

Thoracic ultrasonography and pulmonary function tests in assessing lung function in acromegaly: a prospective matched case-control study

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Abstract

Acromegaly is a rare disease characterized by elevated levels of growth hormone (GH) and insulin-like growth factor 1 (IGF-1), leading to changes in various organ systems. However, the effects of this disease on pulmonary function are often overlooked. Early detection of pleural thickness and pulmonary function changes could offer significant clinical value. This study aimed to assess the role of thoracic ultrasonography (TUS) and pulmonary function tests in evaluating functional lung changes in patients with acromegaly and to explore the potential of ultrasonographic pleural assessment in predicting pulmonary involvement. This prospective single-center study, conducted at Gazi University Hospital between April and September 2022, included 34 patients with acromegaly and 34 healthy controls. Total lung capacity, residual volume, and forced vital capacity were significantly higher in patients with acromegaly compared to the control group ($p=0.004$, $p=0.004$, and $p=0.005$, respectively), while maximal inspiratory pressure and maximal expiratory pressure (MEP) were significantly lower ($p=0.001$ and $p<0.001$, respectively). Additionally, pleural thickness was higher in the acromegaly group ($p<0.001$). In the acromegaly group, MEP was negatively correlated with GH ($r=-0.398$, $p=0.033$), and pleural thickness was positively correlated with IGF-1 upper limit of normal ($r=0.349$, $p=0.047$). In conclusion, our study suggests that TUS combined with pulmonary function tests may help detect subtle thoracic changes in patients with acromegaly. This is the first study to evaluate TUS in these patients, and further research is needed to validate our findings.

Key words: acromegaly, ultrasonography, growth hormone, residual volume, total lung capacity.

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Introduction

Acromegaly is a disease caused by excessive secretion of growth hormone (GH) from pituitary adenomas in adults [1]. This condition affects multiple systems, including cardiovascular, respiratory, endocrine, metabolic, musculoskeletal, and neoplastic comorbidities, due to significantly elevated levels of GH and insulin-like growth factor-1 (IGF-1) compared to normal, healthy individuals. Visceromegaly is a common feature in patients with acromegaly, and the enlargement of several organs, including the prostate, kidneys, liver, and thyroid, has been extensively studied [2]. Patients with acromegaly often exhibit soft tissue enlargement, a characteristic facial appearance (including frontal prominence, a large and coarse nose, and macroglossia) synovial hypertrophy, and cartilage enlargement. Additionally, there is bone and soft tissue hyperplasia around the airways [3]. This can lead to anatomical changes in the airways and result in respiratory dysfunction. Hypertrophy of the pharyngeal and laryngeal cartilages, along with soft tissue thickening, may lead to inspiratory collapse of the hypopharynx and narrowing of the upper airway during sleep, resulting in respiratory

complications such as sleep-disordered breathing, particularly sleep apnea and respiratory failure [4].

The treatment of acromegaly primarily involves a combination of surgical and pharmacological strategies. Surgical intervention, most commonly transsphenoidal surgery, aims to remove the pituitary adenoma, while pharmacological treatment includes the use of somatostatin analogs (SSA), dopamine agonists (DA), and, in some cases, GH receptor antagonists to control hormone levels and tumor growth [1].

Studies have demonstrated that elevated levels of GH and IGF-1 can lead to bronchial wall thickening, decreased lung compliance, small airway stenosis, and increased diameters of both the left and right main bronchi [1]. The release of GH and IGF-1 has been linked to alveolar hyperplasia, alveolar hypertrophy, and an increased number of alveoli in the respiratory systems of patients with acromegaly [5]. Numerous studies examining pulmonary function tests (PFTs) in patients with acromegaly have found that lung volumes increase due to alveolar hypertrophy [6,7]. However, the exercise capacity of patients with acromegaly was assessed using the 6-minute walk test and found to be lower than predicted values [8].

Thoracic ultrasonography (TUS) is utilized for the diagnosis



and follow-up of various lung diseases, as well as to guide interventional procedures [9]. TUS appears to be a rapid, cost-effective, portable, and radiation-free method for both patients and physicians, making it an increasingly preferred imaging modality in clinical practice [10]. In patients with acromegaly, ultrasound is generally used to detect systemic complications such as organomegaly and musculoskeletal changes [2,11]. However, to the best of our knowledge, no studies have used TUS in patients with acromegaly. This study is the first to investigate the potential of TUS as a tool for evaluating functional lung changes and predicting pulmonary involvement in acromegaly, complementing traditional PFTs. By integrating ultrasounds with PFTs, our study aims to provide new insights into the diagnosis and management of respiratory complications in acromegaly patients, offering a non-invasive, accessible method for the early detection of pulmonary issues that may be overlooked using conventional diagnostic approaches. This study aims to determine the role of TUS and PFTs in assessing functional lung changes in patients with acromegaly, as well as to investigate the contribution of ultrasonographic evaluation of the pleura in predicting pulmonary involvement.

Materials and Methods

This prospective, single-center study was conducted with the approval of the Gazi University Faculty of Medicine Clinical Research Ethics Committee on April 18, 2022, under decision number 291. Patients diagnosed with acromegaly who visited the Pituitary Diseases Outpatient Clinic of the Endocrinology and Metabolism Department at our hospital between April 2022 and September 2022 were included in the study. Patients with acromegaly who were 18 years of age or older, either newly diagnosed or already under follow-up, were included in the study after providing written informed consent. Patients with acromegaly who were under 18 years of age, did not provide informed consent, had a history of smoking, had a known chronic pulmonary disease, or were unable to cooperate with pulmonary function testing were excluded from the study. A total of 45 patients were screened for eligibility. Among them, 2 patients declined to participate, 3 were unable to perform PFTs due to lack of cooperation, and 6 had known chronic pulmonary conditions. Consequently, 34 patients were included in the final analysis. As a control group, patients with no history of smoking and no known lung disease who visited the Chest Diseases Outpatient Clinic for routine check-ups were included.

The diagnosis of acromegaly was based on the failure to suppress serum GH concentration below 0.4 ng/mL after 75 g oral glucose tolerance test and an IGF-I $>1.3 \times \text{ULN}$ for age in a patient with clinical signs and symptoms typical of acromegaly [12]. IGF-1 upper limit of normal (IGF-1 ULN) was calculated by dividing IGF-1 by the upper limit of IGF-1 according to age and sex [13]. The postoperative remission criteria included normal IGF-1 levels for the respective age group and a random GH value of less than 1 $\mu\text{g/L}$. Patients with basal GH levels below 1 ng/mL and normal IGF-1 values were classified as having controlled acromegaly, while those with elevated IGF-1 levels for their age were classified as having active acromegaly [12]. Demographic data (age, gender, height, weight), laboratory results (GH, IGF-1), comorbidities (diabetes, hypertension, hepatitis, heart failure, hypothyroidism, etc.), pregnancy status, surgical treatment (including transsphenoidal surgery), and medical treatment (including SSA, DA and other relevant drugs), time of diagnosis were recorded.

Thoracic ultrasonography

All patients were assessed using a HITACHI L2e-EA0388-12 ultrasound device (Tokyo, Japan) equipped with a convex probe (3.5-5 MHz). The ultrasonographic examinations were performed by two experienced physicians with over 5 years of ultrasound experience. The patients were examined either in the sitting or supine position depending on their clinical condition [14]. During the examination, patients were instructed to raise their arms above their head to optimize intercostal space visualization. The probe was moved longitudinally from ventral to dorsal and transversely across intercostal spaces, parallel to the ribs, to ensure a comprehensive pleural assessment. For patients in the sitting position, the anterior, middle, and posterior axillary lines, the mid-scapular line, and paravertebral areas were systematically scanned [15,16].

B-mode ultrasonography was employed to measure pleural thickness bilaterally at the posterior chest wall, specifically at the 8th to 10th intercostal spaces in the paravertebral region at end-expiration. Three measurements were taken at each site, and the average value was recorded. The operators were blinded to the patients' clinical status during the measurements.

M-mode ultrasonography was used to assess diaphragmatic movement (Figure 1). The probe was placed over the diaphragm's thickest portion to observe its motion during inspiration and expiration. No quantitative measurement of diaphragmatic excursion was performed, but movement was recorded as either present or absent during the respiratory phases. In addition to pleural thickness, the presence of pleural masses, nodules, septations, and diaphragmatic movement were qualitatively evaluated using TUS.

Previous studies have reported that the normal pleural thickness in healthy individuals ranges between 0.2 and 0.3 mm, as assessed by high-resolution ultrasound [17].

Pulmonary function test parameters

Spirometry was performed using the Carefusion Masterscreen device (CareFusion, Höchberg, Germany). The measurements included forced vital capacity (FVC), the volume of air expelled in the first second of forced expiration (FEV₁), the FEV₁/FVC ratio, mid-forced expiratory flow rate, carbon monoxide diffusion capacity (DLCO), total lung capacity (TLC, %), residual volume (RV, %), maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP). All steps in the testing procedures were verified for compliance with the guidelines of the American Thoracic Society and the American Thoracic Society/European Respiratory Society [18]. FVC, TLC, and RV values above 120% were considered indicative of increased lung volume.

Statistical analysis

Commercial statistical software, Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA), was used for statistical analyses. In descriptive statistical analyses, the mean $\pm$ standard deviation (SD) and median (minimum-maximum) were reported for continuous variables, while counts and percentages were provided for categorical variables. The distribution of continuous variables was assessed using the Kolmogorov-Smirnov test to determine whether the data followed a normal distribution. Based on the results of this test, parametric or nonparametric tests were applied as appropriate. Specifically, the Pearson's chi-square (χ^2) test was employed for categorical data, Student's *t*-test was used for normally distributed continuous data, and the Mann-Whitney U test was applied for non-normally



distributed data. For normally distributed continuous data, comparisons between groups were made using an independent samples *t*-test. For non-normally distributed data, the Mann-Whitney U test was used to assess differences between the groups. The relationship between continuous variables was evaluated using Pearson's correlation coefficient for normally distributed data and Spearman's rank correlation for non-normally distributed data. The error rate (α) was set at 0.05 for all statistical tests, and a difference was considered statistically significant when $p < 0.05$. The receiver operating characteristic curve analysis was performed to evaluate the diagnostic value of pleural thickness in acromegaly, with sensitivity, specificity, and the area under the curve being calculated. The results were considered statistically significant if $p < 0.05$.

Results

In the acromegaly group, the mean age was 45.4 ± 10.13 (mean $\pm$ SD) years, with 25 patients (73.52%) being female (Table 1). Among the patients included in the study, 21 had controlled acromegaly, whereas 13 continued to exhibit active acromegaly despite the administration of SSA and DA following transsphenoidal surgery. All patients in the controlled acromegaly group underwent transsphenoidal surgery. In the active acromegaly group, 12 out of 13 patients (92.3%) had pre-

viously undergone transsphenoidal surgery but did not achieve biochemical remission. Among them, 8 (61.5%) were receiving SSA, and 5 (38.5%) were treated with both SSA and DA. The diseases commonly associated with acromegaly included hypothyroidism (47.1%), hypertension (26.5%), diabetes mellitus (26.5%), hyperlipidemia (23.5%), and obstructive sleep apnea syndrome (17.64%). A total of 34 patients were included in the study as a control group. The mean age of these patients was 44.07 ± 11.14 years, with 24 (70.58%) being female (Table 1). As shown in Table 2, the acromegaly and control groups demonstrated similarities in terms of age ($p = 0.315$), sex ($p = 1.0$), and body mass index ($p = 0.502$).

As shown in Table 2, the % predicted FVC of patients with acromegaly (113.71 ± 16.78) was significantly higher than that of the control group (94.30 ± 14.45) ($p = 0.005$). However, there were no statistically significant differences between the two groups in % predicted FEV₁ ($p = 0.860$), peak expiratory flow ($p = 0.399$), maximal expiratory flow at 75% of FVC ($p = 0.775$), maximal expiratory flow at 50% of FVC ($p = 0.362$), maximal expiratory flow at 25% of FVC ($p = 0.320$), and DLCO ($p = 0.330$) (Table 2). Additionally, when assessing the degree of airway obstruction, there was no significant difference in the FEV₁/FVC between the two groups ($p = 0.703$) (Table 2). The % predicted TLC in patients with acromegaly (110.57 ± 15.84) was significantly higher than in the control group (89.36 ± 18.99 ; $p = 0.004$) (Table 2).

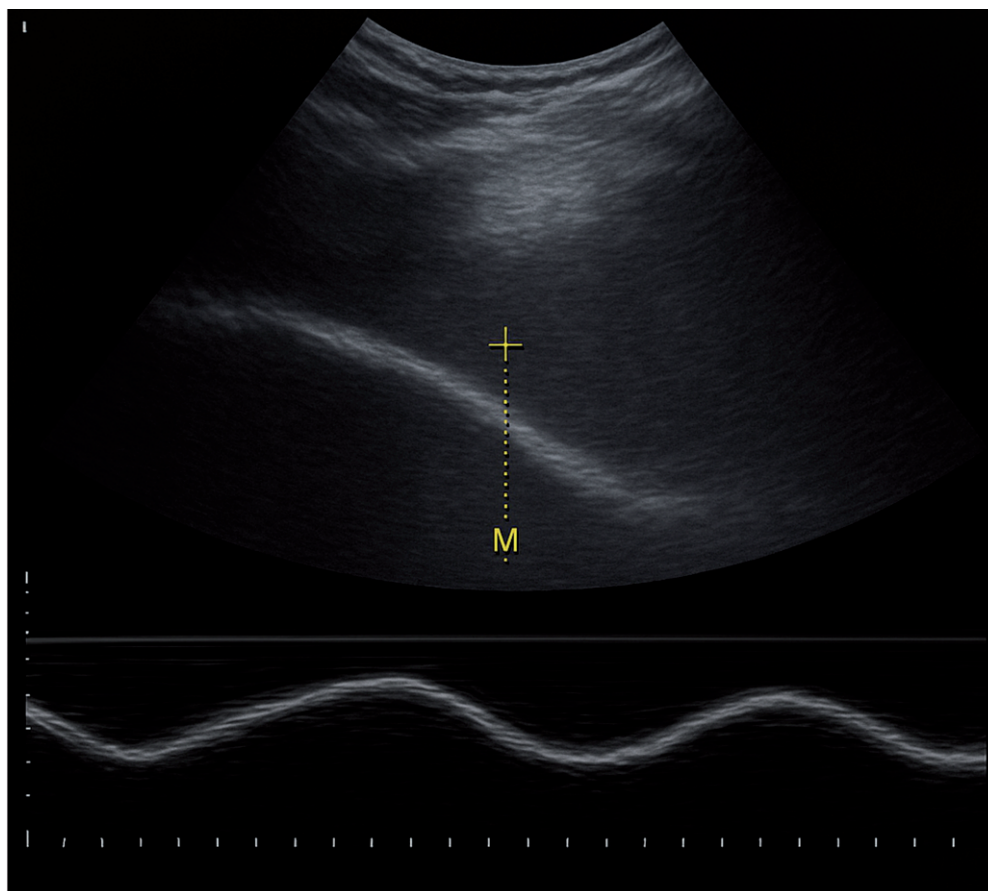


Figure 1. Evaluation of diaphragmatic excursion *via* M-mode ultrasound in an acromegaly case.

Table 1. General characteristics of patients with acromegaly.

Variables	Men (n=9) Mean±SD	Women (n=25) Mean±SD	Total (n=34) Mean±SD
Age (years)	46.00±11.06	45.24±10.01	45.40±10.13
Body composition			
Body mass index (kg/m ²)	28.83±3.88	29.04±5.76	28.88±5.31
Fat percentage (%)	17.80±5.55	31.30±7.38	27.50±9.19
Fat-free mass (kg)	16.07±6.80	24.52±11.24	22.15±10.80
Laboratory findings of the patients			
GH, ng/mL	3.83±8.16	2.02±1.36	2.47±2.45
IGF-1, ng/mL	330.62±289.08	188.73±104.16	224.20±175.54
TSH, μ U/mL	1.65±1.01	2.09±1.63	1.98±1.50
T3, ng/mL	3.23±0.42	3.12±0.39	3.15±0.39
T4, mg/mL	0.89±0.13	0.89±0.15	0.89±0.14
ACRoQoL	93.33±7.58	88.08±16.31	89.51±14.53
Pulmonary functions			
FVC (% predicted)	118.55±22.24	111.82±14.26	113.71±16.78
FEV ₁ (% predicted)	109.87±19.34	104.09±16.07	105.68±16.88
FEV ₁ /FVC (%)	76.62±5.31	82.23±4.72	80.68±5.43
TLC (% predicted)	124.87±19.75	100.45±12.27	110.57±15.84
RV (% predicted)	133.50±39.23	108.90±16.62	115.92±26.86
DLco (% predicted)	103.00±17.27	91.85±10.58	95.03±13.51
MIP (% predicted)	68.87±19.80	63.77±18.46	65.13±18.62
MEP (% predicted)	68.12±21.39	66.68±13.89	67.06±15.84
Thoracic ultrasound			
Right pleural thickness, mm	2.12±0.29	2.16±0.32	2.15±0.31
Left pleural thickness, mm	2.22±0.17	2.09±0.30	2.12±0.28

SD, standard deviation; GH, growth hormone; IGF-1, insulin-like growth factor-1; TSH, thyroid-stimulating hormone; T4, thyroxine; T3, triiodothyronine; ACRoQoL, Acromegaly Quality of Life Questionnaire; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; FEV₁/FVC, ratio of FEV₁ to FVC; DLCO, carbon monoxide diffusion capacity; TLC, total lung capacity; RV, residual volume; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure.

Table 2. Demographic data and laboratory results of patients.

Variables	Active acromegaly (n=13), mean±SD	Controlled acromegaly (n=21), mean±SD	p	Acromegaly group (n=34), mean±SD	Control group (n=34), mean±SD	p
Age, years	41.33±7.43	47.29±10.75	0.315	45.40±10.13	44.07±11.14	0.315
Gender, female, n (%)	7 (53,8)	18 (85,7)	1.001	25 (73,52)	24 (70,58)	1.001
Body mass index, kg/m ²	29.44±4.06	28.64±5.77	0.502	28.88±5.31	30.00±4.28	0.502
GH, ng/mL	5.82±7.46	1.13±1.16	0.008	2.47±2.45	-	
IGF-1, ng/mL	426.88±226.52	154.33±61.93	0.001	224.20±175.54	-	
Pulmonary functions						
FEV ₁ , % predicted	103.87±9.38	106.65±19.59	0.959	105.68±16.88	104.07±16.35	0.860
FVC, % predicted	111.22±14.72	115.27±17.92	0.383	113.71±16.78	94.30±14.45	0.005
FEV ₁ /FVC, %	80.87±5.89	80.40±5.44	0.592	80.68±5.43	80.23±6.07	0.703
PEF, % predicted	83.49±23.64	84.61±21.51	0.366	85.62±24.74	80.23±25.44	0.399
MEF75, % predicted	73.87±21.59	70.60±23.83	0.879	71.89±22.53	74.00±37.01	0.775
MEF50, % predicted	97.87±23.74	90.15±29.46	0.476	93.13±27.56	84.92±20.92	0.362
MEF25, % predicted	111.75±19.98	94.30±23.09	0.063	99.34±22.89	93.46±14.43	0.320
TLC, % predicted	99.89±18.55	93.00±15.29	0.489	110.57±15.84	89.36±18.99	0.004
RV, % predicted	125.85±43.72	112.40±19.29	0.846	115.92±26.86	93.27±11.55	0.004
DLCO, % predicted	97.14±15.06	94.45±13.61	0.293	95.03±13.51	97.27±9.25	0.333
MIP, % predicted	73.50±11.27	61.85±20.47	0.102	65.13±18.62	85.30±13.79	0.001
MEP, % predicted	71.12±15.67	65.38±16.34	0.392	67.06±15.83	87.00±12.91	<0.001
Thoracic ultrasound						
Right pleural thickness, mm	2.10±0.37	2.17±0.29	0.641	2.15±0.31	1.03±0.27	<0.001
Left pleural thickness, mm	2.15±0.32	2.11±0.27	0.733	2.12±0.28	1.00±0.24	<0.001

SD, standard deviation; GH, growth hormone; IGF-1, insulin-like growth factor-1; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; FEV₁/FVC, ratio of FEV₁ to FVC; PEF, peak expiratory flow; MEF25, maximal expiratory flow at 25% of FVC; MEF50, maximal expiratory flow at 50% of FVC; MEF75, maximal expiratory flow at 75% of FVC; DLCO, carbon monoxide diffusion capacity; TLC, total lung capacity; RV, residual volume; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure.



The % predicted RV was also higher in patients diagnosed with acromegaly (115.92 ± 26.86 , predicted) compared to the control group (93.27 ± 11.55), and this difference was statistically significant ($p=0.004$) (Table 2). Furthermore, MIP and MEP values, expressed as percentage of predicted values (% predicted), were significantly lower in the acromegaly group (65.13 ± 18.62 and 67.06 ± 15.83 , respectively) compared to the control group (85.30 ± 13.79 and 87.00 ± 12.91 , respectively) ($p=0.001$ and $p<0.001$, respectively) (Table 2 and Figure 2).

Patients and control groups were evaluated using TUS. TUS was used to assess pleural thickness, pleural masses, pleural nodules, pleural septa, and diaphragmatic movements. No pathological findings were identified in the pleura, and diaphragmatic movement was present. Additionally, right and left pleural thicknesses were found to be significantly higher in the patient group (2.15 ± 0.31 mm; 2.12 ± 0.2 mm, respectively) compared to the control group (1.03 ± 0.27 mm; 1.00 ± 0.24 mm, respectively) ($p<0.001$; $p<0.001$) (Table 2).

GH and IGF-1 levels were significantly higher in patients with active acromegaly (5.82 ± 7.46 ng/mL, 426.88 ± 226.52 ng/mL, respectively) compared to controlled acromegaly (1.13 ± 1.16 ng/mL, 154.33 ± 61.93 ng/mL, respectively) ($p=0.008$, $p<0.001$, respectively), but there was no significant difference in FVC ($p=0.383$), FEV_1 ($p=0.959$), TLC ($p=0.489$), RV ($p=0.846$), MIP ($p=0.102$), MEP ($p=0.392$) and right pleural thickness ($p=0.641$) (Table 2).

As shown in Table 3, in the acromegaly group, MEP was neg-

atively correlated with GH ($r=-0.398$, $p=0.033$), while pleural thickness was positively correlated with IGF-1 ULN ($r=0.349$, $p=0.047$) (Table 3).

Discussion

Acromegaly is a rare disease characterized by somatic and metabolic effects due to prolonged excessive secretion of GH [1]. Respiratory disorders are frequent in acromegaly and can negatively impact both quality of life and mortality. In our study, acromegaly patients showed increased lung volumes—specifically FVC, TLC, and RV—compared to healthy controls, likely reflecting alveolar hypertrophy and altered airway geometry, as previously reported [7]. Despite this increase, respiratory muscle strength was reduced, as evidenced by lower MIP and MEP values [19]. Notably, MEP was negatively correlated with GH levels, suggesting that elevated GH may contribute to respiratory muscle weakness, in contrast to studies reporting no such relationship. Additionally, pleural thickness was increased on ultrasonographic evaluation and showed a positive correlation with IGF-1.

PFTs and assessments of respiratory muscle strength have been the subject of many studies. One study included 20 patients with acromegaly and 20 healthy controls, and it reported higher values of FVC, TLC, and RV, as well as lower MEP and MIP values in acromegaly patients [20]. In another prospective study, patients with active acromegaly were compared with patients who had non-func-

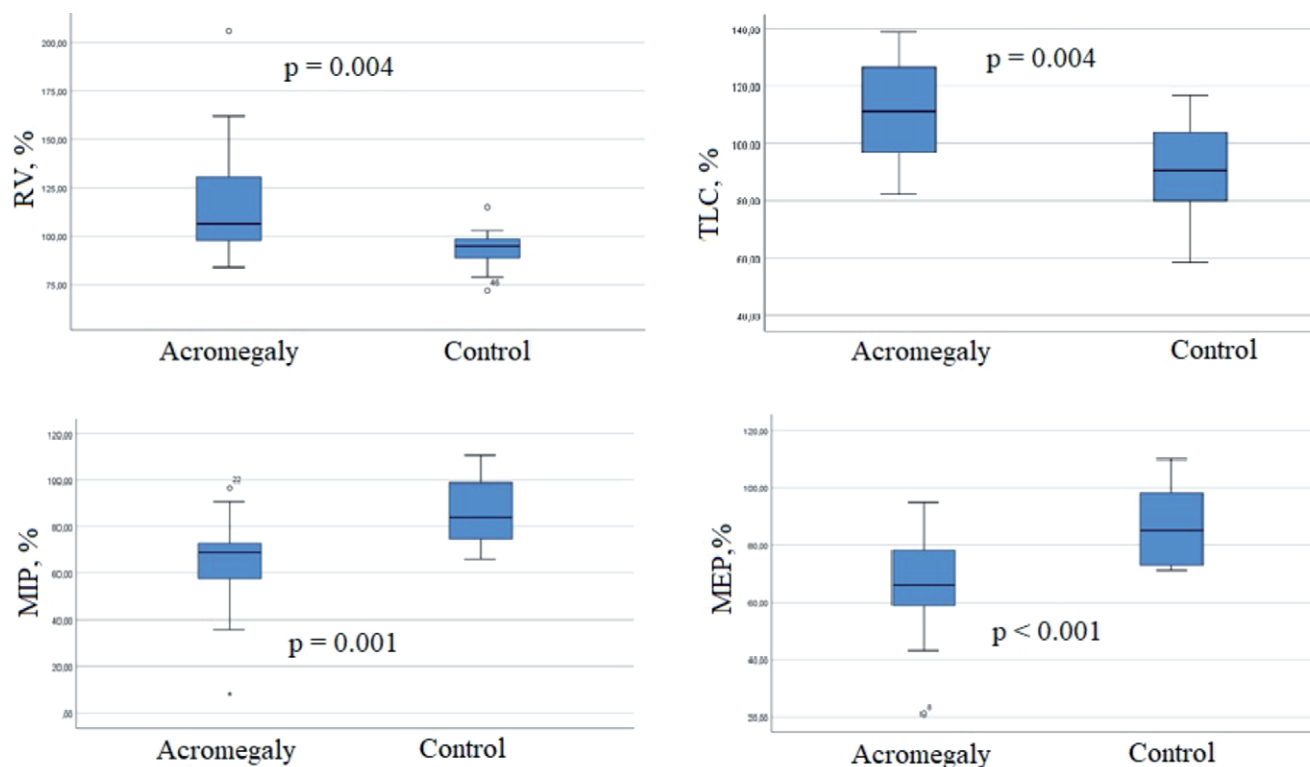


Figure 2. Distributions of residual volume (RV), total lung capacity (TLC), maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP) % values in acromegaly patients and control groups. This figure shows the distribution of the percentage values of RV, TLC, MIP, and MEP in both the acromegaly patient and control groups. The RV, TLC, MIP, and MEP measurements are compared across the two groups, with statistical significance indicated where applicable.



Table 3. Correlation analysis between thoracic ultrasonography parameters, pulmonary function tests and clinical parameters in patients with acromegaly.

		Age	BMI	GH	IGF-1 ULN	Disease age	MEP	MIP	DLCO	RV	TLC	FEV ₁
Right pleural thickness	r	0.050	-0.018	0.037	0.349	0.059	-0.006	0.063	0.025	0.042	0.001	-0.047
	p	0.780	0.919	0.840	0.047	0.744	0.975	0.741	0.901	0.831	0.994	0.809
FEV ₁	r	-0.393	-0.099	-0.099	0.259	-0.199	-0.113	0.209	0.055	0.254	0.787	-
	p	0.035	0.608	0.608	0.174	0.300	0.558	0.276	0.781	0.064	0.000	-
FVC	r	0.527	-0.147	-0.124	-0.120	0.159	0.075	-0.051	0.242	0.062	0.068	
	p	0.002	0.423	0.506	0.513	0.385	0.700	0.792	0.214	0.752	0.731	
TLC	r	-0.126	-0.119	0.089	0.190	-0.015	0.053	0.101	0.412	0.726	-	
	p	0.522	0.545	0.661	0.334	0.938	0.789	0.608	0.029	0.000	-	
RV	r	0.248	-0.132	-0.116	0.064	0.158	0.212	-0.253	0.363	-		
	p	0.204	0.502	0.563	0.747	0.421	0.279	0.194	0.058	-		
DLCO	r	0.167	0.126	0.013	0.228	-0.092	0.396	0.266	-			
	p	0.396	0.522	0.947	0.242	0.641	0.037	0.171	-			
MIP	r	-0.219	0.120	0.024	0.116	0.131	0.319	-				
	p	0.245	0.529	0.900	0.542	0.490	0.086	-				
MEP	r	0.392	0.198	-0.398	-0.070	0.178	-					
	p	0.032	0.293	0.033	0.713	0.347	-					

BMI, body mass index; GH, growth hormone; IGF-1, insulin-like growth factor-1; ULN, upper limit of normal; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; DLCO, carbon monoxide diffusion capacity; RV, residual volume; TLC, total lung capacity; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

tioning adenomas. While the predicted FVC was significantly higher in patients with active acromegaly, there was no significant difference in terms of FEV₁/FVC [6]. Similarly, in our study, no significant differences were found in FEV₁ and FEV₁/FVC between the active and inactive acromegaly groups. However, FVC was significantly higher in acromegaly patients compared to the control group. This suggests changes in the airway structure due to the disease. Some studies evaluating DLCO in patients with acromegaly reported normal values [21], while other studies have reported elevated DLCO values in the literature [22]. In our study, no significant difference was observed between the active and inactive acromegaly groups in terms of DLCO and small airway function, which is consistent with the existing literature [20]. Furthermore, no significant difference in DLCO values was observed between the acromegaly and control groups, despite higher lung volumes in the patient group. This is consistent with the findings of Brody *et al.* (1970), who demonstrated that in acromegalic patients, increased lung volumes do not necessarily result in a proportional increase in DLCO, likely due to the influence of alveolar-capillary membrane integrity and pulmonary vascular factors [5].

The measurement of MIP and MEP is a simple, non-invasive, and rapid test for assessing the strength of respiratory muscles [23]. MIP is the maximum negative pressure that can be generated during forced inspiration, while MEP is the maximum positive pressure that can be generated during forced expiration, when the abdominal muscles tend to reduce thoracic and lung volumes by pushing the diaphragm and internal intercostal muscles upward [24]. MIP and MEP should be evaluated in patients with suspected respiratory muscle weakness [25]. Similar to our study, Iandelli *et al.* showed that MIP and MEP values decreased in patients with acromegaly in a study involving 10 patients [26]. In another study with 32 patients, a positive correlation was found between the 6-minute walk test and MEP, which led us to conclude that better respiratory muscle performance is associated with a longer walking distance [8]. These findings suggest that the reduction in respiratory muscle strength observed in acromegaly may be related to soft tissue hypertrophy, skeletal deformities, and thoracic structural changes—including

impaired diaphragmatic mobility—induced by chronically elevated GH and IGF-1 levels [27].

Systemic complications are a major cause of mortality in acromegaly [1]. The increasing use of ultrasound in recent years has proven effective in detecting acromegaly-related complications when combined with clinical suspicion [2]. Similar to the findings in Parolin *et al.* (2020), which highlight the importance of ultrasound in assessing systemic complications in acromegaly [2], our study demonstrated that pleural thickness was significantly increased in acromegaly patients, potentially influenced by elevated GH levels. In many studies, functional disorders associated with visceromegaly (liver, spleen, kidney, thyroid, prostate) and tissue stiffness in patients with acromegaly have been linked to increased levels of GH and IGF-1 [28–32]. Measurement of pleural thickness using TUS has been the subject of many studies. TUS has also been used to differentiate between exudative and transudative pleural effusions in infectious conditions [33]. Additionally, pleural thickness in patients with malignant pleural mesothelioma is an important clue for the occurrence of postoperative complications [34]. Pleural thickness after neoadjuvant chemotherapy has also been identified as an independent prognostic factor in patients receiving multimodal therapy, including neoadjuvant chemotherapy and curative-intent surgery [35]. To the best of our knowledge, our study is the first in the literature to evaluate the use of TUS in patients with acromegaly. In our study, pleural thickness was found to be significantly higher in the patient group compared to the control group. Additionally, pleural thickness was positively correlated with IGF-1 ULN and also positively correlated with FVC. The results demonstrated that the thickness of the pleura increased in response to IGF-1, accompanied by a secondary effect on functional lung volume.

In our study, diaphragmatic movement was assessed qualitatively using M-mode ultrasonography. Although no abnormal movement was observed in any patient, this assessment was performed visually rather than quantitatively, which limits our ability to detect subtle impairments [36]. Diaphragmatic motion can be affected by thoracic structural changes, increased intra-abdominal pressure, and respiratory muscle weakness—conditions that may occur in patients



with acromegaly due to soft tissue hypertrophy and skeletal alterations. While previous studies on acromegaly have not extensively evaluated diaphragmatic excursion, reduced diaphragmatic mobility has been observed in other systemic diseases with musculoskeletal involvement [37]. Diaphragmatic excursion was visually assessed but not quantitatively measured in this study; therefore, conclusions regarding diaphragmatic function should be interpreted with caution. Future studies using objective measurements are needed to better understand respiratory mechanics in acromegaly. Moreover, correlating diaphragmatic movement with clinical symptoms (*e.g.*, dyspnea, fatigue) and exercise capacity could help clarify its clinical significance.

The pathophysiological basis for pleural thickening in acromegaly remains unclear, but it may represent a manifestation of widespread connective tissue proliferation driven by chronic IGF-1 elevation. IGF-1 has been shown to stimulate fibroblast activity and extracellular matrix deposition in various tissues [38], potentially contributing to pleural fibrosis or subclinical thickening over time. These findings suggest that TUS, particularly the measurement of pleural thickness, could serve as a non-invasive surrogate marker for systemic disease activity and pulmonary involvement in acromegaly. In clinical practice, detecting increased pleural thickness may warrant further assessment of respiratory function, even in asymptomatic patients.

However, it is essential to consider and exclude other potential causes of pleural thickening, especially malignancies and other pleural diseases, to avoid misinterpretation of the findings [34,35]. Therefore, comprehensive clinical and radiological evaluations are necessary to differentiate acromegaly-related pleural changes from other pathological conditions. While current literature does not establish a definitive link between acromegaly and pleuro-pulmonary diseases, similar mechanisms have been proposed to explain tissue stiffness and organomegaly observed in systemic involvement of acromegaly.

In our study, individuals with a history of smoking or known chronic pulmonary diseases were excluded to minimize confounding factors. Nevertheless, given that the study was conducted during the post-pandemic period, the potential impact of prior asymptomatic or mild COVID-19 infection cannot be entirely ruled out. SARS-CoV-2 infection has been demonstrated to induce long-term pulmonary and pleural alterations even in the absence of significant clinical symptoms [39]. Thus, subclinical post-COVID sequelae may have contributed to the observed pleural findings, representing a limitation of the study [39].

Our study had some limitations. Most of the acromegaly patients included in the study had controlled acromegaly, and there were not enough newly diagnosed and active acromegaly cases to demonstrate differences between the active and controlled acromegaly groups. However, the differences in pleural thickness and lung volumes between the acromegaly group and healthy controls indicate that pulmonary problems persist despite disease control. The cross-sectional design of our study may have limited our ability to demonstrate the relationship between disease activity, lung function, and chest ultrasound changes over time. A longitudinal study would be beneficial to observe changes in pleural thickness and diaphragmatic function as the disease progresses. Additionally, diaphragmatic excursion was assessed visually rather than quantitatively in this study, which represents a limitation. Future research should incorporate more objective and quantitative methods for assessing diaphragmatic movement, such as ultrasound-based measurements or other imaging techniques.

Furthermore, the sample size in our study was relatively small,

which may affect the generalizability of our findings. Given that acromegaly is a rare disease, enrolling a larger cohort is challenging, but prospective follow-up studies with larger patient populations are essential to validate and strengthen the robustness of these results.

While we focused on pleural thickness as the primary parameter, other ultrasound findings such as B-lines (vertical artifacts) and diaphragmatic abnormalities were not explored in detail in this study. These markers need further investigation in relation to acromegaly. Finally, this study primarily assessed pleural thickness without delving into the underlying pathophysiological mechanisms driving these changes in acromegaly. Further research is necessary to explore the mechanisms contributing to pleural thickening and to better understand their clinical significance in the disease's progression.

Conclusions

To the best of our knowledge, our study is the first to assess pleural thickness using ultrasound in patients with acromegaly. Increased pleural thickness, caused by elevated levels of IGF-1 and GH in patients with acromegaly, is associated with weak respiratory muscle strength as well as changes in lung capacity. In conclusion, our study suggests that TUS combined with PFTs may help detect subtle thoracic changes in patients with acromegaly. However, further research with detailed clinical characterization is needed to clarify the nature and clinical significance of pulmonary involvement in this population.

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