical resources and sometimes unnecessary over-checks, and these are also dilemmas in China. So, we focused on CT scan and limited preoperative imaging in this study.

Our results showed that 95% of patients with Δ CT value ≤ 6 and age ≤ 44 received nontherapeutic thymectomy. But it does not mean that age and Δ UH could allow surgeons to contra-indicate thymus removal. About 5% of those patients still had therapeutic thymectomy. Rarely, thymic hyperplasia may be difficult to distinguish from diffuse thymoma. Some cases are most suspicious for lymphoma and not for thymoma. For these cases, MRI and PET could prove a good substitute for imaging instead of CT. We suggested surgeons should be cautious to perform thymectomy for those patients with Δ CT value ≤ 6 and age ≤ 44 . Our study found that this simple clinical standard is helpful to reduce the rate of nontherapeutic thymectomy.

There are limitations to our study. First, although our study included a large scale of patients, it solely gathered data from a single institution, and thus these data could not fully represent other regions in China. CT values would have variations in different CT scan imaging protocols. Surgeons should not deal with thymectomy just based on a single imaging decision. There is an obvious place for additional imaging and surveillance. This study provides a clue for lowering the rate of nontherapeutic thymectomy. The cut-off value of Δ CT value might be individual in different institutes. So, the normalization of Δ CT value is our goal in future prospective clinical trials. Second, our study was retrospective and existed potential selection bias, cases with incomplete basic information were excluded. Third, a large proportion of patients with MG ($n = 125$) were excluded according to conventions; however, thymectomy should be

therapeutic in these patients regardless of histology. Nevertheless, we still excluded them because patients with MG included thymoma and thymic hyperplasia and they could confuse the characteristics of CT while differentiating benign and malignant lesions. Fourth, all patients diagnosed with thymic cysts are determined to be nontherapeutic; however, thymic cysts presented with symptoms, bleeding, inflammation or growing tendency for which thymectomy would be therapeutic. Histologically, thymic hyperplasia can be divided into two histologic types: true hyperplasia and lymphoid follicular hyperplasia. True thymic hyperplasia is characterized by an increased mass of the thymus with the preservation of histologic architecture. Lymphoid follicular hyperplasia is characterized by enlarged lymphoid germinal centres in the medulla with infiltration of lymphocytic and plasma cells. Clinically, patients with true thymic hyperplasia can be divided into three groups: rebound hyperplasia recovering from stress such as corticosteroid therapy, radiation therapy, chemotherapy, surgery or infection; abnormal hyperplasia with other diseases such as hyperthyroidism, sarcoidosis or red blood cell aplasia; hyperplasia with unknown reasons. However, lymphoid hyperplasia is commonly associated with chronic inflammatory or autoimmune conditions such as MG, thyrotoxicosis, and connective tissue diseases. Although thymic hyperplasia can often be differentiated from tumours, it is impossible to make a complete correct differential diagnosis based on imaging. Congenital thymic cysts can be found anywhere along the thymopharyngeal duct. Alternatively, acquired thymic cysts may be associated with chemotherapy or thoracotomy. Cystic changes can also be seen in thymic epithelial tumours, lymphomas and germ cell tumours. Thymic cysts have no solid components with thin, perceptible walls lined by stratified or columnar epithelium. While internal contents of the cyst may be proteinaceous or haemorrhagic and create a diagnostic dilemma. Occasionally, those lesions would be likely to grow or infected and cause compression and symptoms. It is a rough diagnostic challenge to distinguish cysts from tumours. Thus, it is not reasonable that all hyperplasia and cystic lesions were considered nontherapeutic. Thymectomies for selected patients with those benign lesions are also therapeutic. Further studies investigating the optimal definition of nontherapeutic thymectomy are warranted.

CONCLUSION

Taken together, we found that only age and Δ CT value were independent significant correlation factors of nontherapeutic thymectomy. We proposed a criterion based on these two factors to judge whether thymectomy surgery should be performed. We believe that this will be helpful in further decreasing the rate of nontherapeutic thymectomy.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Approval was obtained from the Research Ethics Committee of Zhongshan Hospital, Fudan University (B2021-703R).

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Conflict of interest: none declared.

Data Availability Statement

All relevant data are within the manuscript and its Supporting Information files. Our data (including clinical data and anonymized information) are available from the corresponding authors upon request.

Author contributions

Shuai Wang: Conceptualization; Data curation; Funding acquisition; Methodology; Writing—original draft. **Yongqiang Ao:** Data curation; Investigation; Methodology; Resources; Writing—original draft. **Jiahao Jiang:** Investigation; Methodology; Resources; Validation; Visualization. **Miao Lin:** Data curation; Formal analysis; Investigation; Methodology; Project administration; Software; Validation. **Gang Chen:** Data curation; Formal analysis; Investigation; Project administration; Supervision. **Junzhen Liu:** Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Supervision; Validation; Visualization. **Shihai Zhao:** Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Supervision; Validation; Visualization. **Jian Gao:** Data curation; Formal analysis; Resources; Software; Supervision; Validation. **Yi Zhang:** Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Validation; Visualization. **Jianyong Ding:** Conceptualization; Data curation; Funding acquisition; Project administration; Supervision; Writing—review & editing. **Lijie Tan:** Conceptualization; Funding acquisition; Methodology; Project administration; Resources; Supervision; Writing—review & editing.

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