# Diagnostic value and clinical validation of Acute Thyrotoxic Myopathy Symptom Score in acute thyrotoxic myopathy

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## Abstract

# Objectives

Acute thyrotoxic myopathy (ATM) is characterized by bulbar paralysis and limb myasthenia on the basis of hyperthyroidism, which can cause respiratory failure, coma and death. However, the diagnosis of ATM is challenging. The purpose of this study was to develop a symptom rating scale called the Acute Thyrotoxic Myopathy Symptom Score (ATMSS) to assist in the early diagnosis of ATM in clinical practice.

# Methods

(1) the ATM reference sample was constructed by searching for patients diagnosed with ATM or thyrotoxic bulbar palsy in the PubMed, Embase and Web of Science databases (ATM cohort); (2) the ATMSS was formulated based on the ATM cohort after multidisciplinary discussion; and (3)51 patients with ATM and 49 patients with Graves' disease (GD) were enrolled in the study. (4) Receiver operating characteristic (ROC) curve analysis was applied to appraisal diagnostic value of the ATMSS for differentiating patients with ATM from patients with GD. (5) We also evaluated the correlation between ATMSS score and age, sex, thyroid function and thyroid-related antibody.

# Results

The ATMSS score showed better diagnostic value at an optimal cut-off value of 5.5 [area under the curve (AUC) = 0.979; 95% confidence interval (CI) = 0.956-1; $p < 0.0001$; sensitivity = 94.1%; specificity = 93.9%]. The ATMSS score was positively correlated with free triiodothyronine ($FT_3$) [Spearman correlation coefficient ($r_s$) = 0.422, $p < 0.001$] and free thyroxine ($FT_4$) ($r_s$=0.497, $p < 0.001$).

# Conclusions

We developed a symptom rating scale named the ATMSS, which is effective in diagnosing ATM, ATMSS score is positively correlated with thyroid function. ATMSS can be used as an additional tool for diagnosing ATM.

## Introduction

Acute thyrotoxic myopathy (ATM) is a serious and relatively rare clinical complication of hyperthyroidism that mainly manifests as bulbar paralysis and is also known as acute thyrotoxic encephalopathy and acute thyrotoxic bulbar palsy[1, 2]. Symptoms of bulbar paralysis, such as dysphagia, dysphonia and dysarthria, dyspnoea, and muscle weakness of limbs, can quickly appear in this disease and accompanied by aspiration pneumonia and hyperthyroid crisis, causing respiratory failure, drowsiness, and coma until death[3, 4]. With early identification of ATM and timely administration of antithyroid drugs, beta-blockers and other drugs, the disease can significantly recover in a short time[5]. At present, the understanding of this disease is based mainly on case reports. There are no clear diagnostic criteria or specific related tests in domestic or foreign guidelines, the diagnosis is not easy and usually based on the combination of clinical symptoms and retrospective diagnosis after follow-up. Some patients with ATM may not have typical symptoms of bulbar paralysis [6, 7], some patients with hyperthyroidism may also present with muscle weakness [1], or with atypical hyperthyroidism symptoms at the same time[8], in addition, there may be insufficient clinical understanding about ATM, all of these conditions can make the diagnosis of ATM difficult. Therefore, it is necessary to develop an effective method to assist in the diagnosis of ATM.

In this study, by reviewing the clinical cases of ATM publicly reported before 2020 and summarizing the clinical characteristics of the patients, we developed a symptom score called the ATMSS to assist in the diagnosis of ATM. The diagnostic efficacy of ATMSS was evaluated in clinical ATM and GD patients. The ATMSS is simple to administer in the form of questionnaires and physical examinations, which is expected to help clinicians better identify ATM, reduce misdiagnosis, and provide help for the early treatment of ATM. We also evaluated the correlation between ATMSS and thyroid-related markers, providing a clinical basis for further research on the pathogenesis of ATM.

## Methods and Materials

1. Determination of reference cohorts and formulation of ATMSS.

Case reports of patients with acute thyrotoxic myopathy or thyrotoxic bulbar palsy were screened by searching electronic databases (PubMed, Web of Science, Embase) with the following text terms: ‘thyrotoxic myopathy’, ‘thyrotoxic bulbar palsy’, and ‘thyrotoxicosis and dysphagia’. The search time frame was from the establishment of the database to December 31, 2019, and a total of thirty-five patients considered to be acute thyrotoxic myopathy or thyrotoxic bulbar palsy were included in the ATM reference cohort. By analysing the clinical characteristics of the reference cohort, combined with the diagnostic features of bulbar palsy, it was found that ATM patients most commonly had seven clinical features, namely, nasal reflux, dysphagia, hoarseness, dysarthria, dyspnoea, muscle weakness and abnormal gag reflex. The selection of items included in the ATMSS was based on the above clinical features and designed by the available literature, expert opinion, preliminary experiments, the clinical experience of the authors' team and discussion with neurologists from the Department of Neurology of the First Affiliated Hospital of Guangxi Medical University [9–11]. A total of 19 related items were designed in the ATMSS. Each clinical symptom is assigned a total score of 8 points (hoarseness is considered to be a manifestation of pitch and volume changes in dysarthria, combined as dysarthria[12]), except for gag reflex assignment, which is assigned for 2 points as a single test item. the total score

ranges from 0 to 42 consisting of the sum of the scores for each item, with higher scores predicting more significant clinical presentation. The ATMSS was previously evaluated in 10 newly diagnosed ATM patients to confirm that their ATM-related symptoms were adequately detected.

2. Subjects and verification of the application of ATMSS

The ATM group included 51 ATM patients who were diagnosed and treated at the Department of Endocrinology of the First Affiliated Hospital of Guangxi Medical University from January 2020 to February 2024. The diagnosis was based on the following criteria: (1) a definitive diagnosis of hyperthyroidism; (2) one or more symptoms of bulbar palsy, such as nasal reflux, hoarseness, dysarthria, dysphagia, or dyspnoea; and (3) bulbar palsy cannot be explained by other causes. Patients who met the above three criteria were considered patients with suspected ATM. (4) If the above symptoms were significantly relieved after treatment for hyperthyroidism by follow-up for one week to two months, the patient was considered to have ATM. In addition, we recruited 49 patients with GD as a control group. GD was confirmed by hyperthyroidism, increased TRAb, diffuse goitre on ultrasound. Exclusion criteria for all subjects were as follows: (I) aged < 14 years; (II) pregnant; and (III) had central or peripheral nervous system diseases such as stroke, intracranial tumors or neuromuscular causes, myasthenia gravis, electrolyte disorders, throat and esophagus disorders or mechanical causes.

All patients with suspected ATM and GD underwent the detection of thyroid function such as $FT_3$, $FT_4$, thyrotrophin receptor thyroid stimulant hormone (TSH), thyroid-related antibody, such as thyrotrophin receptor antibody (TRAb), thyroglobulin antibody (TGAb), thyroid peroxidase antibody (TPOAb) and ATMSS evaluation. $FT_3$, $FT_4$ and TSH were tested by electrochemiluminescence (Beckman Coulter Inc.). TRAb, TGAb and TPOAb were measured by radioimmunoassay. The ATMSS is implemented by clinicians within the study group through training.

3. Protocol approval and patient consent

This study was performed in line with the principles of the declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University. All participants or their legal guardian provided informed consent.

4. Statistical analysis

SPSS 26.0 was used for the statistical analysis. Normally distributed data are expressed as the mean ± standard deviation ($\bar{x}\pm s$). Independent sample t tests and one-way analysis of variance (ANOVA) were used for comparisons. Nonnormally distributed measurements are presented as the median (M), 25th to 75th percentiles (P25-P75) and were compared using the Mann–Whitney U test. Spearman correlation analysis was used to analyse the correlation between nonnormally distributed variables. The ROC curve was used to analyse the sensitivity and specificity of the ATMSS score for the diagnosis of ATM. The optimal cut-off was determined as the value corresponding to the maximum Youden index (sensitivity + specificity-1). $p < 0.05$ was considered to indicate statistical significance.

## Results

1. Reference cohort of patients with ATM

Thirty-five patients screened out in the databases with the diagnosis of ATM or thyrotoxic bulbar palsy were selected for the ATM cohort. In the cohort, the male to female ratio was 1:1.06, the mean age at first manifestation was 50.77 (± 18.05) years, all patients underwent thyroid function testing and were diagnosed with hyperthyroidism in the ATM cohort, 33/35 patients had dysphagia, 21/35 had varying degrees of hoarseness, 4/35 had dysarthria, 14/35 had nasal reflux, 28/35 had muscle weakness predominantly proximal limb weakness, 6/35 had dyspnoea, and another 4/35 had abnormal gag reflex. The above clinical manifestations were significantly relieved after treatment with antithyroid drugs (ATDs) or combined beta-blockers, steroids or iodine for a mean of 4 weeks. Patients with other disorders that cause bulbar paralysis symptoms, such as central nervous system lesions, myasthenia gravis, throat and oesophagus imbalances, were excluded from the diagnosis. The ATM cohort data, such as sex, age at onset, bulbar palsy-related symptoms, response to treatment, therapeutic medications, and disease duration, are displayed in Table 1.

Table 1
Overview of the ATM reference cohort of patients[3–7, 13–26]

| | Age of Onset (years) | Sex(M:F) | Hoarseness (N/T) | Dysarthria (N/T) | Nasal reflux (N/T) | Dysphagia (N/T) | Muscle weakness (N/T) | Dyspnoea (N/T) | Abnormal gag reflex (N/T) | Treatment | Time to resolution (Weeks) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ATM reference cohort of 35 patients | 50.77 (± 18.05) | 1:1.06 | 21/35 | 4/35 | 14/35 | 33/35 | 28/35 | 6/35 | 4/35 | ATDs or combined BBs, steroid, iodine | 4(1,8) |

The data are expressed as the mean ± standard deviation and 25th–75th percentile (P25–P75). ATDs, antithyroid drugs; BBs, beta-blockers; F, female; M, male. N, number of people with symptoms, T, total number of people.

2. Diagnostic score scale ATMSS

Our constructed Acute Thyrotoxic Myopathy Symptom Score (ATMSS) is shown in Box 1. Before the scale is applied, the following conditions must be met:

I. The use of this scale should be based on a clear diagnosis of hyperthyroidism;

II. ATMSS should be performed on the basis of exclusion of other diseases causing bulbar palsy;

III. Patients with positive limb strength assessment alone are not suitable for this scale.

Box 1: Symptom scores of patients with ATM

| Acute Thyrotoxic Myopathy Symptom Score (ATMSS) |
|---|
| **A. Nasal reflux** |
| 1. Do you have a cough or feel like coughing after drinking water? 0: None; 1: Only choking; 2: Cough after drinking water. |
| 2. Is there regurgitation from the nasal cavity? 1: Yes; 0: No. |
| 3. In the drinking water test, the patient sits upright, drinks 30 ml of warm water and observes (if the patient chokes severely, the test will be stopped).<br>0: Swallowed water smoothly once; 1: Swallowed more than 2 times without choking; 2: Swallow it once, but choke; 3: Swallow more than 2 times, but choke; 4: Frequent choking and not being able to swallow it all. |
| **B.** Dysphagia |
| 1. Is it difficult to swallow when eating? 1: Yes; 0: No. |
| 2. Is it more strenuous to eat solid foods than to eat semiliquid (or liquid) foods? 1: Yes; 0: No. |
| 3. Is there a situation where medicine hangs in the throat and is difficult to swallow when taking medicine? 1: Yes; 0: No. |
| 4. Does you vomit after swallowing food or medicine? 1: Yes; 0: No. |
| 5.Repetitive saliva swallowing test: The patient swallows as quickly as possible within 30 seconds, and the number of completed swallows is recorded as 0: ≥3 times; 1: 2 times; 2: 1 time; 3: 0. |
| **C.** Dysarthria |
| 1. Whether there is a hoarseness or slurred pronunciation that is unconsciously or noticed by family members? 1: Yes; 0: No. |
| 2. Which of following is the case?<br>0: None of following cases exist; 1: Pitch becomes low or pronunciation is not fluent; 2: Nasal or slurred articulation (usually none); 3: inability to complete long sentences or fatigue after normal speaking for a long time (can be observed during examination to distinguish); 4: Inability to speak. |
| 3. Patients were asked to sit and count from 1 to 100 at a constant rate.<br>0: can be counted smoothly; 1: can be counted, but it requires multiple pauses or slurred pronunciation; 2: can count over 50; 3: cannot count past 50. |
| **D.** Dyspnoea |
| 1. Is cough laborious? 1: Yes; 0: No (It is recommended that the patient cough forcefully and observe whether cough is strong). |
| 2. Whether there is any sputum that is difficult to cough up. 1: Yes; 0: No. |
| 3. Is there chest tightness or difficulty breathing? 1: Yes; 0: No. |
| 4. Can a decrease in respiratory mobility be observed under calm conditions? 1: Yes; 0: No. |
| 5. Is it possible to take 5 deep breaths in a row? 3: Can be done fewer than two times; 2: can be performed less than three times; 1: can be performed less than four times; 0: can be performed. |
| **E.** Gag reflex |
| Gag reflex. 0: sensitive; 1: sluggish; 2: not elicited. |
| **F.** Muscle weakness |
| 1. The induced upper limb fatigue time was recorded with the arms raised horizontally, and the angle between the upper limb and body was 90° for 120 s.<br>0: Can be completed; 1: Can maintain ≥ 90 but < 120 s; 2: Can maintain ≥ 60 but < 90 s; 3: Can maintain ≥ 10 but < 60 s; 4: Can maintain < 10 s. |
| 2. The patient attempted to complete 10 squats in a row, with both arms raised as flat as possible. 0: Can be done almost without support; 1: Can complete 10 squats but need to be supported by arms; 2: Can complete 5 reps or more and less than 10 reps of squats with support of arms; 3: Cannot complete 5 squats with arm support; 4: Cannot done once. |

3. Evaluation of the diagnostic efficacy of ATMSS in ATM patients

3.1 Table 2 displays the demographic and laboratory data of all the subjects, including 51 patients in the ATM group and 49 patients in the GD group. Patients with ATM were younger (age 32.45 ± 11.14 years *vs.* age 36.92 ± 11.84; $p = 0.043$) and had higher $FT_3$, $FT_4$, TRAb, and TPOAb levels but lower TSH levels than those in the GD group ($p < 0.05$). Females were heavily overrepresented in both the ATM (F/M:42/9) and GD (F/M:42/7) groups.

Table 2
Demographic and laboratory data of the ATM group and GD group

| | ATM(n = 51) | GD(n = 49) | p Value |
|---|---|---|---|
| Gender(F/M) | 42/9 | 42/7 | 0.845 |
| Age of Onset (years) | 32.45 ± 11.14 | 36.92 ± 11.84 | 0.043 |
| $FT_3$(nmol/L) | 22.41(13.44, 32.76) | 8.82(6.67, 20.49) | < 0.001 |
| $FT_4$(pmol/L) | 59.16(34.33, 77.22) | 28.19(17.38, 42.87) | < 0.001 |
| TSH(mIU/L) | 0.01(0.01, 0.01) | 0.01(0.01, 0.15) | 0.006 |
| TRAb(IU/L) | 15.10(10.17, 30.00) | 8.55(2.62, 20.80) | 0.015 |
| TgAb(%) | 35.7(10.73, 53.66) | 23.25(10.09, 52.92) | 0.312 |
| TPOAb(IU/ml) | 775.6(427.4, 1000) | 504(63.65, 873) | 0.022 |

The data are expressed as the mean ± standard deviation and 25th–75th percentile (P25–P75). p values are shown for differences between groups. ATM, acute thyrotoxic bulbar myopathy; GD, Graves' disease. F, female; M, male. FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyrotrophin receptor thyroid stimulant hormone; TRAb, thyrotrophin receptor antibody; TGAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody.

3.2 Compared with GD group, ATM group reported a ninefold greater symptom score [median total ATMSS score [9 (3,14) *vs.* 1 (0, 2) $p < 0.001$] (Fig. 1 and Fig. 2). The highest score reported by patients with ATM was dysarthria [4 (2, 6)], and the highest score reported by patients with GD was muscle weakness [0 (0, 0)]. Each symptom score was greater in the ATM group than in the GD group ($p < 0.001$) (Fig. 2b).

3.3 ROC curve analysis shows that ATMSS had an excellent diagnostic value in the distinguishing ATM group from GD group [ AUC = 0.979, 95% CI: 0.956-1.000; $p < 0.001$], and when the cutoff value was greater than 5.5, ATMSS demonstrated the highest sensitivity and specificity (sensitivity 94.1%, specificity 93.9%) (Fig. 3).

4. Correlation between ATMSS scores and hyperthyroidism.

Spearman analysis was used to analyse 100 patients in the ATM group (51 patients) and GD group (49 patients), and correlations between ATMSS scores and thyroid function-related indices were analysed. The results showed a positive correlation between ATMSS score and $FT_3$ ($r_s$=0.422, $p < 0.001$) and $FT_4$ ($r_s$=0.497, $p < 0.001$) but no significant correlation with sex, age at first manifestation, TSH, TRAb, TGAb or TPOAb (Table 3 and Fig. 4).

Table 3
Spearman correlation coefficient ($r_s$) between ATMSS scores and demographic and laboratory data for all subjects

| | ATMSS | |
|---|---|---|
| | $r_s$ | p |
| Gender | 0.029 | 0.772 |
| Age of Onset | -0.34 | < 0.001 |
| $FT_3$(nmol/L) | 0.422 | < 0.001 |
| FT4(pmol/L) | 0.497 | < 0.001 |
| TSH(mIU/L) | -0.25 | 0.012 |
| TRAb(IU/L) | 0.33 | < 0.001 |
| TGAb(%) | 0.177 | 0.079 |
| TPOAb(IU/ml) | 0.258 | 0.01 |

ATMSS, Acute Thyrotoxic Myopathy Symptom Score; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyrotrophin receptor thyroid stimulant hormone; TRAb, thyrotrophin receptor antibody; TGAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody.

## Discussion

Hyperthyroidism complicated by bulbar weakness is rare and occurs in only 21% of patients with thyrotoxic myopathy[7]. Early on, it was believed that isolated bulbar paralysis would not occur without associated chronic thyrotoxic myopathy (CTM), but in recent years, several authors have reported the presence of acute bulbar paralysis in the absence of overt muscle atrophy, which is characterized by rapid progression and high mortality [2, 27]. Here, we hypothesized that a standardized and easy-to-apply ATM scoring table could be used to assist in early ATM diagnosis.

In our study, due to the lack of a certain consensus on the diagnosis of ATM, we specifically performed follow-up observations after the use of antihyperthyroidism drugs for one week to two months to ensure the accuracy of ATM diagnosis. After assessing ATMSS scores for patients with ATM and GD, patients with ATM reported nine times more bulbar paralysis symptom scores than did GD patients in all symptom categories [median total ATMSS score 9 (3,14) *vs.* 1 (0, 2)](Fig. 1), suggesting that ATM patients showed symptoms associated with bulbar paralysis [27], and ROC curve analysis showed that the ATMSS had good diagnostic sensitivity and specificity(AUC = 0.979, 95% CI: 0.956-1.000; P < 0.001, sensitivity 94.1%, specificity 93.9%) for distinguishing ATM from GD Fig. 3 , it could be used as an effective tool for ATM screening. In addition, the ATMSS is simple to operate, clinicians are expected to use the ATMSS screening for ATM before conducting more difficult examinations to reduce the misdiagnosis and delay treatment of ATM patients.

ATM patients were younger (32.45 ± 11.14 years) and predominantly female (F/M:42/9) in our study (Table 2), which was inconsistent with the average onset age of 50.77 ± 18.05 years and the almost equal sex ratio in the reference cohort(M/F:1/1.06) (Table 1). This may be because GD tends to occur in young women, when ATM screening is performed in all patients with hyperthyroidism like our study, a large number of ATM patients with mild early symptoms can be detected, while almost all patients with ATM in the reference cohort are hospitalized patients with severe conditions, elderly patients are more prone to have severe conditions. more clinical data are needed to support this view in the future.

There was one patient in the GD group had an ATM symptom score as high as 8 points in our study.

the increased score was mainly attributed to limb weakness. Meanwhile, the most common symptom reported by patients with GD was muscle weakness (Fig. 2b), which is consistent with what were reported by Michael et al.[28–30] that 80% of patients with hyperthyroidism commonly exhibit myasthenic symptoms, especially proximal muscle weakness. In addition, CTM mainly manifests as obvious myasthenia[2]. Therefore, before ATMSS is used, if the patient mainly manifests with myasthenia and other bulbar paralysis symptoms that are not obvious, ATM needs to be diagnosed with great caution, and it is necessary to exclude myasthenia caused by CTM and hyperthyroidism to avoid misdiagnosis.

In our study, dysarthria was most evident by assessing ATMSS in patients with ATM, but in the reference cohort, dysphagia was the most prevalent symptom (Table 1 and Fig. 2b). The possible reason is that early mild manifestations of ATM may include mild abnormalities in pronunciation, such as pitch reduction and dysphasia, which can improve over time after related treatment or are easily overlooked, while dysphagia is more likely to predict the severity of disease and progressing to a serious complication, Wei et al. [4] reported that ATM patients with dysphagia were prone to have aspiration pneumonia. Further studies with larger sample sizes are needed to clarify the relationships between symptoms of bulbar palsy, ATMSS scores, severity, complications, and prognosis.

The pathogenesis of ATM is still unclear. It has been suggested that thyroid hormone could have a direct influence on neuromuscular function, potentially resulting in neuromuscular dysfunction and oropharyngeal peristalsis[13, 31], Some studies believe that it may be an encephalopathy in which $T_3$ receptors on brain neurons and thyroid hormones can regulate brain function[32]. Li et al [33] have shown that bulbar palsy in patients with ATM may be related to functional connectivity changes in the resting-state sensorimotor network and left frontoparietal network. Our study confirmed that there were positive correlations between ATMSS scores and the levels of $FT_3$ ($r_s$=0.422, p < 0.001) and $FT_4$ ($r_s$=0.497, p < 0.001) (Fig. 4), which suggests that thyroid hormones may have a direct effect on the occurrence of ATM from a clinical point of view. To validate the pathological effects of thyroid hormone on ATM, further fundamental research is essential.

In our study, the performance of the ATMSS in CTM patients could not be clarified, Second, future prospective studies should aim to test the utility of the ATMSS for evaluation symptom progression or recovery over time, and patient outcomes in different ethnic and clinical settings. Finally, comparative studies with validated symptom scores, such as the Frenchay Aphasia Screening Test, are needed.

This article is one of the few that investigates the diagnosis of ATM and establishes a questionnaire-based scoring system to assist in the diagnosis of ATM. The ATMSS has excellent specificity and sensitivity for the diagnosis of ATM. In addition, the easy-to-administer nature of ATMSS could eliminate possible interviewer bias. The limitations of this study are its single centre, sample size, observational nature, and referral bias.

## Declarations

# Conflict of interest

The authors declare no competing interests.

# Author Contribution

YZ, CW, ZL provided the design and conception of the study, YZ, TW, XC, QL, XL, HY and HZ contributed to the diagnosis of ATM and the formulation of ATMSS, CW, LL, JX, JZ, DL and YQ completed the selection of reference cases, the collection and analysis of the cases studied. The first draft was written by YZ, ZL completed the final manuscript, all authors participated in the revision and approved the final manuscript.

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# Data Availability

Data is provided within the manuscript or supplementary information files

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## Figures

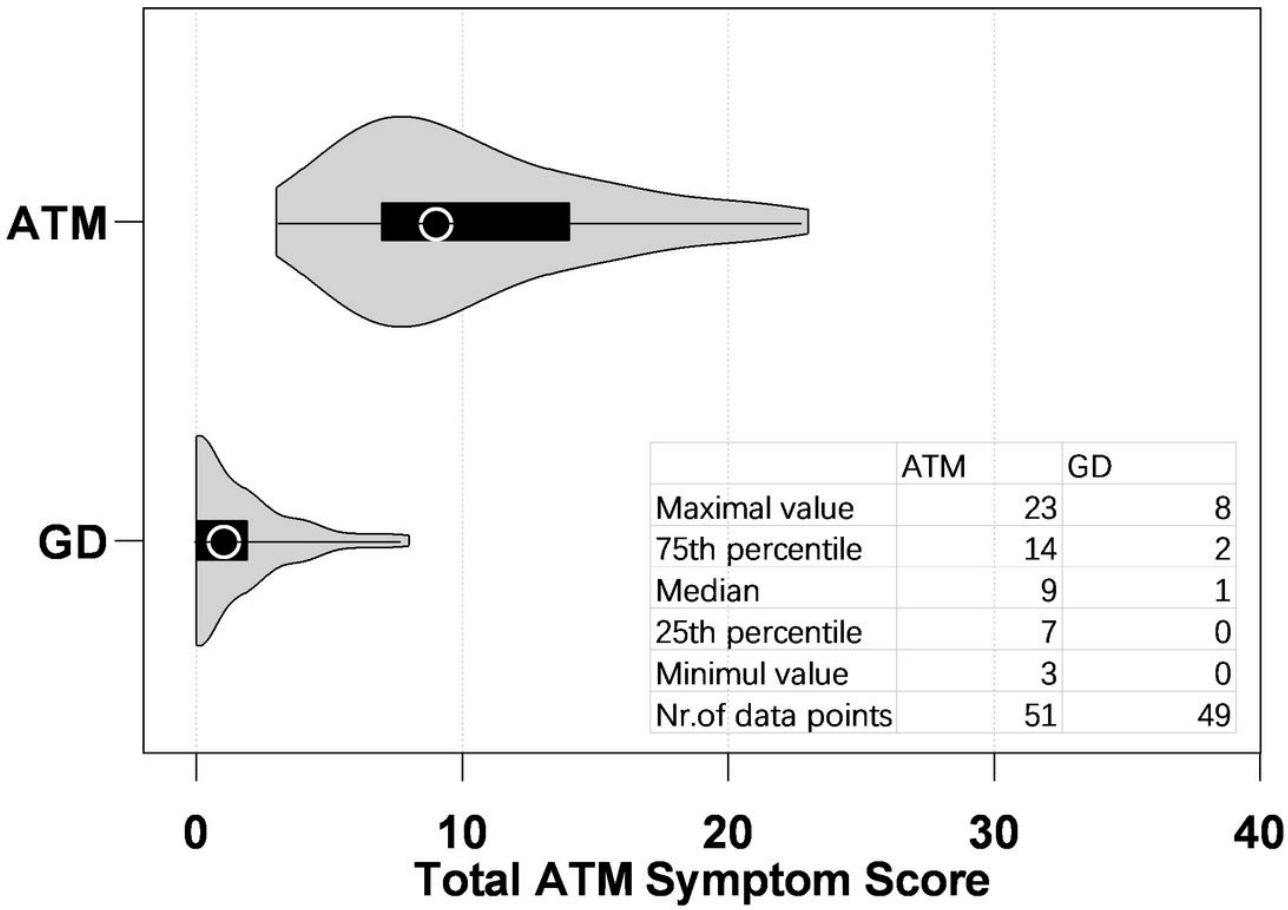


**Figure 1**

Total ATM symptom score(ATMSS) in acute thyrotoxic bulbar myopathy (ATM) and Graves' disease (GD) patients. Distribution of ATMSS by violin plots.

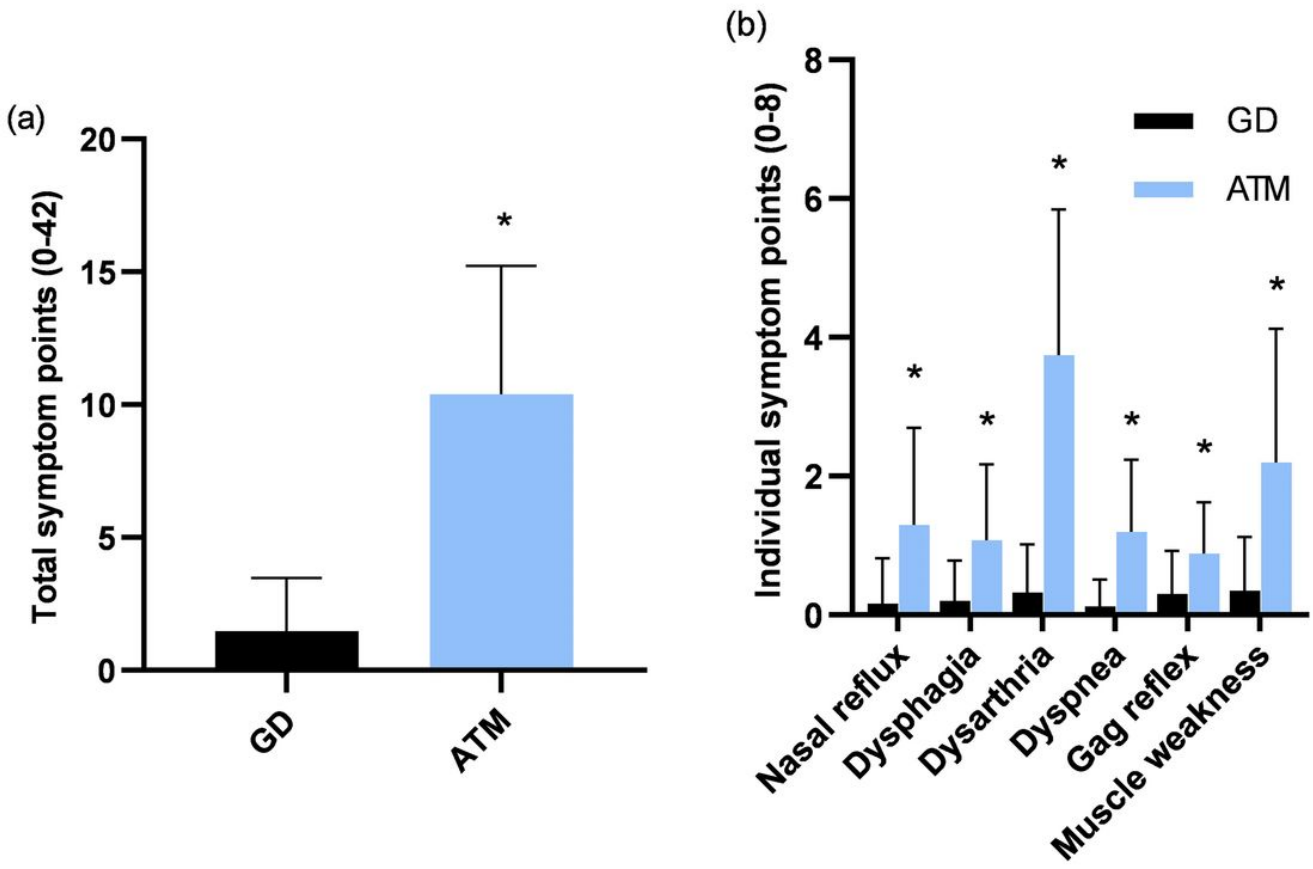


Figure 2

Total ATM symptom score (ATMSS) and individual symptom score. (a) Total ATMSS score; (b) individual symptom score; $p < 0.001$ for all pairwise comparisons. *, $p < 0.001$ *vs.* GD group. ATM, acute thyrotoxic bulbar myopathy; GD, Graves' disease.

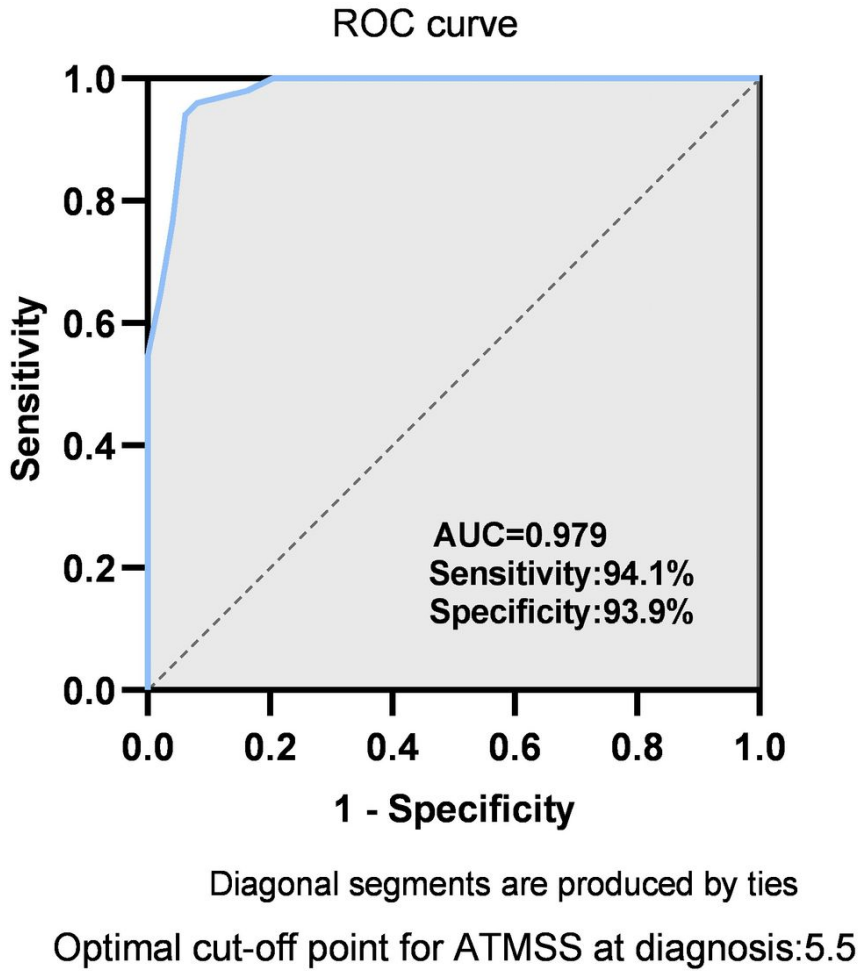


Figure 3

ROC curve for evaluating ATMSS indices for differentiating ATM from GD. ROC curve: receiver operating characteristic curve; ATM, acute thyrotoxic bulbar myopathy; GD, Graves' disease.

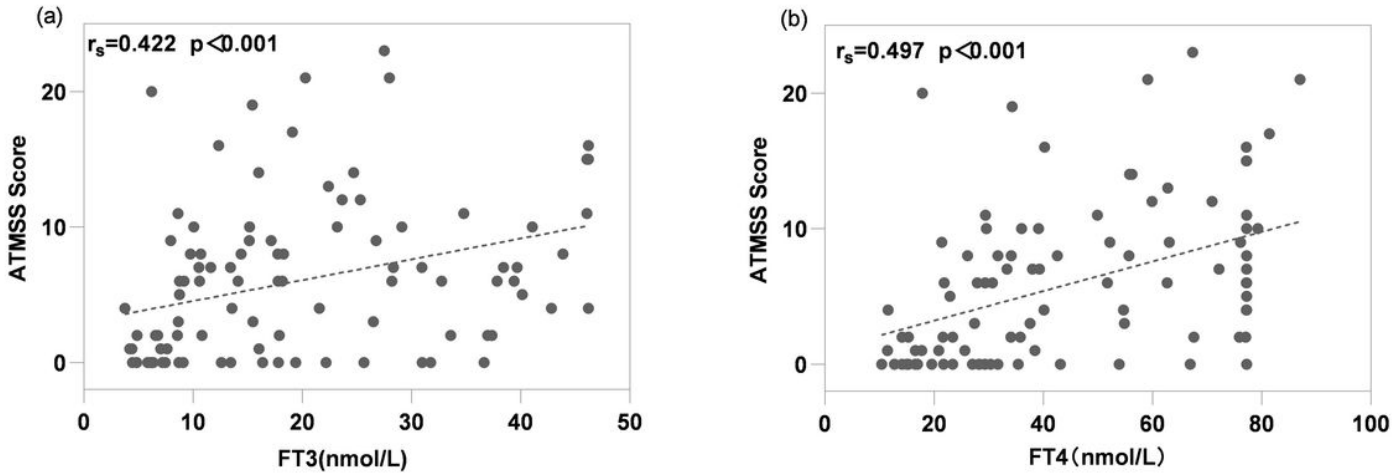


Figure 4

Spearman correlation coefficient ($r_s$) between the ATM symptom score (ATMSS) and thyroid function-related indices, (a) $FT_3$ and (b) $FT_4$ in all subjects. $FT_3$: free triiodothyronine, $FT_4$: free thyroxine.