学位論文

表　題

Age dependency of effectiveness of chemical-shift magnetic resonance imaging for differentiation of thymic hyperplasia from thymic tumors -Pitfall in childhood-

（胸腺過形成と胸腺腫瘍の鑑別における化学シフト MRI の有用性の年齢依存性ー小児におけるピットフォールー）

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Age dependency of effectiveness of chemical-shift magnetic resonance imaging for differentiation of thymic hyperplasia from thymic tumors -Pitfall in childhood-

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Key words

Thymic hyperplasia, chemical-shift MR imaging, chemical-shift ratio, childhood

Abstract

Purpose: To clarify the correlation between the chemical-shift ratio (CSR) and age in thymic hyperplasia and to examine its usefulness for detecting thymic tumors in children (≤ 15 years).

Materials and methods: The subjects were 19 patients with thymic hyperplasia and included two groups, the pediatric group (n = 5) and an adult group (n = 14). We investigated the correlation between the CSR and age, and the difference in the CSR between the pediatric and adult groups. In addition, the subjects with thymic tumors (n = 18) were included, and compared with the pediatric group with thymic hyperplasia. The CSR was determined by comparing the signal intensity of the thymus with that of the para-spinal muscle on both in-phase and opposed-phase MR images.

Results: A significant second curvilinear correlation was detected between the CSR and age in thymic hyperplasia ($r = 0.865$, $P < 0.001$). The CSR of the pediatric group with thymic hyperplasia was significantly greater than that of the adult group ($P < 0.001$). The CSR of the pediatric group with thymic hyperplasia and that of groups with thymic tumors partly overlapped.

Conclusion: The CSR of thymic hyperplasia demonstrated a significant correlation with age. The CSR of pediatric patients with thymic hyperplasia might partly overlap with that of tumors.

Introduction

Chemical-shift magnetic resonance imaging (MRI) consisting of in-phase and opposed-phase T1-weighted gradient-echo sequences is a useful tool for depicting small amounts of adipose tissue within lesions [1-5]. It is already widely used for the assessment of fatty liver and adrenal adenoma [5, 6]. Adrenal adenoma is often differentiated from adrenal metastasis based on the detection of small amounts of adipose tissue within adenomas using chemical-shift MRI.

Chemical-shift MRI has recently been shown to be useful for characterizing the normal thymus and differentiating thymic hyperplasia from thymic tumors as it can depict age-dependent fatty degeneration within the thymus, which is not seen in tumors [2, 4]. However, it should be stressed that the utility of chemical-shift MRI for characterizing the normal thymus is age-dependent. For example, it can successfully depict fatty degeneration within the thymus in nearly 100% of patients over the age of 16, whereas it can only show such changes in 50% of patients aged between 10 to 15 years, and 0% of those under the age of 10 years, as only relatively minor fatty changes are seen within the thymus in younger patients [1].

Thymic hyperplasia can be confusing, especially in young patients, in which the appearance of the thymus varies markedly. Priola AM et al. [4] reported that dual-echo chemical-shift MRI exhibits high accuracy for distinguishing thymic hyperplasia from tumors. They also suggested that the chemical-shift ratios (CSR) of these two entities can overlap in early adulthood, but did not include subjects aged ≤ 15 years.

Some studies have examined the differentiation of thymic lesions from thymic tumors using computed tomography (CT) or positron emission tomography (PET)/CT in subjects aged ≤ 15 years [7-11], but they did not include chemical-shift MRI. However, evaluations of the thymus are very important in this age group because myasthenia gravis (MG) is strongly associated with thymic hyperplasia.

The purpose of the present study was to clarify the correlation between the CSR and

age in thymic hyperplasia and to examine the usefulness of chemical-shift MRI for diagnosing thymic hyperplasia in children (age: ≤ 15 years).

Materials and methods

Subjects

Our institutional review board approved this observational retrospective study.

From May 2006 to May 2016, all subjects (n = 86) underwent MRI, including dual-echo chemical-shift image, of anterior mediastinum were given to the candidate of present study.

In them, 19 subjects fitting the following *Diagnostic Proof* of thymic hyperplasia were included in present study (an age range: 6-59 years, median age: 37 years, mean age ± standard deviation: 32.8 years ± 17.74 [9 males, age range: 7-53 years, median age: 25 years, mean age: 25.8 ± 18.05; 10 females, age range: 6-59 years, median age: 40.5 years, mean age: 39.1 ± 15.70 years]). The subjects included 5 patients with MG and a patient with pure red cell aplasia. The patients were assigned to two groups, the pediatric group with thymic hyperplasia (PTH) (age: ≤ 15 years) and the adult group with thymic hyperplasia (ATH) (age: ≥ 16 years). PTH included 5 patients [Fig. 1-5] (age range: 6-12 years, median age: 9.00 years, mean age: 8.6 years ± 2.30) and ATH included 14 patients [Fig. 7] (age range: 25-59 years, median age: 41.50 years, mean age: 41.43 years ± 11.35).

Moreover, 18 subjects with thymic tumor diagnosed pathologically was also included for comparing with that of thymic hyperplasia, were assigned two groups, pediatric group with thymic tumors (PTT) and adult group with thymic tumors (ATT). ATT included 17 patients (age range: 19-77 years, median age: 67.00, mean age: 60.71 years ± 16.03, pathological findings: 7 thymoma, 5 invasive thymoma, 4 thymic carcinoma, 1 anaplastic large B cell lymphoma) and PTT included a patient [Fig. 6] (age: 12 years old, pathological findings: lymphangioma).

Subjects with normal thymus (n = 16), thymic cystic lesions (n = 22) and thymic tumors without pathological diagnosis (n = 8) were excluded. In addition, subjects whom region of interest (ROI) was not placed within paraspinal muscle for its atrophy were also excluded (n = 3).

We investigated the correlation between the CSR of all subjects with thymic hyperplasia and age and compared CSR of thymic hyperplasia with that of thymic tumors in both pediatric group and adult group.

Diagnostic Proof of thymic hyperplasia

A histopathological diagnosis of thymic lymphoid hyperplasia was made in 2 patients.

In the remaining 17 cases, a diagnosis of thymic hyperplasia was made based on the patients' imaging findings. In 15 patients, thymic hyperplasia was suspected based on the size and shape of the thymus gland on CT as follows: the biconvex margin and/or the thickness of the thymus gland was ≥ 19 mm in the pediatric group or ≥ 14 mm in the adult group [Fig. 1-3]. The thickness of the thymus was measured as the maximum dimension perpendicular to the long axis of each lobe. In 2 cases, a diagnosis of rebound hyperplasia was made based on the patients' clinical information and imaging findings. An enlarged thymus gland was found on CT and/or MRI after chemotherapy in 2 patients (due to nodular sclerosis classical Hodgkin's lymphoma and Langerhans cell histiocytosis, respectively) [Fig. 4, 5]. No further increase in the size of the thymus, which would have been suggestive of tumor recurrence, was identified on CT or PET-CT during the 6-month follow-up period.

MRI Sequence

MRI was performed with 1.5T units (Intera Achieva, Philips Healthcare, Best, the Netherlands [n = 11]; Magnetom Sonata, Siemens Medical Systems, Erlangen, Germany [n = 8]). The patients were assigned to the MRI units on the basis of the availability of the machines. All patients underwent chemical-shift MRI (transverse

gradient dual-echo T1-weighted in-phase and opposed-phase imaging). These images were acquired using gradient-echo sequences during a single breath hold. The sequence parameters were as follows: image matrix, 256×256-512×512; section thickness, 3-5 mm; intersection gap, 0.2-1.0 mm; flip angle, 70°or 75°; repetition time, 94.15-244.27 msec; and in-phase and opposed-phase echo times, 4.6-4.8 and 2.3-2.4, respectively. T2-weighted imaging (T2WI) was also performed in all patients. The T2WI parameters were as follows: image matrix, 256×256-512×512; section thickness, 3-5 mm; intersection gap, 0.2-1.5 mm; flip angle, 90°or 180°; repetition time, 600-4953 msec; and echo time, 80-95 msec. In addition, diffusion-weighted imaging and/or Gd-enhanced MRI were performed as necessary.

MRI Analysis

The signal intensity of the thymus gland (tSI) and that of the para-spinal muscle (mSI) were obtained using standard region-of-interest (ROI) electronic cursors on both the in-phase (tSI_{in} and mSI_{in}) and opposed-phase images (tSI_{op} and mSI_{op}). These measurements were obtained by a single radiologist (T.Y., who has 15 years' experience of clinical MRI) in all cases. The tSI measurements were obtained at the level of the maximum axial surface of the thymus gland, and the ROI was selected by surrounding the whole circumference of the thymus gland, avoiding any cystic, necrotic, or calcified components. The ROI used to obtain the mSI measurements was positioned so as to exclude fat striations as much as possible. The relative change in the ratio of the signal intensity of the thymus gland to that of the para-spinal muscle (the CSR) was calculated according to the following formula: $CSR= (tSI_{op}/mSI_{op})/ (tSI_{in}/mSI_{in})$

Statistical Analyses

The CSR of all groups are expressed as mean ± standard deviation (SD) values.

The relationship between the CSR of thymic hyperplasia and age was evaluated via regression analysis involving a correction coefficient. To evaluate the significance of the differences between the two groups, *t*-test was performed after the variances of the data

had been examined with the F test. In addition, significant differences between CSR of PTH and PTT, significant differences between CSR of ATH and ATT, and significant differences between CSR of PTH and ATT were also evaluated. *P*-values of < 0.05 were considered to indicate a statistically significant difference. All statistical analyses were performed using software (IBM SPSS statistics ver.19).

Results

PTH (≤ 15 years) included 5 patients (4 males and 1 female) and ATH (≥ 16 years) included 14 patients (5 males and 9 females). The mean thickness (± SD) of the thymus was 2.2 cm (± 0.33) in PTH and 1.7 cm (± 0.34) in ATH, respectively, and the difference between the two groups was not significant ($P = 0.670$). A significant correlation (second-order regression curve) was found between the CSR of thymic hyperplasia and age ($r = 0.865$, $P < 0.001$) [Fig. 8].

The mean CSR (± SD; range) of PTH and ATH were 0.923 (± 0.058; 0.854-0.985) and 0.454 (± 0.165; 0.168-0.724), respectively. The difference between the two groups was significant ($P < 0.001$), and the CSR of the two groups did not overlap on box plots [Fig. 9]. The mean CSR (± SD; range) of ATT was 0.988 (± 0.036; 0.931-1.047) and did not overlap with that of ATH. PTT was only a case (pathological finding: lymphangioma, CSR: 0.952) and CSR of PTT overlapped with that of PTH [Fig. 9].

There was significant difference in the CSR between PTH and ATT ($P = 0.006$), but they were also partly overlapped [Fig. 9].

Discussion

Several previous studies have examined the age-related appearance of the normal thymus on CT or MRI [1, 8, 12]. Baron RL et al. [12] reported that the CT attenuation values of the normal thymus decrease with age, and in the majority of patients over 40 years of age the thymus shows similar attenuation values to fat. While the width of the

thymus tends to decrease with age it varies markedly in young adults.

Inaoka T et al. [1] detected a strong correlation between signal intensity loss (SIL) of normal thymus and age ($r = 0.750$, $P < 0.001$), and the SIL increased with age in subjects aged ≥ 11 years. In addition, they found that chemical-shift MRI could depict physiological fatty replacement of the normal thymus in nearly 100% of patients over the age of 15 years.

In the present study, the CSR of thymic hyperplasia exhibited a significant association (a second-order regression curve) with age in subjects aged 6-59 years old ($r = 0.842$, $P < 0.001$). The reason of second curvilinear correlation can be explained by the reason that out-of-phase value constituting numerator of CSR is dependent on deduction of signal intensity of water and that of fat tissue in thymic hyperplasia. Thus, it is thought that out-of-phase value in the 30-40 years old shows minimum by deduction of those intensity because fat tissue will deposit moderately as same as water. In 30 years of age younger or 40 years of age older, out-of-phase value shows higher than 30-40 years old by deduction of those intensity because in 30 years of age younger water will relatively exist more than fat tissue and in 40 years of age older fat tissue will relatively exist more than water in thymic hyperplasia. On the other hand, age-related change of in-phase value constituting denominator of CSR is slight, and the signal intensity of paravertebral muscle also hardly change according to age. Therefore, it is thought that CSR shows a second-order regression curve that the top is formed in 30-40 years old, under the influence of change of out-of-phase value.

Accordingly, the CSR of the normal thymus and thymic hyperplasia will display similar correlations with age, because the correlation between CSR of normal thymus and age will be also a second curvilinear correlation in chemical-shift MRI for aging change of quantity of fat within thymus as with thymic hyperplasia. Therefore, it was suggested that the quantity of fat within thymic hyperplasia lesions might be depend on that within the original normal thymus.

When a soft tissue mass is found in the anterior mediastinum, the differentiation of a residual or hyperplastic thymus from a thymic tumor is very important for determining the necessity of further examinations or treatment, e.g., whether observation, needle biopsy, or surgery is required. Inaoka T et al. [2] reported that the mean CSR of their hyperplasia group was 0.614 ± 0.130, whereas that of their tumor group was 1.026 ± 0.039 ($P < 0.001$) (age range, 16-78 years). Priola AM et al. [4] demonstrated that on dual-echo chemical-shift MRI, the signal intensity index and CSR are highly accurate tools for distinguishing thymic hyperplasia from tumors (age range, 18-84 years). In the present study, the CSR of ATH were not overlapped with that of ATT (age range, 19-77 years) and could distinguish thymic hyperplasia from thymic tumors.

Many previous studies have suggested that MG is frequently associated with thymic abnormalities, including thymic hyperplasia and thymomas. MG is classified into thymoma-associated MG, early-onset MG (onset age: < 50 years), and late-onset MG (onset age: ≥ 50 years) [13]. In addition, MG that occurs in patients aged ≤ 15 years old is generally called childhood MG (CMG). In East Asian nations, such as Japan and China [14], the onset of CMG peaks in infancy (around 5 years old). The treatment of MG is broadly divided into two methods: conservative drug treatment and surgical resection of the thymus. Generally, thymic resection is accepted to be effective against thymoma-associated MG, but not non-thymoma-associated MG and thymic resection is scarcely performed for MG, especially for CMG [15, 16]. Thus, it becomes particularly important that the differentiation with thymic tumor (thymoma) and thymus hyperplasia in under 15 years old. Furthermore, the ability to differentiate between thymic hyperplasia and thymic tumors is also required in cases of rebound thymic hyperplasia in patients who are receiving chemotherapy for malignancy, especially in pediatric patients.

In the present study, The CSR of PTH overlapped with that of PTT which was only a case (Lymphangioma, CSR: 0.95). In addition, significant difference was seen in the

CSR of PTH with that of ATT (P = 0.006), however the overlap was also seen. If it was assumed that the CSR of ATT and PTT were same value, it supports that the CSR of PTH overlapped with that of PTT, but there are too few cases in this study for it. And in comparison with the data of other articles, CSR of thymoma: 0.974-1.081, non-invasive thymoma: 0.849-1.276, and Hodgkin's lymphoma: 0.870-1.186 [2, 4], the CSR of PTH in present study partly overlapped with them, too. The fat quantity of the thymic hyperplasia and that of the tumors are not proved pathologically, but it is supposed that thymic hyperplasia 15 years or younger is hardly included fat tissue as same as thymic tumors.

Therefore, it is generally difficult to differentiate between thymic hyperplasia and thymic tumors in pediatric patients, unlike in adults (≥ 16 years). Thus, chemical-shift MRI is of limited use for characterizing thymic lesions in children, unlike in adults (≥ 16 years), and hence, children with suspected thymic lesions should be comprehensively evaluated using other MRI sequences and other modalities, including CT, PET-CT, and follow-up examinations.

The present study has some limitations. First, it was a retrospective study. Second, no pathological proof of the diagnosis was obtained in most cases with thymic hyperplasia. However, it might be difficult to acquire pathological proof in many patients because thymic hyperplasia is basically a benign process, and most patients that are suspected to suffer from thymic hyperplasia do not require any further treatment (e.g., an operation or biopsy). Third, the sample size was small, and no power analysis was performed. Forth, there was a gap in the age distribution of the data (no data for patients aged between 13 and 22 years old were included in the present study), which might have reduced the reliability of our results. Finally, the data that were taken by different MR apparatus and from other articles are mixed. It is thought that there are some consistency because CSR is not absolute value and is ratio, but it cannot be secured the equitableness.

In conclusion, the CSR of thymic hyperplasia was found to be associated with age, as has been demonstrated for the normal thymus. Furthermore, in pediatric patients (particularly those younger than 15 years old) the CSR of thymic hyperplasia might partly overlap with the CSR of tumors, and clinicians should be aware of that the utility of the CSR for characterizing the thymus is age-dependent.

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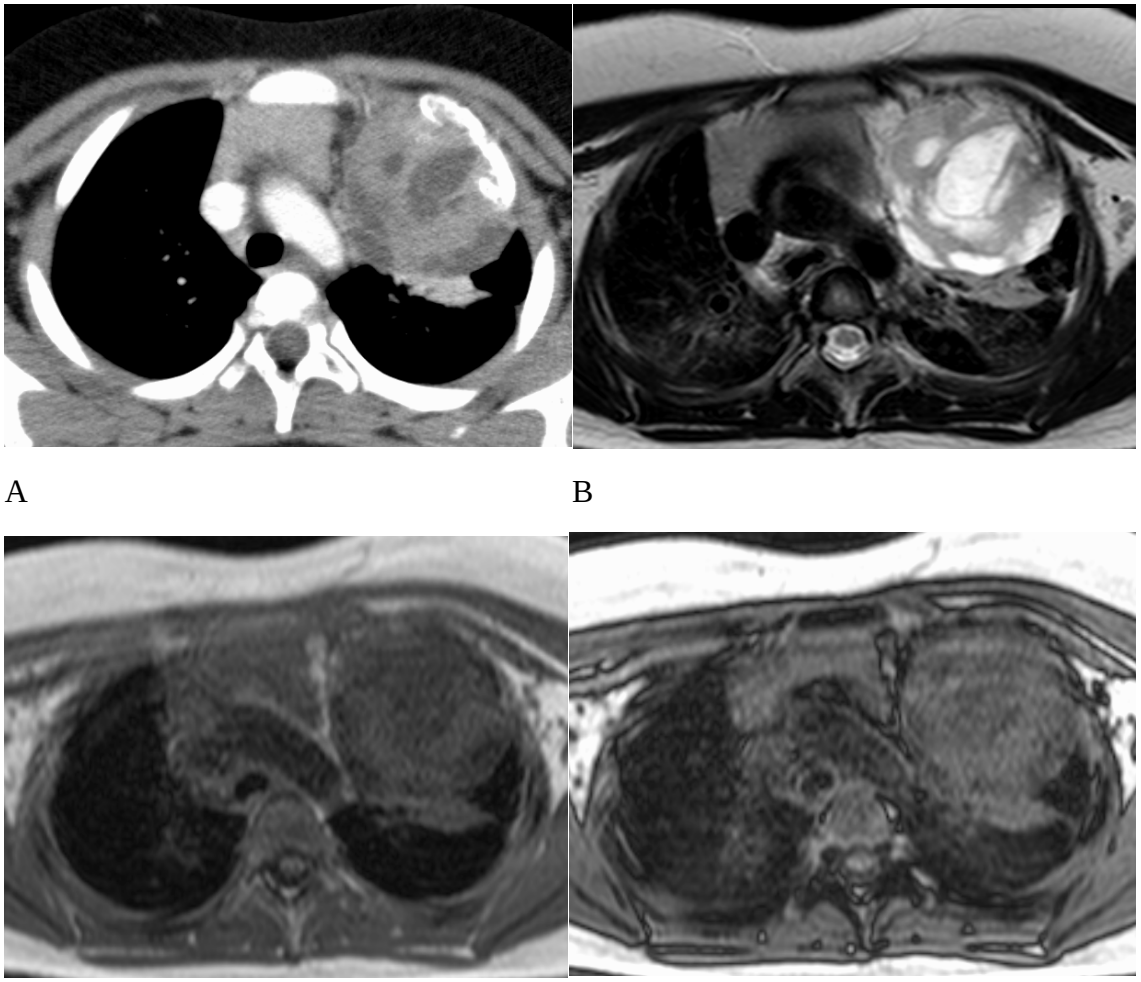
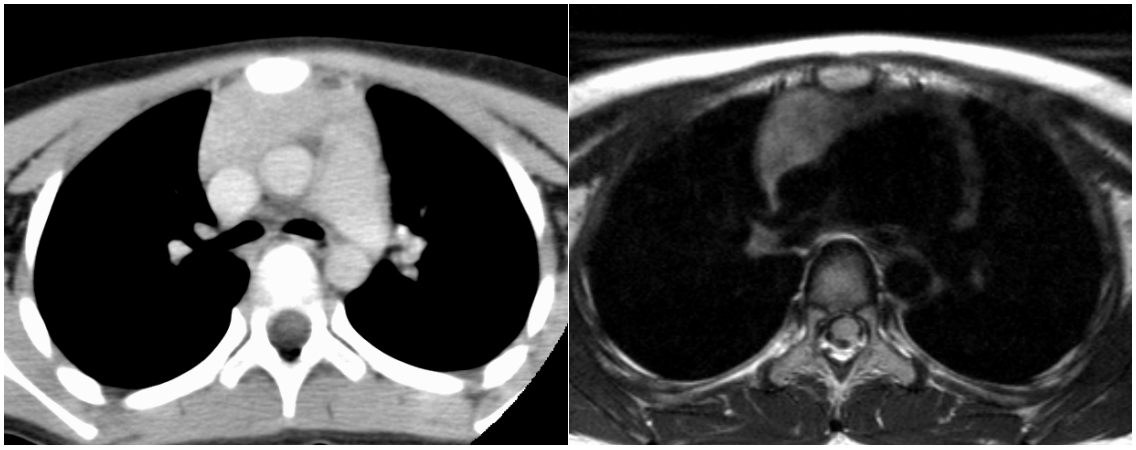


A B

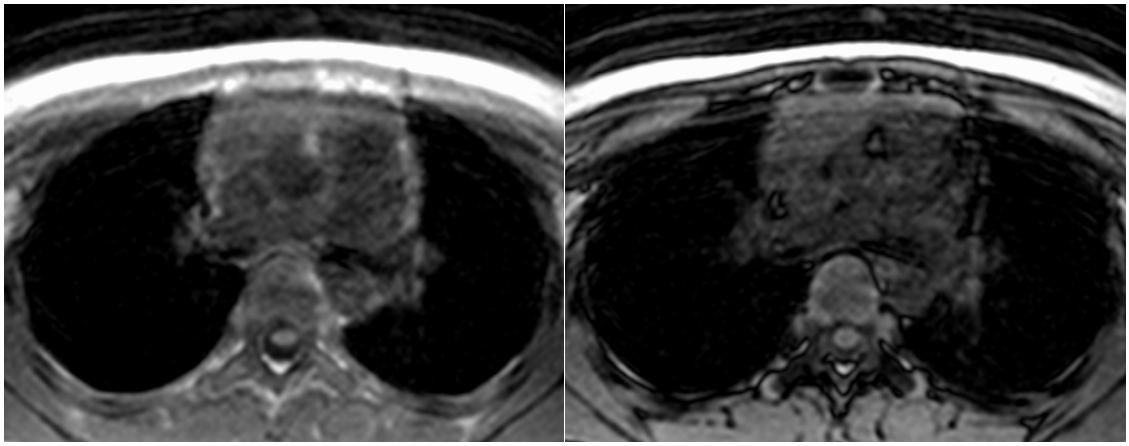
C D

Fig. 1 — 6-year-old female with thymic hyperplasia that morphologically diagnosed, coexisting with peripheral primitive neuroectodermal tumor.

(A, B) The maximal thickness of the thymus gland was 19 mm, which falls outside of the normal range (< 19 mm) for pediatric on contrast-enhanced CT and T2WI. (C, D) During a comparison of (C) in-phase (94.15/4.6) and (D) opposed-phase (94.15/2.3) chemical-shift MRI, no marked changes in the signal intensity of the thymus were seen. The CSR was 0.98.



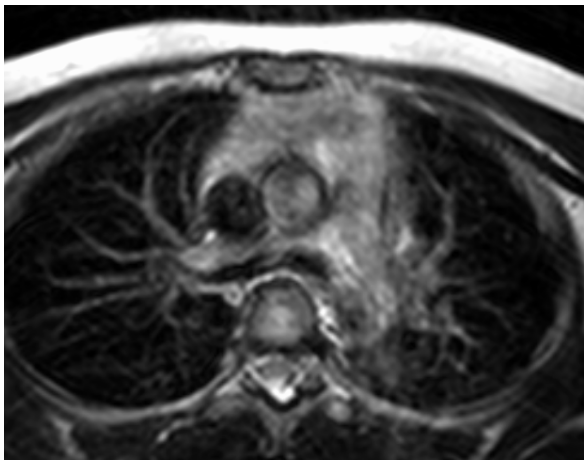
A B



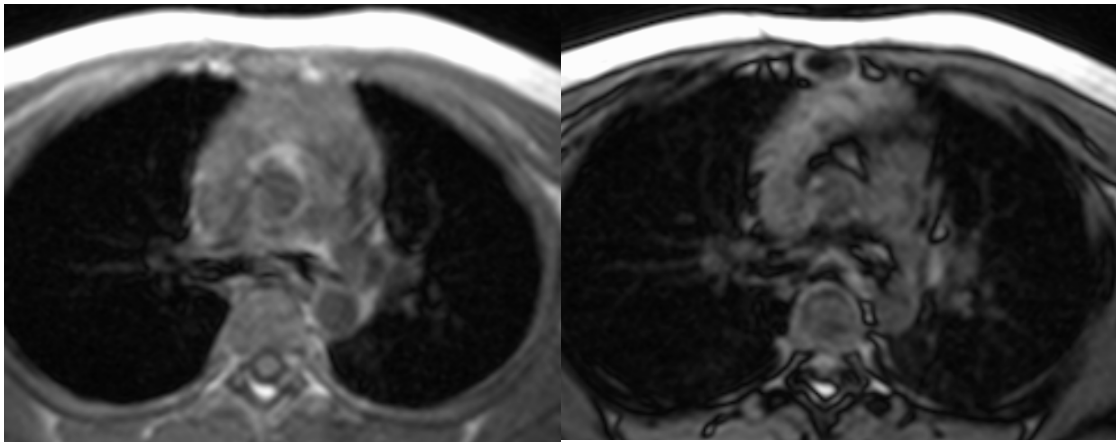
C D

Fig. 2－7-year-old male with thymic hyperplasia that morphologically diagnosed, that suspected mediastinal neoplasm.

(A, B) The maximal thickness of the thymus gland was 21 mm, which falls outside of the normal range (< 19 mm) for pediatric on contrast-enhanced CT (A) and T2WI (B). (C, D) During a comparison of (C) in-phase (130/4.8) and (D) opposed-phase (130/2.4) chemical-shift MRI, no marked changes in the signal intensity of the thymus were seen. The CSR was 0.85.



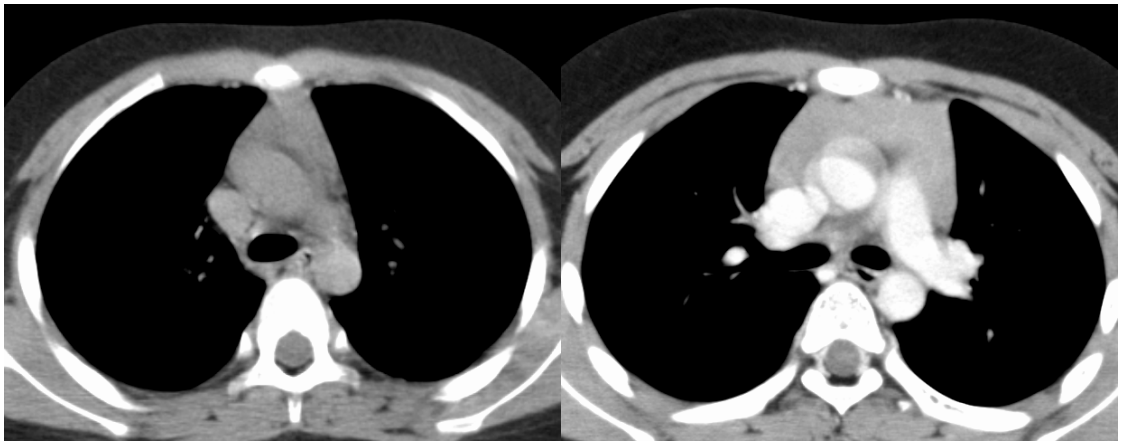
A



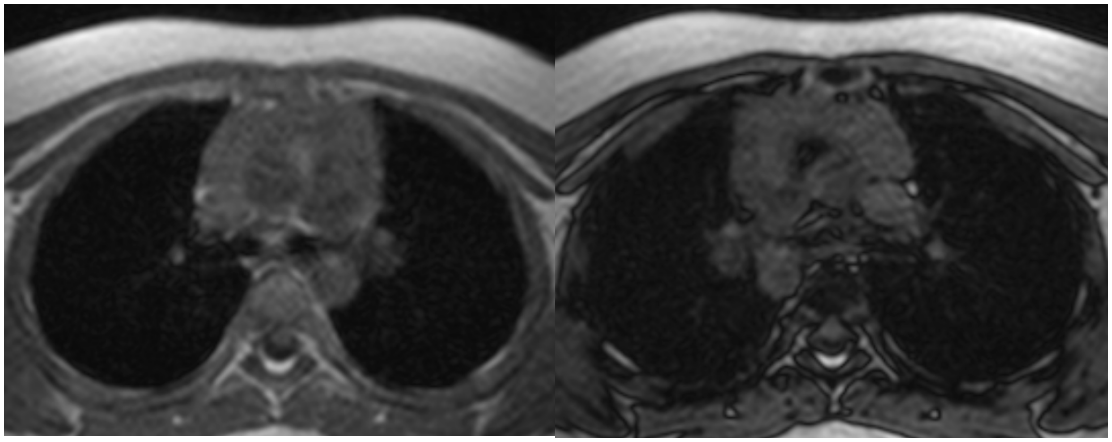
B C

Fig. 3－9-year-old male with thymic hyperplasia that morphologically diagnosed.

(A) The maximal thickness of the thymus gland was 22 mm, which falls outside of the normal range (< 19 mm) for pediatric on T2WI. (B, C) During a comparison of (B) in-phase (122/4.8) and (C) opposed-phase (122/2.4) chemical-shift MRI, no marked changes in the signal intensity of the thymus were seen. The CSR was 0.97.



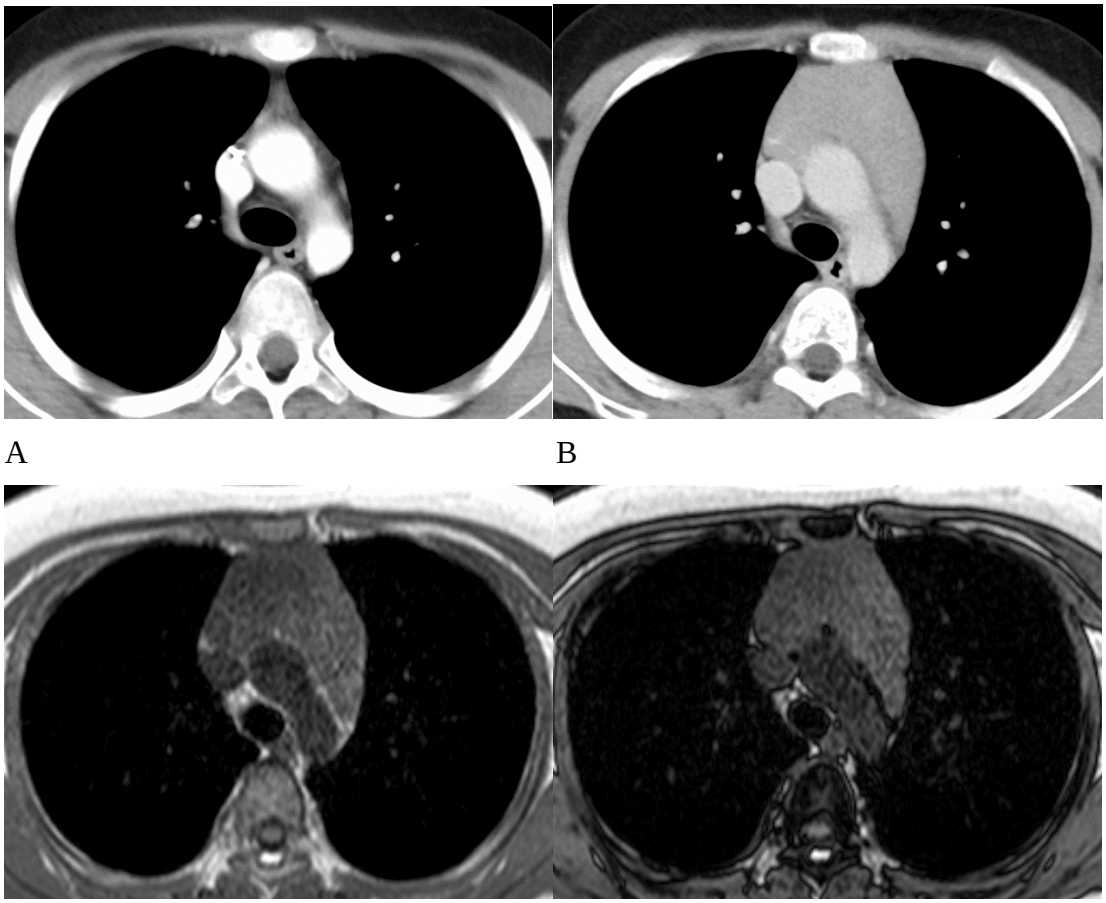
A B



C D

Fig. 4－9-year-old patient with rebound thymic hyperplasia that developed after chemotherapy for Langerhans cell histiocytosis.

(A) Plain CT obtained just before chemotherapy. (B) In contrast enhanced CT obtained 6 months after chemotherapy, it was revealed that the thymus enlarged than before chemotherapy. These findings are suggestive of rebound thymic hyperplasia. The maximal thickness of the thymus gland was 19 mm. (C, D) During a comparison of (C) in-phase (122/4.8) and (D) opposed-phase (122/2.4) chemical-shift MRI taken 6 months after systemic chemotherapy, no marked changes in the signal intensity of the thymus were seen. The CSR was 0.87.

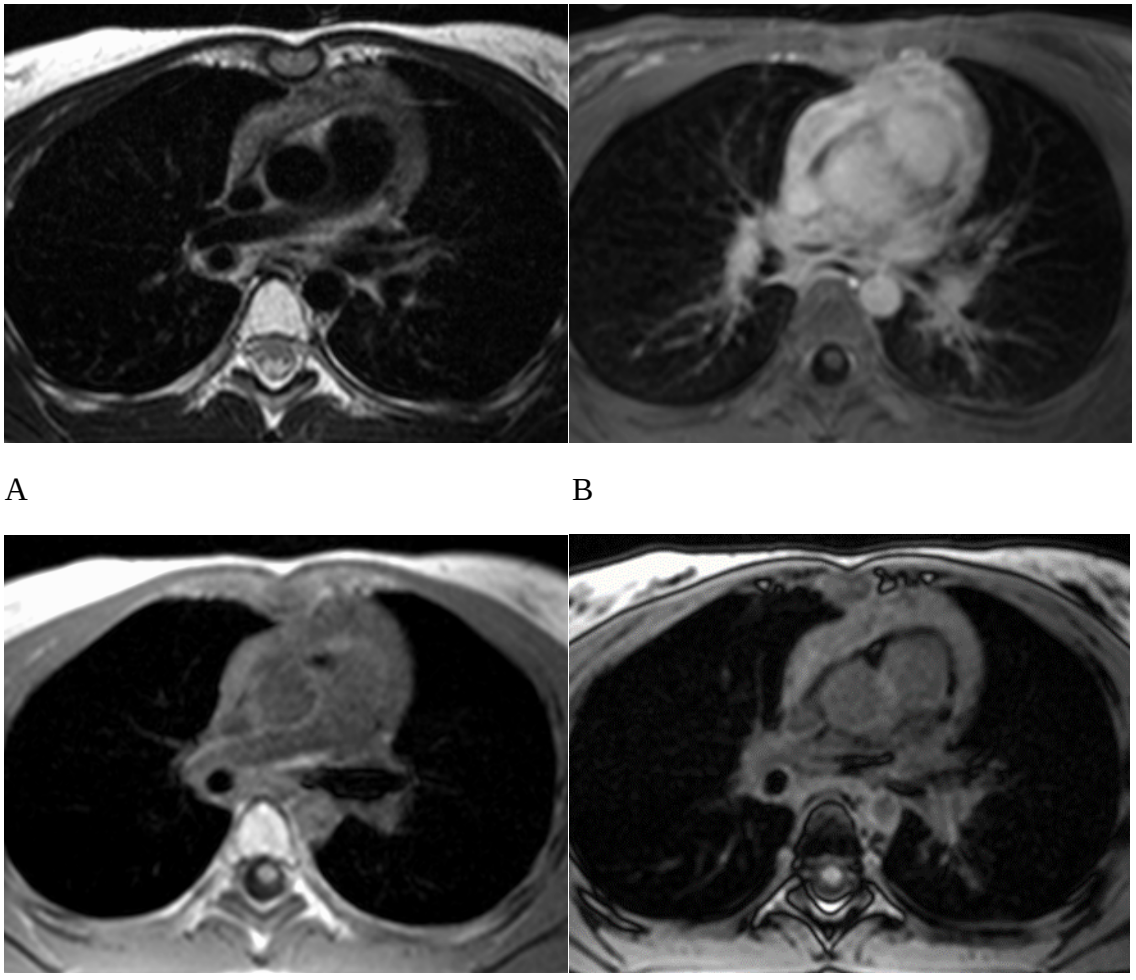


A B

C D

Fig. 5－12-year-old patient with rebound thymic hyperplasia who developed nodular sclerosis classical Hodgkin’s lymphoma after chemotherapy.

(A) Contrast-enhanced CT obtained just before chemotherapy and (B) 4 months after chemotherapy. After initially shrinking after chemotherapy, the thymus enlarged markedly. These findings are suggestive of rebound thymic hyperplasia, but recurrent lymphoma should be excluded. The maximal thickness of the thymus gland was 27 mm. (C, D) During a comparison of (C) in-phase (124/4.6) and (D) opposed-phase (124/2.3) chemical-shift MRI taken 4 months after systemic chemotherapy, no marked changes in the signal intensity of the thymus were seen. The CSR was 0.93.

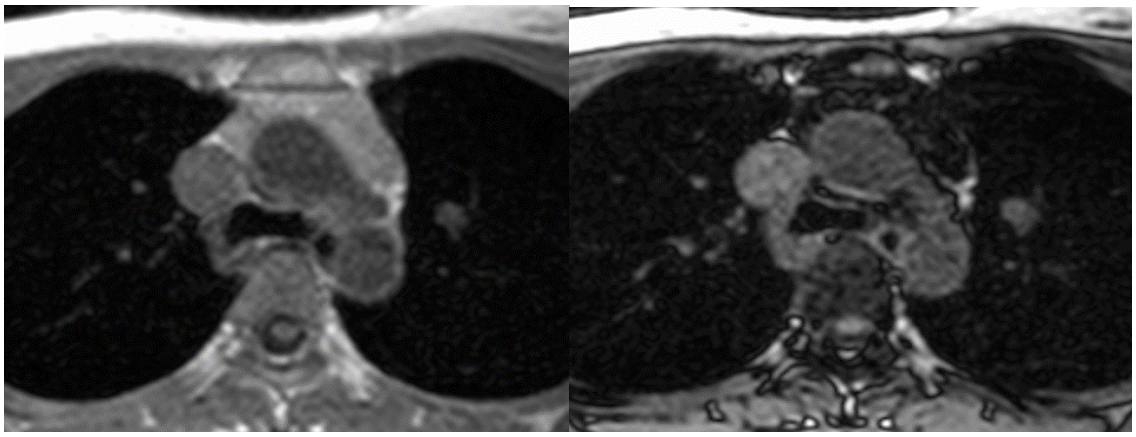


A B

C D

Fig. 6－12-year-old patient with Lymphangioma of thymus that pathologically diagnosed.

(A) T2WI and (B) contrast enhanced T1WI revealed thymic lesion. (C, D) During a comparison of (C) in-phase (122/4.8) and (D) opposed-phase (122/2.4) chemical-shift MRI, no marked changes in the signal intensity of the thymus were seen. The CSR was 0.952.



A B

Fig. 7－37-year-old male with thymic hyperplasia that morphologically diagnosed, without myasthenia gravis.

MRI depicted an enlarged thymus with marginal lobulation. The maximal thickness of the thymus gland was 19 mm, which falls outside of the normal range (<14 mm) for adults. (A, B) During a comparison of (A) in-phase (163/4.8) and (B) opposed-phase (163/2.4) chemical-shift MRI, a marked reduction in the signal intensity of the anterior mediastinum was seen on the opposed-phase images, which was considered to be indicative of thymic hyperplasia with fatty degeneration. The CSR was 0.170.

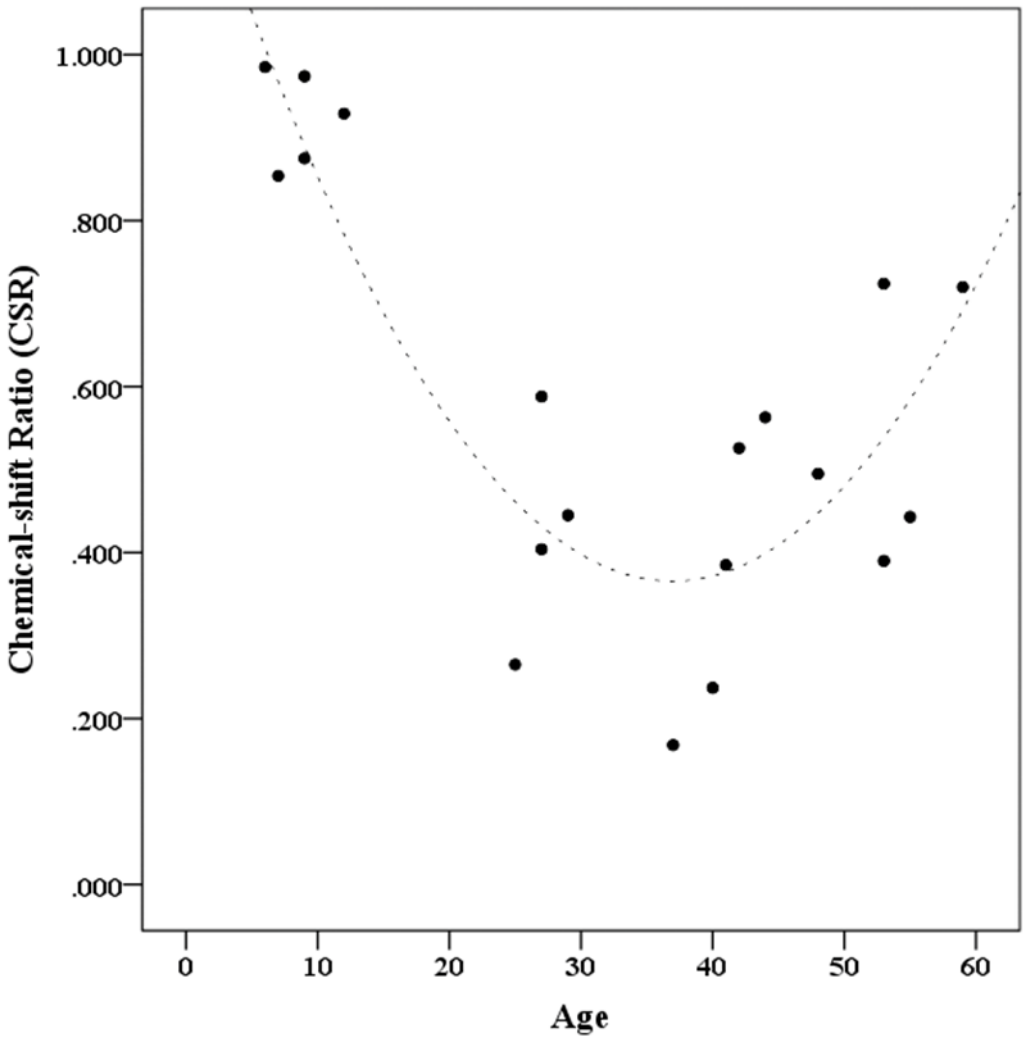


Fig. 8—Correlation between the CSR of thymic hyperplasia and age.

A significant correlation (a second-order regression curve) was detected between the CSR of thymic hyperplasia and age ($r = 0.865$, $P < 0.001$).

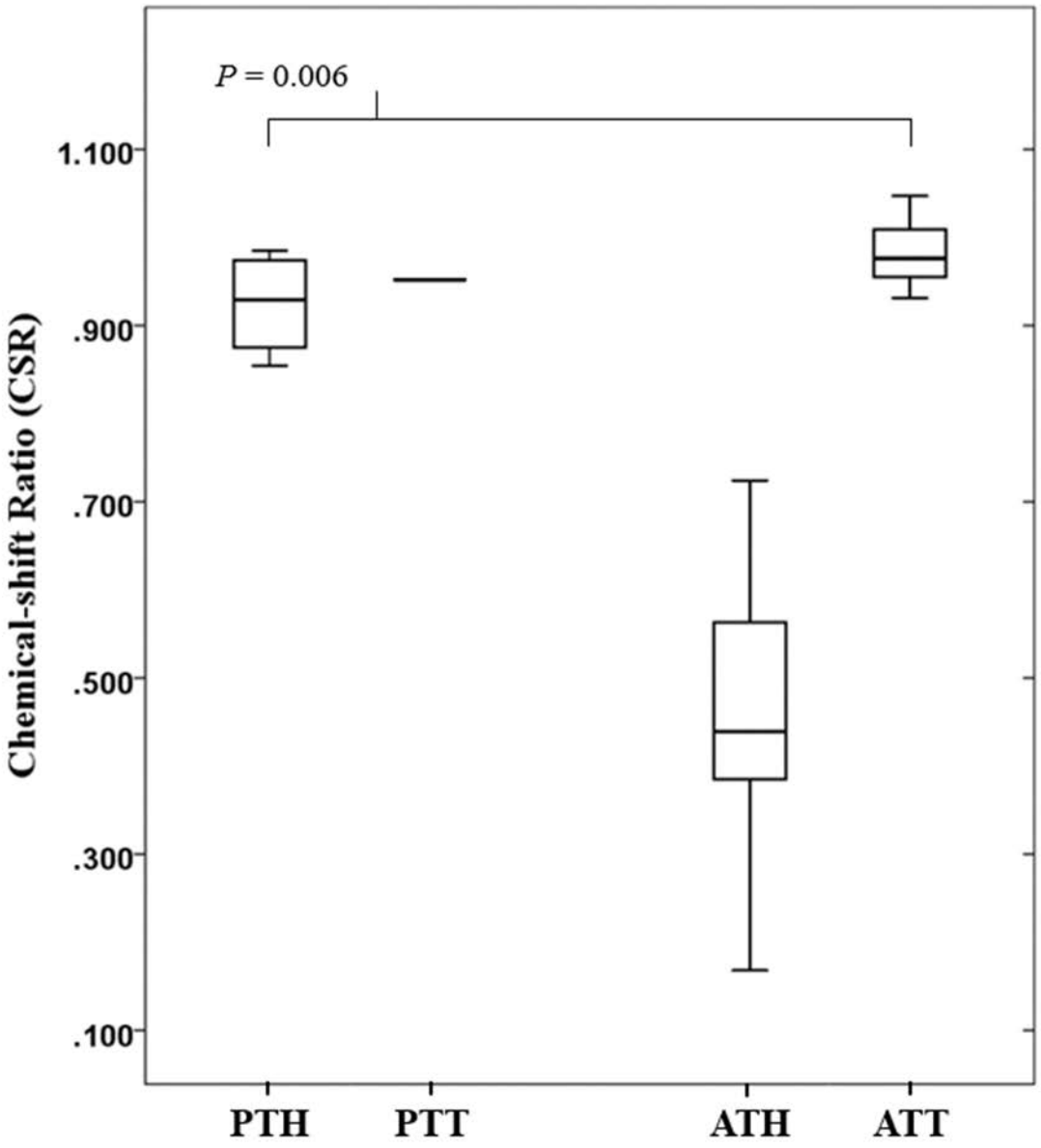


Fig. 9－Box plots of the CSR values of PTH, PTT, ATH, and ATT.

The mean CSR (± SD; range) of PTH, ATH and ATT were 0.920 (± 0.058; 0.854-0.985), 0.454 (± 0.165; 0.168-0.724), and 0.988 (± 0.036; 0.931-1.047). The CSR of PTT was 0.952.

Note, that the CSR of the two groups with thymic hyperplasia did not overlap and that the CSR of PTH overlapped with that of PTT. In addition, note, that there was significant difference in the CSR between PTH and ATT (P = 0.006), however the CSR

of PTH overlapped with that of ATT.

*PTH: pediatric group with thymic hyperplasia

*PTT: pediatric group with thymic tumor

*ATH: adult group with thymic hyperplasia

*ATT: adult group with thymic tumors