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ORIGINAL RESEARCH

# The Diagnostic Value of Musculoskeletal Ultrasound in the Quantitative Evaluation of Skeletal Muscle in Chronic Thyrotoxic Myopathy: A Single-Center Study in China

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**Objective:** This study aimed to evaluate the quadriceps femoris in patients with chronic thyrotoxic myopathy (CTM) using musculoskeletal ultrasound and to explore its practical clinical value for the diagnosis of CTM.

**Methods:** A total of 241 subjects recruited from the First Affiliated Hospital of Guangxi Medical University were surveyed for detailed medical history and underwent grip strength tests, fixed-distance walking, and quadriceps femoris ultrasound examinations. Differences in muscle parameters between the CTM, non-CTM, and healthy groups were analyzed. An Receiver operating characteristic (ROC) curve was established to analyze the predictive value of various ultrasound measurements for CTM, and Spearman correlation analysis and binary logistic regression were applied to explore the factors associated CTM.

**Results:** The quadriceps femoris contraction index, muscle thickness, muscle cross-sectional area, and pennation angle in the CTM group were significantly lower than those in the non-CTM and healthy groups ($p<0.01$). The ROC curve prediction showed that the pennation angle had the best sensitivity and specificity for diagnosing myogenesis, with an area under the curve of 89%. Moreover, the pennation angle of the CTM group was positively correlated with step speed (r=0.245, $p=0.031$) and body surface area (r=0.276, $p=0.014$), but negatively correlated with age (r=−0.306, $p=0.007$). Regression analysis showed that the quadriceps femoris contraction index, muscle thickness, pennation angle, and cross-sectional area were factors that related the CTM. After adjusting for potential confounding factors, the association between Muscle Bundle Length and CTM became significant (OR=1.99, 95% CI: 1.22, 3.35, $p=0.007$). Muscular echo in patients was observed to varying degrees of enhancement.

**Conclusion:** Musculoskeletal ultrasonography in the quantitative analysis of muscle parameters and muscle echo of the quadriceps femoris can provide essential imaging evidence for predicting CTM.

**Keywords:** chronic thyrotoxic myopathy, musculoskeletal ultrasound, muscle echo intensity, Heckmatt Scale

## Introduction

Hyperthyroidism, an endocrine disorder, stems from elevated thyroid hormone levels, causing systemic dysfunctions and clinical symptoms.[1] Hyperthyroid myopathy, a common complication of hyperthyroidism, is characterized by induced muscular pathology. The incidence of muscle weakness is as high as 80% in patients with hyperthyroidism.[2] Hyperthyroid myopathy can be categorized into five types based on disease features and pathological sites. Among these, chronic thyrotoxic myopathy (CTM) is the most prevalent.[3] The onset of CTM is often subtle, and the disease progresses slowly. It primarily manifests as symmetrical proximal muscle atrophy and weakness, particularly in the scapular and pelvic girdle muscle groups. This then advances to the limbs' extremities, resulting in generalized muscle



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weakness.[4,5] There are two causes of its pathogenesis. The first is that the increase in reactive oxygen species causes lipid peroxidation and mitochondrial rupture, leading to cell dysfunction and, consequently, muscle cell energy metabolism disorders. In contrast, the second cause is due to excess thyroid hormones that inhibit the activity of phosphocreatine kinase, lowering the levels of creatine and phosphate in skeletal muscles.[6] Adverse events prompted by CTM, such as difficulty standing, slow gait, and falls resulting in fractures, severely affect quality of life. Consequently, there is an urgent need to explore methods for early identification of CTM.

Common diagnostic techniques for myopathic diseases include electromyography, magnetic resonance imaging, computed tomography, bioelectrical impedance analysis, dual-energy X-ray absorptiometry, and ultrasonography.[7] These are aimed at achieving localized diagnoses and implementing muscle biopsy, genetic sequencing, and antibody detection for qualitative diagnosis. However, muscle biopsy is an intrusive examination with space limitations and fails to provide comprehensive monitoring of global muscle pathology.[8] Musculoskeletal ultrasound (MSUS) effectively displays muscle, fat, and subcutaneous fibrous tissue. It provides relevant muscular echo information based on the infiltration depth of fat and fibrous tissues within the muscle and has capabilities for bedside rapid evaluation and real-time dynamic monitoring.[9–11] Given the diverse characteristics of different musculoskeletal disorders, MSUS can guide the location of muscle biopsy and narrow the differential diagnosis.[12] Thus, MSUS serves as an effective research method for assessing muscle quality.[13–15]

Current CTM diagnosis is without explicit global guidelines and is subjective, based on patient history and clinical indications. Although muscle biopsy, electromyography, magnetic resonance imaging, and computed tomography have been used in clinical research, these methods have associated issues, including intrusiveness, high cost, significant radiation exposure, and infeasibility for further tracking. In contrast, MSUS can display the structures of muscle fat and fibrous tissues, and possesses advantages such as noninvasiveness, no radiation, and real-time imaging.[16] Current procedures for diagnosing and treating CTM rely primarily on clinical observations and lack referenceable quantitative indicators. To address this problem, this study targets the quadriceps femoris for ultrasound examination to investigate the clinical significance of MSUS in diagnosing and treating CTM patients.

# Materials and Methods

## Research Subjects

### Origin of Cases

In this single-center study, data were prospectively collected from 151 hyperthyroidism patients who underwent treatment at the First Affiliated Hospital of Guangxi Medical University between December 2021 and February 2023. Of these, 78 were diagnosed with hyperthyroidism myopathy (CTM) and 73 with non-CTM. Ninety healthy adults were selected during the same period as controls. The three groups exhibited no significant differences in age or sex ($p>0.05$), which ensured their comparability. All participants provided informed consent.

### Diagnostic Criteria

The most commonly used diagnostic criteria for CTM are: (1) Clinically diagnosed hyperthyroidism. (2) Patients often exhibit symmetrical muscle weakness and atrophy. (3) Electromyography or muscle biopsy findings consistent with myogenic disease. (4) Exclusion of other causes of neuromuscular disease. (5) Significant improvement in myopathy symptoms after treatment for hyperthyroidism.

### Inclusion Criteria

The inclusion criteria for the CTM group were as follows: (1) Clinically diagnosed hyperthyroidism with no or less than one month of treatment. (2) Frequent patient complaints of difficulty in performing activities such as climbing stairs or squatting, or an inability to engage in extended use of a hair dryer, combing hair, etc., due to progressive muscular weakness, accompanied by weight loss, reduction of muscle strength, and muscular atrophy. (3) Exclusion of other causes of neuromuscular disease. (4) All CTM patients were evaluated by a clinician based on their medical history, symptoms, and physical signs. In cases where CTM was suspected but symptoms of muscle weakness were not evident, further electromyography was performed to confirm the diagnosis.

The inclusion criteria for the non-CTM group were as follows: (1) Met the diagnostic criteria for hyperthyroidism; no treatment or less than one month of treatment. (2) Was not taking medication for a year or more, and thyroid function testing within the past month indicated hyperthyroidism. (3) No muscular weakness, atrophy, or other muscle-related symptoms.

The healthy group inclusion criteria were as follows: (1) Absence of symptoms, such as heat intolerance, hand tremors, increased appetite, and irritability. (2) Absence of signs, such as neck swelling and exophthalmos. (3) Physically fit with a body mass index (BMI) within the normal range (18.5–23.9 kg/m$^2$), and willing to participate in the study.

### Exclusion Criteria

The exclusion criteria were as follows: (1) History of lower limb damage or neuromuscular diseases. (2) Long-term corticosteroid treatment or other treatments/behaviors (such as prolonged bed rest) that affect skeletal muscle metabolism. (3) Diseases affecting skeletal muscle metabolism such as diabetes. (4) Serious diseases pertaining to systems, including the cardiovascular, digestive, respiratory, circulatory, and immune systems. (5) History of radioactive iodine, thyroid surgery, or other thyroid-related diseases. (6) Pregnant or nursing. (7) Age < 18 or > 65 years or those whose who were uncooperative or had incomplete clinical data.

## Methodology

### General Information

A thorough history was obtained for all study participants, noting general data such as age, sex, height, weight, blood pressure, and heart rate.

### Skeletal Muscle Strength and Functional Analysis

Grip Strength Measurement: The grip strength of the dominant hand was measured three times, with a break exceeding 30 seconds between each attempt, using an electronic hand dynamometer. The highest values (kg) were recorded.

Fixed Distance Walking Test: Each participant was instructed to walk a distance of 9 meters at their usual pace and maintain their speed throughout the trial. The time required was recorded for two trials, with the fastest time recorded at an accuracy of 0.01 m/s.

### Ultrasonic Measurement

A Clover50 color Doppler ultrasonic diagnostic device was used. A high-frequency linear array probe with a frequency of 4–15 MHz was selected. The ultrasound scan was conducted in muscle bone mode, with the participant instructed to lie flat with the entire body stretched and relaxed. The probe was attached vertically to the skin surface, and the image depth was adjusted for a relatively complete and clear display of the rectus femoris muscle.

A conventional two-dimensional ultrasound was performed at 33% and 50% of the distance from the anterior superior iliac spine to the upper edge of the kneecap, scanning the dominant rectus femoris muscle. The ultrasound probe was rotated 90° to scan along the long axis, observing the muscle size, shape, and inner echo. The quadriceps femoris contraction index (QF-SI), subcutaneous fat thickness (SFT), muscle thickness (MT), pennation angle (PA), Muscle Bundle Length (MBL), and cross-sectional area (CSA) were measured (Figures 1 and 2). Three or more pictures were frozen and saved, relevant parameters were measured in the later stages, and the average value was calculated three times.

### Image Processing and Analysis

Improved skill levels of professionals, specifically sonographers who have undergone specialized training, coupled with accurate operational methods, rigorous observational analysis, and enhancements in instrumentation and adjustability, contribute to improved quality control of ultrasonography. All ultrasound examinations were conducted by the same operator, and at least three images were retained for each standard cross-section. The average value was obtained from three measurements of all included ultrasound indices. Regarding the qualitative evaluation of muscle echo, studies have demonstrated that the echogenicity of healthy muscles changes with age and is replaced by adipose and fibrous tissues, leading to an increase in muscle echo on ultrasonography[18,19] (Figure 3). In the echo intensity analysis, we focused on

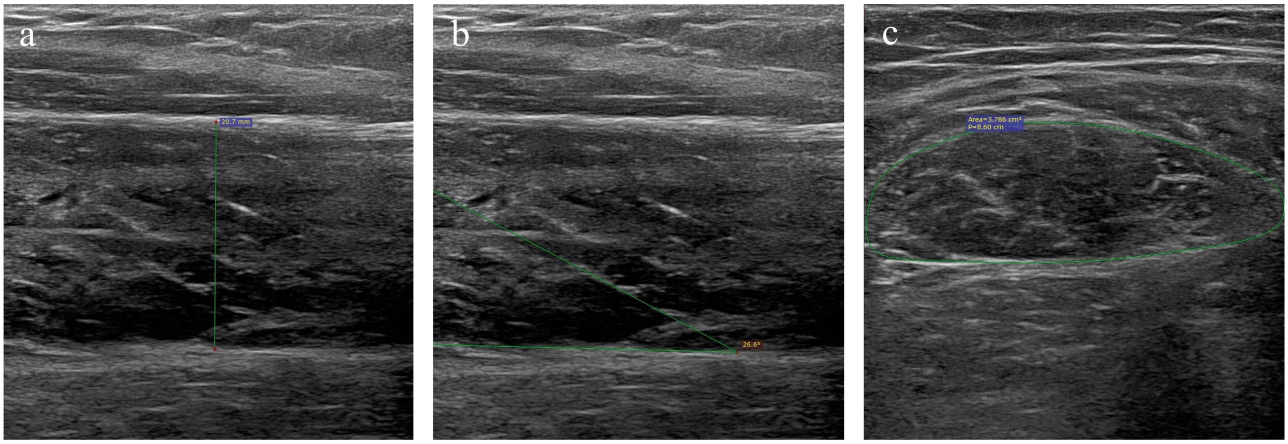


**Figure 1** Measurement of MT, PA, CSA.

**Notes**: (**a**) MT was the distance between the deep and superficial fascia of the muscle in a long-axis image. (**b**) PA was the angle between the muscle fascicle and the deep fascia in a long-axis image; the MBL was the fascicle length between the superficial and deep fascia of the muscle in a long-axis image, with some lengths not clearly shown, and therefore calculated as MBL (L) = h/sinα (h is the muscle thickness, and α is the pennation angle). (**c**) The CSA was measured in a short axis image.

**Abbreviations**: MT, muscle thickness; PA, pennation angle; MBL, Muscle Bundle Length; CSA, cross-sectional area.

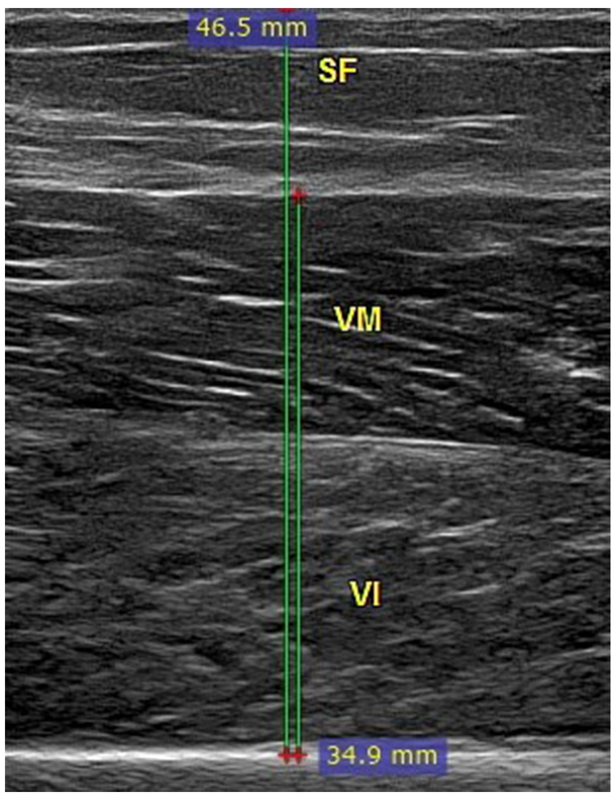


**Figure 2** Measurement of QF-SI.

**Notes**: The QF-SI measurement location (approximately 50% of the distance from the anterior superior iliac spine to the upper edge of the patella): In the long-axis image, the quadriceps femoris total thickness (sum of the rectus femoris and intermedius muscle thickness measurements) is divided by the total thickness of the anterior part of the thigh (distance from the skin to the anterior edge of the femur).[17]

**Abbreviation**: QF-SI, quadriceps femoris contraction index.

comparisons within the same age groups. Muscle echo quality was semiquantitatively assessed using the Heckmatt scale, and an assigned Heckmatt score of ≥ 2 indicates an anomaly in the image[20] (Table 1). The Heckmatt scoring system has a degree of subjectivity to minimize visual errors. Two separate sonographers (A and B) used the Heckmatt score to grade patient echogenicity.

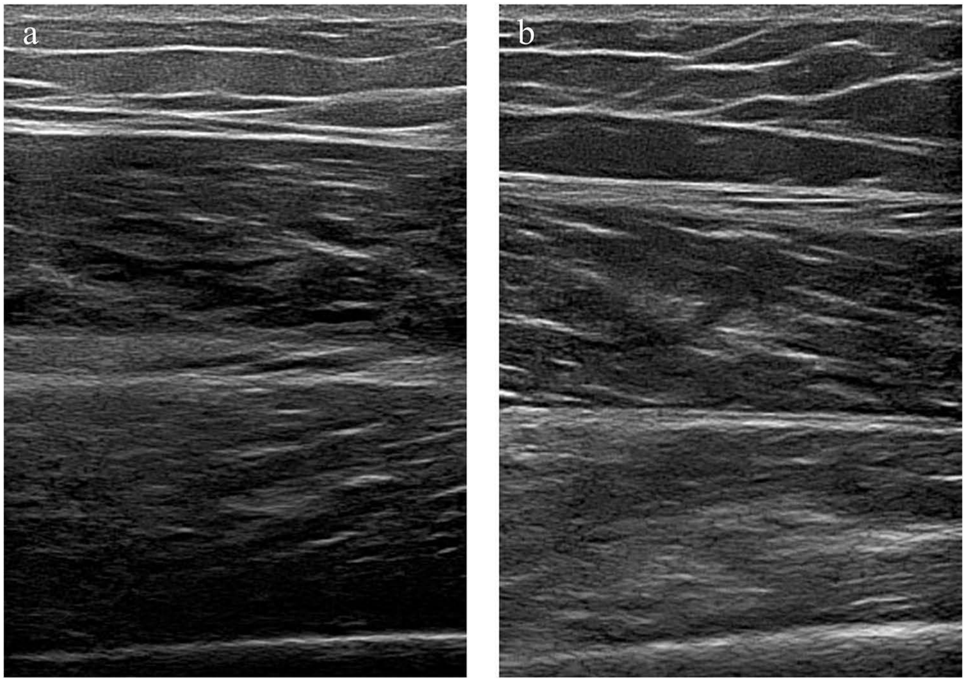


**Figure 3** Variations in Echo Intensity Among Healthy Adults of Different Ages.
**Notes**: The Figure 3 show the measurements taken from the same location—in the middle point between the anterior superior iliac spine and the top edge of the patella—for a 27-year-old healthy male (**a**) and a 57-year-old healthy male (**b**). It is observed that muscle echogenicity is enhanced in the 57-year-old male compared to the 27-year-old, indicating an age-related change in muscle echo. Attention should be paid to comparing individuals within the same age group when using the Heckmatt rating scale.

### Statistical Methods

Statistical analysis was performed using SPSS 26.0 software. Count data were expressed as frequencies, and comparisons between groups were performed using the chi-square test. Normally distributed measurements are presented as mean ± standard deviation ($\bar{x} \pm s$), and one-way ANOVA was applied for comparisons among multiple groups. Non-normally distributed measurement data are expressed as medians (interquartile range), and comparisons among multiple groups were conducted using the *H*-test. Receiver operating characteristic (ROC) curves were plotted to analyze the statistical differences in various ultrasonic parameter indicators for predicting the optimal threshold, sensitivity, specificity, and area under the curve (AUC) for CTM. The binary logistic regression analysis was applied for predicting the relevant factors associated with CTM. The associations among different indicators were assessed using Spearman correlation test. Additionally, the weighted kappa coefficient test was used to investigate inter-observer consistency among different ultrasonographers using the Heckmatt scale for the quantitative rating of muscle echo in patients with CTM. Statistical significance was set at $p<0.05$.

## Results

### Clinical Data Comparison

This study included 241 subjects segmented into three categories: the healthy (n=90), non-CTM (n=73), and CTM (n=78) groups. The mean ages for the healthy, non-CTM, and CTM groups were 32.78±10.91, 35.53±10.97, and 36.01±13.58

**Table 1** Heckmatt Assessment Scale

| Grade | Criteria |
|---|---|
| Grade I | Normal muscle structure and echo |
| Grade II | Increased muscle grayscale, normal adjacent bone echo |
| Grade III | Markedly increased muscle grayscale, diminished adjacent bone echo |
| Grade IV | Extremely high muscle grayscale, absent adjacent bone echo |

years, respectively. The healthy group comprised 58 females and 32 males; the non-CTM group comprised 42 females and 31 males; and the CTM group comprised 58 females and 20 males. There were no statistically significant differences in age or sex among the three groups ($p$>0.05). However, significant differences were observed in BMI, body surface area, blood pressure, heart rate, grip strength, and walking speed ($p$<0.01). Detailed comparisons are presented in Table 2.

## Comparison of Quadriceps Muscle Mass

This study found significant differences in ultrasonic indicators related to the rectus femoris muscle mass among the CTM, non-CTM, and healthy groups, with lower values in the CTM group implying a reduction in rectus femoris mass. The comparison results for QF-SI among the three groups showed that measures in the CTM group (0.65 ± 0.08) were significantly lower than in the non-CTM (0.71 ± 0.08) and healthy (0.75 ± 0.07) groups, and the difference was statistically significant ($p$<0.001). However, there was no significant difference in SFT between these groups ($p$=0.293). The PA measures were significantly lower in the CTM group 17.4 (16.2, 19.1) than the healthy 21.3 (20.4, 23.3) and non-CTM 20.0 (19.0, 21.3) groups, and the difference was statistically significant ($p$<0.001). Finally, we observed significant differences in the parameters of ML, MBL, and CSA ($p$<0.05), as detailed in Table 3.

## Analyzing the Diagnostic Value of Ultrasonic Indicators for CTM

The rectus femoris MT, CSA, PA, and QF-SI of CTM patients were included in the ROC curve analysis. Each of these muscle ultrasonic parameters holds certain value in the diagnosis of CTM, and PA is the best predictive indicator. In the

**Table 2** Comparisons of Subject's Fundamental Data and Skeletal Muscle Strength

| | Healthy Group (n=90) | Non-CTM Group (n=73) | CTM Group (n=78) | $p$ |
|---|---|---|---|---|
| Age (years) | 32.78±10.91 | 35.53±10.97 | 36.01±13.58 | 0.163 |
| Sex (Female/Male) | 58/32 | 42/31 | 58/20 | 0.090 |
| BMI (kg/m$^2$) | 21.73±2.86 | 21.42±2.99 | 19.63±3.10 | <0.001[bc] |
| Body Surface Area (m$^2$) | 1.55 (1.45, 1.65) | 1.56 (1.44, 1.68) | 1.47 (1.36±1.54) | <0.001[bc] |
| Systolic Blood Pressure (mmHg) | 117.44±14.03 | 125.27±14.03 | 129.56±15.44 | <0.001[ab] |
| Diastolic Blood Pressure (mmHg) | 74.50 (68.00, 82.25) | 76.00 (68.5, 80.50) | 74.50 (69.75, 79.25) | 0.889 |
| Heart Rate (beats/min) | 69.50 (61.75, 77.00) | 95.00 (84.00, 105.50) | 109.00 (96.00, 125.00) | <0.001[abc] |
| Grip Strength (kg) | 27.10 (23.25, 34.70) | 25.30 (20.00, 30.35) | 19.40 (15.03, 23.53) | <0.001[abc] |
| Walking Speed (m/s) | 1.11 (1.01, 1.21) | 1.10 (1.00, 1.21) | 1.01 (0.91, 1.13) | 0.001[ab] |

**Note**: [a]Comparing the Health group and non-CTM group, $p$< 0.05. [b]Comparing the Health group and CTM group, $p$< 0.05. [c]Comparing the non-CTM group and CTM group, $p$< 0.05.
**Abbreviation**: CTM, chronic thyrotoxic myopathy.

**Table 3** Comparison of Rectus Femoris Muscle Mass in Subjects

| | Healthy Group (n=90) | Non-CTM Group (n=73) | CTM Group (n=78) | $p$ |
|---|---|---|---|---|
| QF-SI | 0.75 ± 0.07 | 0.71 ± 0.08 | 0.65 ± 0.08 | <0.001[abc] |
| SFT | 1.25 (1.00, 1.59) | 1.22 (0.87, 1.54) | 1.38 (0.99, 1.69) | 0.293 |
| PA | 21.3 (20.4, 23.3) | 20.0 (19.0, 21.3) | 17.4 (16.2, 19.1) | <0.001[abc] |
| MT | 1.96 ± 0.31 | 1.88 ± 0.29 | 1.69 ± 0.30 | <0.001[bc] |
| CSA | 6.28 (5.39, 7.75) | 6.03 (4.70, 7.29) | 4.55 (3.83, 5.18) | <0.001[bc] |
| MBL | 5.26 (4.83, 5.68) | 5.32 (4.98, 5.91) | 5.58 (5.06, 6.06) | 0.047[b] |

**Notes**: [a]Comparing the Health group and non-CTM group, $p$< 0.05. [b]Comparing the Health group and CTM group, $p$< 0.05. [c]Comparing the non-CTM group and CTM group, $p$< 0.05.
**Abbreviations**: CTM, chronic thyrotoxic myopathy; QF-SI, quadriceps femoris contraction index; SFT, subcutaneous fat thickness; MT, muscle thickness; PA, pennation angle; MBL, Muscle Bundle Length; CSA, cross-sectional area.

**Table 4** Diagnostic Value of Ultrasonic Indicators for CTM

| | AUC | 95% Lower Limit | 95% Upper Limit | Sensitivity | Specificity | Youden Index | Cut-off Value |
|---|---|---|---|---|---|---|---|
| QF-SI | 0.82 | 0.75 | 0.88 | 0.81 | 0.71 | 0.52 | 0.72 |
| MT | 0.74 | 0.67 | 0.82 | 0.81 | 0.59 | 0.40 | 1.90 |
| PA | 0.89 | 0.84 | 0.94 | 0.83 | 0.86 | 0.69 | 19.63 |
| CSA | 0.82 | 0.76 | 0.89 | 0.77 | 0.81 | 0.58 | 5.24 |

**Abbreviations**: CTM, chronic thyrotoxic myopathy; AUC, area under the curve; QF-SI, quadriceps femoris contraction index; MT, muscle thickness; PA, pennation angle; CSA, cross-sectional area.

ROC curve results, PA showed the best sensitivity and specificity for diagnosing CTM, with an AUC of 0.89 and an optimal threshold of 19.63. Further details are provided in Table 4 and Figure 4.

## Analysis of related Factors of CTM

Our study analyzed data from 151 subjects with hyperthyroidism, including patients with and without CTM, and constructed five regression models to evaluate various influencing factors while adjusting for age, sex, and BMI.

Models 1, 2, 3, and 5 incorporated MT, QF-SI, PA, and CSA, respectively. Both initial and adjusted odds ratios (OR) exhibited negative correlations, revealing that these predictors were significant contributors to the disease. Notably, PA displayed a negative correlation with CTM (OR=0.60, 95% CI=0.49–0.72, $p$<0.001), showing slight improvement after adjustment (OR=0.55, 95% CI=0.43–0.68, $p$<0.001). Model 4 contained MBL, which initially showed a non-significant association (OR=1.35, 95% CI: 0.88–2.09, $p$=0.171), but became significant after adjustment (OR=1.99, 95% CI: 1.22–3.35, $p$=0.007). The constructed models yielded an Akaike information criterion (AIC) value of 163.9, and a C-statistic of 0.831. The Hosmer-Lemeshow goodness-of-fit test yielded a chi-square value of 3.41 ($p$=0.906), supporting the robust fitness of the models. Further details are provided in Table 5.

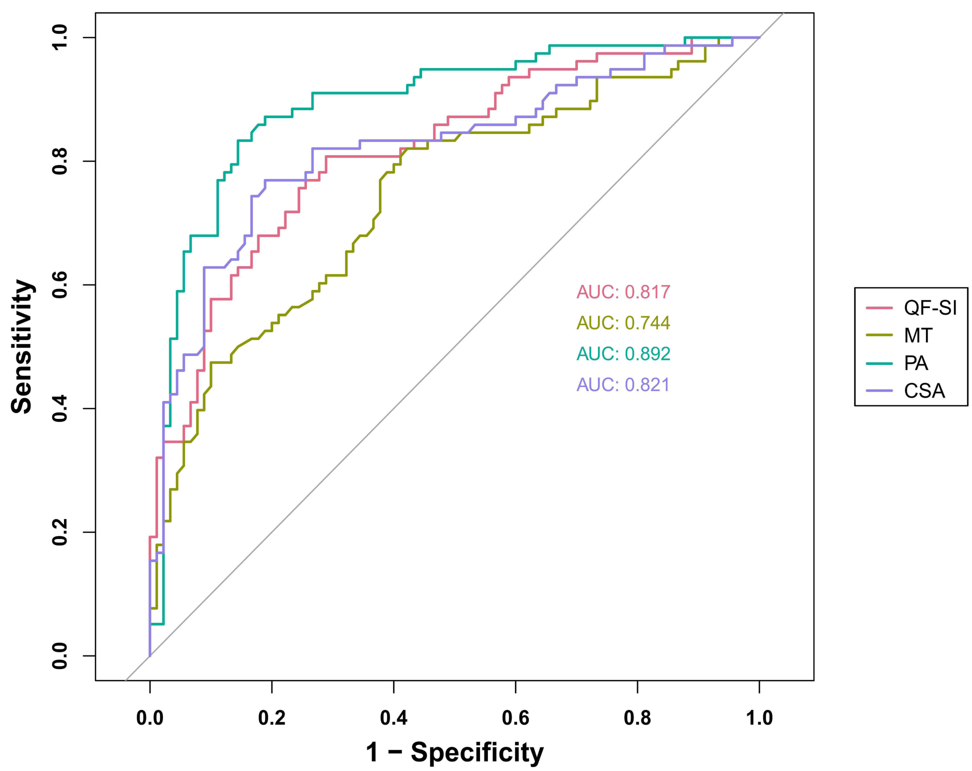


**Figure 4** ROC Curve of Rectus Femoris Ultrasonic Parameters Analysis of Risk Factors Contributing to CTM.
**Abbreviations**: ROC, receiver operating characteristic; CTM, chronic thyrotoxic myopathy. AUC, area under the curve; QF-SI, quadriceps femoris contraction index; MT, muscle thickness; PA, pennation angle; CSA, cross-sectional area.

**Table 5** Univariate and Multivariate Regression Analysis Evaluating Various Influencing Factors of CTM

| Characteristic | Univariable | | | | | | Multivariable | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N | Event N | B | OR | 95% CI | *p* | B | OR[l] | 95% CI[l] | *p* |
| QF-SI[b] | 151 | 78 | −8.25 | 0.00 | 0.00,0.02 | <0.001 | −11.37 | 0.00 | 0.00,0.01 | <0.001 |
| PA[c] | 151 | 78 | −0.51 | 0.60 | 0.49, 0.72 | <0.001 | −0.60 | 0.55 | 0.43, 0.68 | <0.001 |
| MT[a] | 151 | 78 | −2.25 | 0.11 | 0.03, 0.33 | <0.001 | −1.98 | 0.14 | 0.03, 0.56 | 0.007 |
| MBL[d] | 151 | 78 | 0.30 | 1.35 | 0.88, 2.09 | 0.171 | 0.69 | 1.99 | 1.22, 3.35 | 0.007 |
| CSA[e] | 151 | 78 | −0.51 | 0.60 | 0.47, 0.74 | <0.001 | −0.75 | 0.47 | 0.32, 0.67 | <0.001 |

**Notes**: [a]Model 1, [b]Model 2, [c]Model 3, [d]Model 4. [e]Model 5 Al models adjusted for Age, Sex, BMI.
**Abbreviations**: CTM, chronic thyrotoxic myopathy; QF-SI, quadriceps femoris contraction index; MT, muscle thickness; PA, pennation angle; MBL, Muscle Bundle Length; CSA, cross-sectional area; [l]OR, Odds Ratio, CI, Confidence Interval.

## Correlation Between Clinical Indicators and Ultrasonic Measurements

Negative correlations were observed between the age of patients with CTM and MT, PA, MBL, and CSA, with the strongest correlation found for MT (r=−0.382, *p*=0.001). A positive correlation was observed between BMI and SFT, MT, MBL, and CSA, with MBL being the most strongly correlated factor (r=0.421, *p*<0.001). Body surface area had positive correlations with QF-SI, MT, PA, MBL, and CSA, with the strongest correlation observed for CSA (r=0.685, *p*<0.001). Further observations revealed positive correlations between PA and step speed (r=0.245, *p*=0.031) and body surface area (r=0.276, *p*=0.014), and a negative correlation with age (r=−0.306, *p*=0.007). Overall, this study identified correlations between clinical indicators and ultrasonic measurements in patients with CTM. Further details are provided in Table 6.

## Qualitative Analysis of Muscle Echo Intensity

Two different ultrasonographers (A and B) used the Heckmatt scale for the quantitative analysis of muscle echo in patients with CTM. The concordance in the scoring outcome between the two was high (weighted kappa coefficient 0.61, *p*<0.05), indicating good agreement in their diagnoses. Further details are presented in Figure 5 and Table 7.

# Discussion

Chronic thyrotoxic myopathy (CTM) is a common but easily overlooked condition in clinical practice. Currently, knowledge regarding CTM remains limited, with a lack of relevant domestic and international guidelines that clearly stipulate diagnostic methods. To bridge this knowledge gap, this investigation explored the potential of using MSUS as

**Table 6** Correlations Between Clinical Indicators and Ultrasonic Measurements in CTM Patients

| | | QF-SI | SFT | MT | PA | MBL | CSA |
|---|---|---|---|---|---|---|---|
| Age | r | −0.048 | −0.209 | −0.382** | −0.306** | −0.225* | −0.301** |
| | *p* | 0.673 | 0.067 | 0.001 | 0.007 | 0.048 | 0.007 |
| BMI | r | −0.030 | 0.356** | 0.326** | −0.031 | 0.421** | 0.401** |
| | *p* | 0.793 | 0.001 | 0.004 | 0.789 | 0.000 | 0.000 |
| Body Surface Area | r | 0.302** | 0.055 | 0.577** | 0.276* | 0.457** | 0.685** |
| | *p* | 0.007 | 0.634 | 0.000 | 0.014 | 0.000 | 0.000 |
| Grip Strength | r | 0.108 | −0.035 | 0.043 | −0.175 | 0.222 | −0.105 |
| | *p* | 0.345 | 0.762 | 0.707 | 0.125 | 0.051 | 0.358 |
| Walking Speed | r | 0.086 | −0.015 | 0.205 | 0.245* | 0.019 | 0.168 |
| | *p* | 0.452 | 0.898 | 0.072 | 0.031 | 0.869 | 0.140 |

**Notes**: **Correlation is significant at the 0.01 level (two-tailed). *Correlation is significant at the 0.05 level (two-tailed).
**Abbreviations**: CTM, chronic thyrotoxic myopathy; QF-SI, quadriceps femoris contraction index; SFT, subcutaneous fat thickness; MT, muscle thickness; PA, pennation angle; MBL, Muscle Bundle Length; CSA, cross-sectional area.

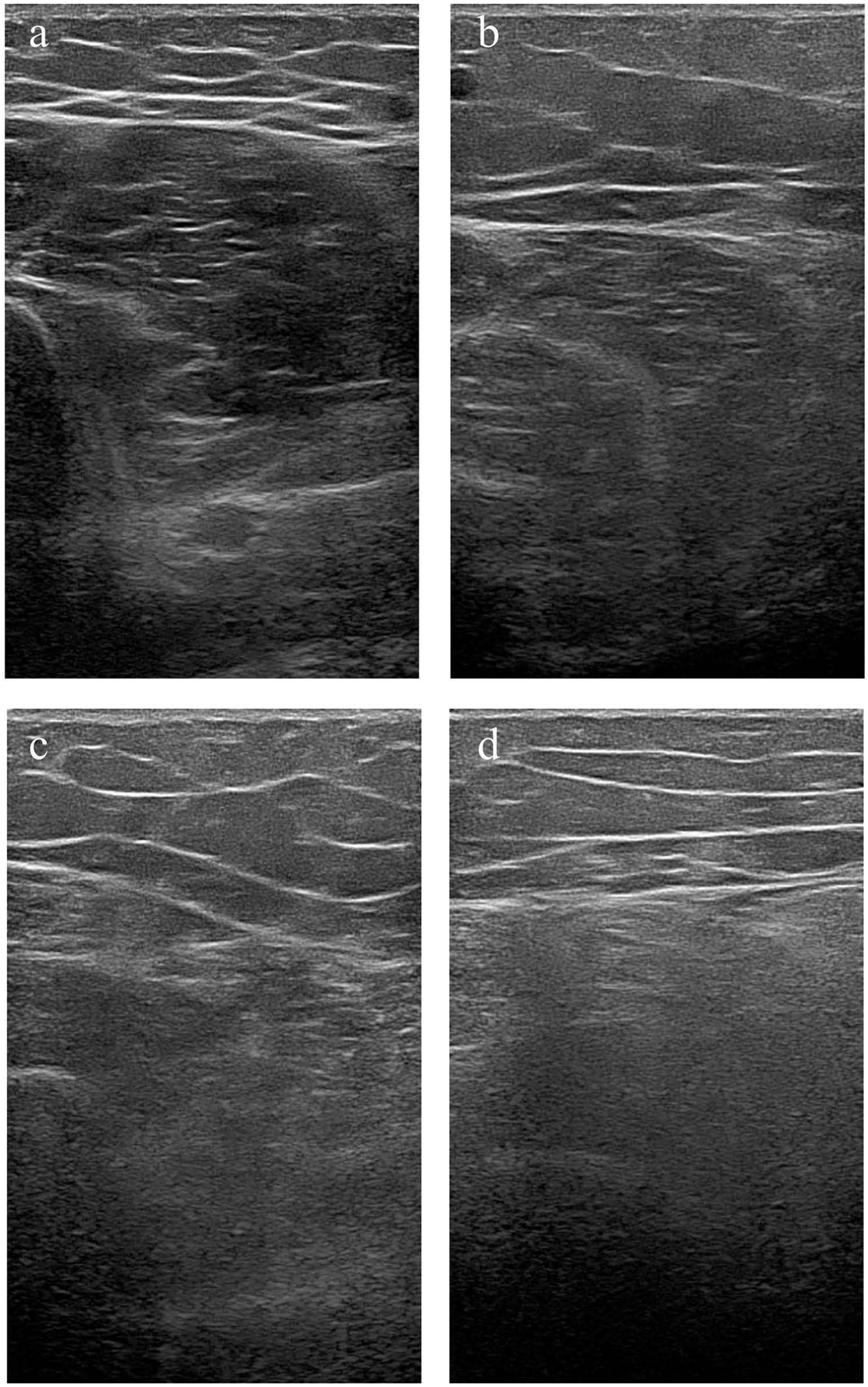


**Figure 5** Semi-quantitative Assessment of Muscle Images of CTM Patients Using the Heckmatt Scale.
**Note**: (**a**–**d**) sequentially represents levels I, II, III, and IV of the Heckmatt scale. (**a**) Muscle structure and echo appear normal (a 28-year-old male CTM patient). (**b**) Increased muscle grayscale intensity, but the adjacent bone echo is normal (a 31-year-old female CTM patient). (**c**) with a highly increased muscle grayscale, while the adjacent bone echo is diminished (a 36-year-old female CTM patient). (**d**) presents an extremely high muscle grayscale level with a vanished adjacent bone echo (an 18-year-old female CTM patient). This study designates an abnormal condition with a Heckmatt score≥ 2.
**Abbreviation**: CTM, chronic thyrotoxic myopathy.

**Table 7** Weighted Kappa Coefficient Testing Consistency Between the Scoring of Two Sonographers

| | | Physician B | | | | Total |
|---|---|---|---|---|---|---|
| | | Level I | Level II | Level III | Level IV | |
| Physician A | Level I | 6 | 2 | 0 | 0 | 8 |
| | Level II | 2 | 25 | 8 | 0 | 35 |
| | Level III | 0 | 4 | 22 | 3 | 29 |
| | Level IV | 0 | 0 | 1 | 5 | 6 |
| | Total | 8 | 31 | 31 | 8 | 78 |

a diagnostic standard for CTM. MSUS is a non-invasive, radiation-free, and ideal mode of neuromuscular imaging capable of identifying muscle physiological parameters, such as PA and CSA.[19,21] In clinical practice, the quality of muscle is often described and evaluated by observing factors, such as the size, shape, echo intensity, and hardness of the patient's muscles. This study comparatively analyzed the QF-SI, MT, MBL, CSA, PA, and muscle echo intensity of patients with CTM against those of patients without CTM and healthy individuals to determine a suitable diagnostic standard for CTM. Results from the differences analysis highlighted that MT in patients with CTM was significantly less than that in the non-CTM and healthy groups. Previous studies have noted that the size of the MT directly reflects muscle mass: a thicker MT corresponds to a larger mass, and the MT has a significant positive correlation with total body muscle mass.[22] The patients with CTM in this study exhibited noticeably decreased muscle mass, consistent with previous research. Patients with CTM displayed a negative correlation between MT and age, which coincided with the skeletal muscle mass deterioration and muscle strength reduction associated with aging. Previous research has indicated that MT positively correlates with walking speed.[23] However, quadriceps MT and walking speed of patients with CTM showed no obvious correlation. The decreasing trend in walking ability cannot be attributed to a single factor, necessitating further studies to clearly establish the relationship between walking speed and MT. The CTM group also showed significantly shorter MBL than the non-CTM and healthy groups. Previous research has shown a relationship between MBL, muscle strength, range of motion, and contraction speed,[24] and that MBL changes with age.[25] In this study, patients with CTM presented a negative correlation between MBL and age and a positive correlation with BMI and body surface area. Therefore, both MT and MBL are reliable indicators of muscle mass evaluation.

Different muscles exhibit different PA. There is a relationship between PA and muscle strength, with larger measurements indicating more muscle fibers within a certain volume, and thus greater force generated by the muscle. Changes in PA affect the biomechanical characteristics of muscles.[26] In this study, the PA of the CTM group was significantly smaller than that of the non-CTM and healthy groups, and PA was positively correlated with gait speed, which is consistent with the findings of previous studies. Their results showed a decrease in PA in patients with muscle atrophy and stroke, and PA was significantly correlated with lower limb function.[27] Studies have found that muscle PA increases with age from birth, stabilizes at a certain value after puberty, and does not change significantly until 70 years of age.[28] This study found a negative correlation between PA and age, consistent with the findings of Westbury et al.[29] In addition, PA had the best sensitivity and specificity for diagnosing CTM in the ROC curve results of this study, with an AUC of 0.89, indicating a good predictive value in CTM screening.

In this study, a new ultrasound measurement index, QF-SI, was introduced. Previous studies have demonstrated that QF-SI is feasible, rapid, simple, and reliable for ultrasound evaluation in patients with chronic obstructive pulmonary disease, and that it is related to disease severity, clinical symptoms, and prognosis. QF-SI could potentially provide a better estimate of muscle contractility than MT, which may depend more on other factors, such as weight and height.[17] In this study, the QF-SI of the CTM group was significantly lower than that of the non-CTM and healthy groups, and the QF-SI of patients with CTM was positively correlated with body surface area. There are few domestic and foreign studies on QF-SI; however, QF-SI may effectively predict CTM. To further clarify the correlation between QF-SI and related parameters and the predictive value of QF-SI in CTM, more samples and studies are needed to validate the ultrasound measurements.

CSA has been shown to be a reliable estimate of muscle quality.[30] In this study, the CSA of the CTM group was significantly lower than that of the non-CTM and healthy groups. Patients with CTM exhibit symptoms such as muscle weakness and muscle atrophy, leading to a decrease in skeletal muscle cross-sectional area, which is consistent with the results of Yoo et al.[31] Additionally, we found that CSA in patients with CTM was negatively correlated with age but positively correlated with BMI and body surface area, consistent with previous research.[32] In addition to muscle atrophy symptoms, the SFT thickness of the CTM group was lower than that of the non-CTM and healthy groups, indicating the loss of other body components, such as fat, in patients with hyperthyroidism. These results suggest that MSUS can be used to assess disease status in patients with CTM.

This study applied binary logistic regression analysis to explore the factors related CTM, and the results showed that QF-SI, MT, MBL, CSA, and PA were significant factors related CTM. The results of the multiple regression analysis showed that when PA increased, the risk of CTM was reduced by 45% (OR: 0.55, $p<0.001$). In the univariate analysis, MBL did not reach statistical significance; however, according to the results of previous studies, it was included in the multiple logistic regression analysis. We observed that MBL, initially not significantly associated, became a significant risk factor for CTM after adjusting for age, sex, and BMI, and the risk of CTM occurrence was 1.99 times higher when MBL increased compared to normal (OR=1.99, $p=0.007$). Therefore, these ultrasound indicators are important factors influencing the diagnosis of CTM.

Ultrasound (US) is an important method for measuring muscle quality.[33] US can detect muscle necrosis, providing deeper insights into changes in muscle atrophy and structure during critical recovery periods. In this study, changes in muscle echo intensity in patients with CTM were observed using ultrasound. Similar to MT, echo intensity can be used to evaluate muscle tissue.[34] A study conducted by Watanabe et al[35] highlighted that echo intensity could serve as an indicator of fat infiltration within muscle tissue, thereby correlating with muscle quality. Evaluation of biomarkers such as muscle thickness and echo intensity can assist in predicting sarcopenia in older adults.[36] Furthermore, Fukumoto et al[37] showed that changes in echo intensity with age precede changes in MT, and demonstrated that muscle echo intensity in elderly individuals is significantly higher than that in younger individuals. Many muscle diseases typically exhibit increased muscle echo.[38] For example, myogenic and non-myogenic torticollis can be differentiated based on changes in sternocleidomastoid muscle thickness and echo of the sternocleidomastoid muscle.[39] Additionally, research has indicated that muscle echo is abnormally increased in patients with type 2 and type 3 spinal muscular atrophy, and patients with a more severe phenotype exhibited the highest muscle echo.[40] In this study, enhanced muscle echo intensity and unclear muscle texture were observed in patients with CTM, with changes in the surrounding tissues such as bone tissue. It is inferred that muscle atrophy leads to increased muscle echo. Previous studies have confirmed that in denervated muscle atrophy, an increased echo is caused by the loss of low-echo muscle fibers and the growth of connective tissue, leading to fiber atrophy.[41,42] This study used the Heckmatt scale for the visual assessment of muscle echo intensity. In the early 1980s, Heckmatt et al studied the appearance of the lower limb muscles in 10 children with muscular atrophy using US and found consistent differences compared to 40 healthy controls. They believed that US could be used to assess the degree of pathological changes in malnourished patients and that it was a valuable diagnostic aid. Subsequently, Heckmatt et al[43,44] visually observed muscle echo intensity and proposed the Heckmatt scale. In this study, two ultrasound physicians quantitatively analyzed muscle echo intensity in patients with CTM using the Heckmatt scale, achieving high consistency (weighted kappa coefficient of 0.61) and a diagnostic rate of over 85%. Therefore, the use of the Heckmatt scale for the quantitative evaluation of muscle echo intensity in patients with CTM is feasible. Thus, combining echo intensity with ultrasound indicators, such as MT or CSA measurements, may improve the diagnostic rate.

The sample size of our research is relatively small, and the study is further limited by the selection of participants from a single center. Subsequent research will aim to incorporate a more geographically diverse cohort. The relatively higher proportion of females in this study might be attributable to the higher prevalence of hyperthyroidism among women.[45,46] Additionally, this study did not group participants based on relevant factors. In the future, grouping based on different age groups, disease courses, and daily activity levels should be performed before conducting quantitative indicator tests to further explore the degree of muscle pathology in different subgroups of patients with CTM. Our study controlled for age, sex, and BMI in the regression models; however, there may be additional characteristics that could influence the results which were not included in the analysis. Further research is necessary to determine how factors like comorbidities, medication usage, and lifestyle choices may impact ultrasonography parameters and their association with CTM. Future research should incorporate new technologies, such as ultrasound elastography and contrast-enhanced ultrasound, as they can observe muscle function and microcirculation, predict the occurrence of CTM before morphological changes occur, and thus better apply quantitative ultrasound evaluation of muscle pathology in clinical practice.

## Conclusion

This study revealed a significant decline in muscle mass in patients with CTM and irregularities in skeletal muscle function. PA serves as a primary indicator with the highest sensitivity and specificity in diagnosing CTM and is positively correlated with step speed and body surface area and negatively correlated with age. Factors such as QF-SI, MT, MBL, CSA, PA, and MBL are thought to be related to CTM, and therefore serve as reliable predictive indicators. By combining clinical assessments with ultrasound measurements, this study sheds light on muscle state research and provides substantial imaging evidence for predicting CTM. Hence, the utilization of musculoskeletal ultrasound in clinical settings augments the capabilities for early detection, prompt intervention, and accurate assessment, which significantly improve the precision of diagnosing CTM. This modality stands out as a favorable screening instrument, holding great promise as a tool for future clinical application.

## Abbreviations

CTM, chronic thyrotoxic myopathy; MSUS, musculoskeletal ultrasound; ROC, receiver operating characteristic; AUC, area under the curve; QF-SI, quadriceps femoris contraction index; SFT, subcutaneous fat thickness; MT, muscle thickness; PA, pennation angle; MBL, Muscle Bundle Length; CSA, cross-sectional area.

## Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Ethics Approval and Consent to Participate

The authors ensured that the research involving human participants complied with the Declaration of Helsinki. This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (approval number: 2023-E218-01). All participants provided informed consent.

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## Author Contributions

Each author has made a substantial contribution to all areas of the significant work reported. These areas encompass the inception, study design, execution, acquisition of data, analysis and interpretation. They have also been engaged in drafting, revising, and critically reviewing the article; they have collectively given final approval for the publication version and consented to the chosen submission journal for the article. Moreover, they agreed to be responsible for every aspect of the project.

## Disclosure

The authors report no conflicts of interest in this work.

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