

Original Article



An Important Question: Can Serum Chitotriosidase Enzyme Predict the Activity and Clinical Course of Sarcoidosis Disease?

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Abstract

OBJECTIVE: Serum chitotriosidase (CHIT) is a promising biomarker that has shown high specificity and sensitivity in patients with sarcoidosis. Our study aimed to evaluate the CHIT enzyme concerning the activity, prognosis, and treatment decision of sarcoidosis.

MATERIAL AND METHODS: The patients with the following characteristics were included in our single-center study as long as they agreed to participate. These patients were newly or previously diagnosed with sarcoidosis according to American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Disorders and consulted the outpatient clinic of chest diseases in our university hospital between August 2020 and April 2021. The patients with sarcoidosis were categorized into 3 groups: 1) diagnosed as sarcoidosis but not having the treatment indication; 2) previously treated or currently receiving treatment; and 3) newly diagnosed and having a treatment indication.

RESULTS: A total of 126 sarcoidosis patients and 43 healthy volunteers were included. The median value of serum CHIT enzyme levels in patients with sarcoidosis was determined to be 9.8 ng/mL, while it was 5.1 ng/mL in the control group. It was determined that the serum CHIT levels were notably higher in patients with sarcoidosis ($P = 0.000$). In the serum CHIT levels of the newly-treated patient, a significant reduction was observed after the 6-month treatment ($P = 0.008$), in comparison with these levels noted at the time of diagnosis.

CONCLUSION: Our study demonstrated that the serum CHIT has a high sensitivity and high specificity in the diagnosis of sarcoidosis and a reduction in the level of that enzyme occurs upon treatment.

KEYWORDS: Sarcoidosis, biomarker, chitotriosidase, disease activity, clinical course

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INTRODUCTION

Sarcoidosis is a systemic granulomatous disease of unknown etiology, characterized by a heterogeneous clinical course and unpredictable outcomes.¹ It affects multiple organ systems, particularly the lungs and lymphatic system.² The natural course and prognosis of sarcoidosis are highly variable. The disease may spontaneously remit, but progression is also a potential outcome. Spontaneous remission occurs in approximately two-thirds of patients.¹

Even though many biomarkers have been studied to determine disease activity, a biomarker with high sensitivity, specificity, and satisfactory prognostic value has yet to be identified. Angiotensin-converting enzyme (ACE) is the most frequently used laboratory test in sarcoidosis and is considered an indicator of the total granuloma burden in the body.^{3,4} Despite its frequent use in assessing sarcoidosis activity, the diagnostic and prognostic values of ACE remain uncertain. In their study, Gungor et al.⁵ (2015) reported that the sensitivity and specificity of serum ACE levels in diagnosing sarcoidosis are 72% and 60%, respectively. The weak correlation between serum ACE levels and sarcoidosis activity or response to treatment has been observed.⁶

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The human chitotriosidase (CHIT) enzyme, a chitinase secreted by activated macrophages and neutrophils, is considered responsible for the degradation of chitin and chitin-like substrates and associated with defense against chitin-containing pathogens.^{7,8} This enzyme is secreted by pulmonary macrophages and neutrophils in response to the stimulation of toll-like receptors by interferon- γ , tumor necrosis factor (TNF), and granulocyte/macrophage colony-stimulating factor.⁹ The procedure for measuring serum CHIT levels in patients with sarcoidosis is based on the direct involvement of activated macrophages and granulomatous inflammation in the disease's pathogenesis.¹⁰⁻¹³ The first report evaluating serum CHIT activity in patients with sarcoidosis was published in 2004 by Grosso et al.¹⁰ The report determined that significantly high chitinase activity was present in sarcoidosis patients compared to the control group.

The aim of our study is to evaluate the significance of the CHIT enzyme in sarcoidosis regarding activity, prognosis, and treatment decisions.

MATERIAL AND METHODS

Study Subjects

Our study is prospective, single-centered and cross-sectional. According to the American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders (ATS/ERS/WASOG) guidelines, patients who presented to Kocaeli University Faculty of Medicine Chest Diseases Outpatient Clinic between August 2020 and April 2021, with either a prior or new diagnosis of sarcoidosis, were included in the study upon providing informed consent. Patients with sarcoidosis were divided into three groups: those diagnosed with sarcoidosis but without a treatment indication (treatment-naïve group), those previously treated or currently receiving treatment (treated group), and those newly diagnosed with a treatment indication (newly-treated group). There were 57 patients in the treatment-naïve group, 60 patients in the treated group, and 9 patients in the newly treated group. The control group consisted of 43 healthy volunteers with the following criteria: being over the age of 18, having no comorbidities or history of drug use, being non-smokers, and consenting to participate in our study. The study was initiated after approval from Kocaeli University Medical Faculty Hospital Ethics Committee (project number: GOKAEK-2020/14.06, 2020/243, approval date: 20/08/2020). Informed consent was obtained. This is my thesis study, which

I conducted while I was a resident at the Department of Pulmonary Diseases, Faculty of Medicine Kocaeli University, Kocaeli.

For all patients with sarcoidosis, demographic data [sex, age, height, weight, body mass index (BMI)], comorbidities, pulmonary function test results (FVC liters, FVC%, FEV1 liters, FEV1%, FEV1/FVC ratio, DLCO, DLCO%), symptoms, radiological findings [lung radiography and high-resolution computed tomography (CT)], presence of extrapulmonary involvement, laboratory findings (serum calcium, albumin, CHIT enzyme level, serum ACE levels, and 24-hour urine calcium), the 6-minute walk test results, and modified Medical Research Council (mMRC) dyspnea scale scores were recorded. The serum CHIT enzyme levels of patients who were newly diagnosed and were to be treated were measured twice: once before treatment and again in the sixth month of treatment. At the sixth month, respiratory function tests, carbon monoxide diffusion tests, 6-minute walking tests, and mMRC dyspnea scores were repeated and recorded. The serum CHIT enzyme levels were measured once for the other sarcoidosis patient groups and the control group.

Chitotriosidase Measurement

Blood samples collected from patients and the control group were kept at room temperature for approximately 30 minutes and then centrifuged at 3000 rpm for 10 minutes to obtain serum. They were stored frozen at -80 °C until needed. CHIT (human chitinase 1 enzyme, Cat. No. E4540Hu) levels were measured using the enzyme-linked immunosorbent assay. The plates in the assay have been coated with CHIT antibodies, and the addition of CHIT to these plates allows the binding of the enzyme to the antibodies. The markers, the samples, and the standards were prepared. 40 microliters of serum sample, followed by 10 microliters of anti-CHIT antibody and 50 microliters of streptavidin-HRP, was transferred into each sample well. The plates were sealed with covers and incubated at 37 °C for 1 hour, followed by washing with wash buffer five times. 50 μ L of substrate solution A, followed by 50 μ L of substrate solution B, was placed in each well. The plates were covered and incubated in the dark at 37 °C for 10 minutes. 50 μ L of stop solution was added to each well, and the rapid change from blue to yellow was observed. Ten minutes after adding the stop solution, the optical density values were determined at 450 nm using a microplate reader. Serum CHIT concentrations were expressed in ng/mL.

Pulmonary Function Tests

The pulmonary function tests were carried out according to the ATS criteria using a ZAN brand (Germany) pulmonary function test device. Spirometry was automatically calibrated with the flow sensor on a daily basis. Before the test, each participant was informed about the test protocol. After the participants rested for 15 minutes, at least three tests were performed in a sitting position. The test was repeated up to eight times to ensure three acceptable maneuvers, with the difference between the two best FVC and FEV1 measurements being ≤ 200 mL. Nevertheless, the test was terminated if a valid maneuver could not be obtained or if the patient became tired.

Main Points

- Serum chitotriosidase (CHIT) is a promising biomarker that has shown high specificity and sensitivity in patients with sarcoidosis.
- This study demonstrated that serum CHIT has high sensitivity and specificity in diagnosing sarcoidosis, and that a reduction in enzyme levels occurs with treatment.
- Multicenter studies involving a larger patient population and performing serial CHIT measurements with extended follow-up times may be planned.

The parameters of FVC, FEV1, FEV1/FVC, and DLCO were evaluated in pulmonary function tests.

Computed Tomography

CT images were obtained at our center using 64-slice CT (Toshiba Aquilion Medical Systems, Japan) and 16-slice CT (Toshiba Alexion Medical Systems, Japan). The parameters used in imaging with the 64-slice CT device were as follows: pitch 0.8-1.5, rotation time 0.5 sec, tube voltage 120 kV, tube current 50-220 mAs (with automatic exposure control), and slice thickness 1-5 mm. In comparison, the parameters used in imaging with the 16-slice CT device were as follows: pitch 0.6-1.7, rotation time (0.75 sec), tube voltage (120 kV), tube current (50-300 mAs) (with automatic exposure control), and slice thickness (1-5 mm).

Statistical Analysis

Statistical analyses were performed using the IBM Statistical Package for the Social Sciences 20.0 software package (IBM Corp., Armonk, NY, USA). In determining the power and sample volume of the study, the G*Power version 3.1.9.2 software package (Kiel University, Kiel, Germany) was used. The test for conformity to normal distribution was evaluated using the Kolmogorov-Smirnov test. Numerical variables were presented as median (25th to 75th percentile), and categorical variables as frequency (percentage). Using the Kruskal-Wallis one-way analysis of variance and Dunn's multiple comparison test, the differences between groups/materials were compared for numerical variables that did not have a normal distribution. The Pearson chi-square test was used to evaluate the differences between groups for the categorical variables. The relationship between numerical variables was evaluated using Spearman's correlation analysis. $P < 0.05$ was considered sufficient for statistical significance in two-way tests.

RESULTS

A total of 126 sarcoidosis patients and 43 healthy volunteers were included in the study. The patterns of the patient profiles in the study are as follows: 57 (45.2%) patients had no indication

(treatment-naïve group); 60 (47.6%) patients were previously diagnosed with sarcoidosis and either received treatment or were receiving treatment (treated group); and 9 (7.1%) were newly diagnosed with a treatment indication (newly treated group). Forty-three healthy volunteers were included in the control group.

The mean ages of patients in these groups were 44.1 ± 10.9 years in the treatment-naïve group, 49 ± 9.6 years in the newly treated group, and 47.6 ± 11.6 years in the treated group. The mean age of the control group was 36.6 ± 10 . In the treatment-naïve group, 77.2% ($n = 44$) of patients were female, while 70% ($n = 42$) of those in the treated group were female, and 77.8% ($n = 7$) of the newly treated patients were female. In contrast, 62.8% ($n = 27$) of the healthy control group were female. There was no significant difference in gender distribution between the groups, as determined by the Pearson chi-square test. Additionally, there was no notable difference in comorbidities among the sarcoidosis patient groups.

The median serum CHIT enzyme levels were 9.8 ng/mL in patients with sarcoidosis, compared to 5.1 ng/mL in the control group; the serum CHIT level was significantly higher ($P < 0.001$). The comparison of the groups' CHIT values indicates a significant difference between the three patient groups and the control group ($P < 0.001$). However, no significant difference was detected between the patient groups. Changes in serum CHIT levels were assessed in the newly-treated group by comparing levels at diagnosis to levels at the sixth month of treatment. A significant decrease in serum CHIT levels was observed after six months of treatment ($P = 0.008$). Comparison of CHIT value, mMRC and pulmonary function test parameters at the time of diagnosis and the 6th month of treatment is shown in Table 1. The number of cases and the distribution of serum CHIT levels in the sarcoidosis patient group and the control group are shown in Table 2.

Prior to treatment, nine patients in the newly treated group were classified as having stage 2 radiological disease. After six months of therapy, all patients remitted to stage 0 radiological disease ($P = 0.03$).

Table 1. Comparison of CHIT value, mMRC and pulmonary function test parameters at the time of diagnosis and the 6th month of treatment

Newly-treated group	The time of diagnosis Median (25-75%)	The 6 th month of treatment Median (25-75%)	P value
CHIT value	10.5 (9.5-14.0)	7.1 (5.5-7.9)	0.008
FEV1 (lt)	2.02 (1.78-3.26)	2.05 (1.7-3.16)	0.86
FEV1 (%)	90 (74.5-101.5)	82 (76-97)	0.106
FVC (lt)	3 (2.735-3.44)	2.64 (2.34-3.295)	0.05
FVC (%)	99 (86-106)	93 (82-96)	0.058
FEV1/FVC	76 (69-85)	78	0.151
DLCO (lt)	7.47 (6.005-7.93)	7 (5.525-7.295)	0.314
DLCO (%)	93 (73-99)	85 (72.5-92)	0.312
mMRC	1 (0-2)	1 (0-1)	0.83

CHIT: chitotriosidase, mMRC: modified Medical Research Council

The serum CHIT values of all 126 sarcoidosis patients were examined according to the stages, and no significant difference was found between the stages and serum CHIT values ($P = 0.844$). Table 3 presents the serum CHIT median, the percentile values (25th to 75th percentiles) of the patients based on their stages, and the P value. The distribution of the number and percentage of patients according to the stages is shown in Figure 1.

In the examination of serum ACE, calcium, and urine calcium values among 126 sarcoidosis patients according to the stages (shown in Table 4), no significant difference was observed for any of these. In the evaluation of patients based on their extrapulmonary involvement (shown in Table 5), the only involvement that showed a significantly higher serum CHIT level was eye involvement ($P = 0.03$). The median serum CHIT value and percentile range (25th-75th) for patients with eye involvement were 12.1 ng/mL (10.2-17.4), while these values

for patients without eye involvement were 9.8 ng/mL (7.6-12.1), respectively. No relationship was found between serum CHIT levels and the ages, heights, weights, or BMIs of the sarcoidosis and control groups.

In the receiver operating characteristic (ROC) analysis, the area under the curve (AUC) was calculated. The diagnostic cutoff value of the CHIT enzyme for sarcoidosis was determined to be 6.7 within a 95% confidence interval, with a sensitivity of 86.51% and a specificity of 93.02%. ROC analysis data are summarized in Tables 6 and 7. The ROC curve is shown in Figure 2.

Treatment indications are present in symptomatic patients, individuals with impaired pulmonary function test results, and those exhibiting signs of organ dysfunction. All patients in the treated group ($n = 60$) received corticosteroid therapy. Ten of them required the addition of methotrexate as a

Table 2. The number of patients and the distribution of serum CHIT levels according to the sarcoidosis patient group and the control group

Groups	Serum CHIT Median (25-75%)
Treatment-naïve group ($n = 57$)	10.1 (7.3-12.4)
Treated group ($n = 60$)	9.8 (8-11.8)
Newly-treated group ($n = 9$)	10.5 (9.5-14)
Control group ($n = 43$)	5.1 (4.7- 6.2)

CHIT: chitotriosidase

Table 3. Serum CHIT values of patients according to stages and the p value

Stages	Serum CHIT median (25-75%)	P value
0	10.3 (8.8-13.8)	0.844
1	9.5 (7.0-11.4)	
2	9.9 (7.9-12.4)	
3	10.1 (7.0-17.4)	
4	10.0 (8.3-14.1)	

CHIT: chitotriosidase

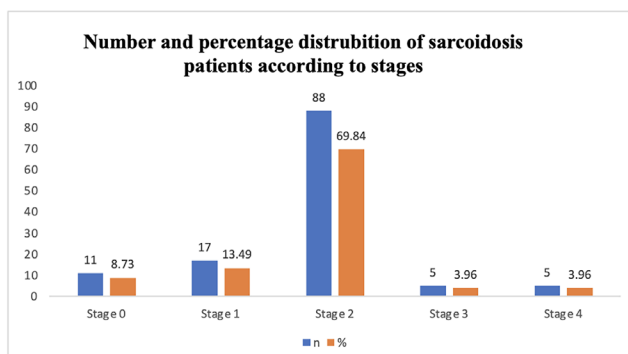


Figure 1. The graph showing the number and percentage distribution of sarcoidosis patients according to the stages

Table 4. Serum ACE, calcium and urine calcium values

Parameters	Treatment-naïve group	Newly-treated group	Treated group	P
sACE	42 (26.5-66)	40 (29-56.5)	38.5 (27.5-55)	0.329
Serum calcium	9.8 (9.5-10)	9.7 (9.25-10.35)	9.8 (9.5-10)	0.803
Urinary calcium	152 (82.75-229.85)	223.2 (117.4-491.6)	131.5 (91.8-259.15)	0.601

ACE: angiotensin-converting enzyme

Table 5. Extrapulmonary involvement

Organ involvement	Number of patient (n)	Percentile (%)
Arthritis	41	32.5
Erythema nodosum	16	12.7
Peripheral lymph node	15	11.9
Ocular	8	6.3
Bone marrow	5	4

Table 6. ROC analysis of CHIT level

	Under the curve area	95% confidence interval	P value
Serum CHIT	0.954	0.911-0.980	<0.0001

CHIT: chitotriosidase, ROC: receiver operating characteristic

Table 7. The sensitivity and specificity of CHIT level

Serum CHIT level (ng/mL)	Sensitivity (%)	Specificity (%)
6.6	88.1	88.37
6.733	86.51	93.02
8.521	67.46	100

CHIT: chitotriosidase

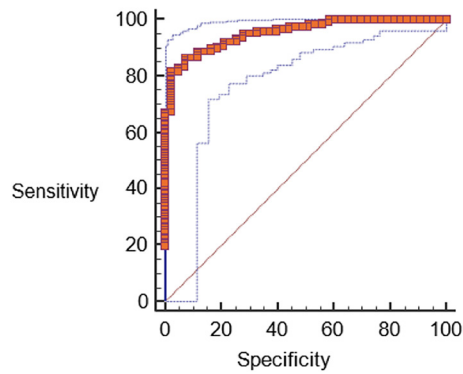


Figure 2. The graph that shows CHIT level and the ROC curve
CHIT: chitotriosidase, ROC: receiver operating characteristic

second-line therapy. Only one patient was treated with an anti-TNF agent.

DISCUSSION

In our study, we found that serum CHIT enzyme levels were significantly elevated in patients with sarcoidosis when compared to healthy individuals in the control group. Thus, the sensitivity and specificity are high for the diagnosis of sarcoidosis. This supports the potential use of CHIT enzyme levels as an auxiliary biomarker for diagnosing sarcoidosis. Moreover, its use in monitoring treatment response may be considered beneficial due to the reduction in serum CHIT enzyme values in patients with sarcoidosis, and the regression of radiological stages from 2 to 0 who have recently initiated treatment. The initial report indicating that serum CHIT enzyme levels are significantly elevated in sarcoidosis patients compared to healthy controls was published by Grosso et al.¹⁰ in 2004, and these findings were subsequently confirmed by Bargagli et al.¹⁴ in further research.

The results of our study are consistent with the literature, which demonstrates that serum CHIT enzyme levels are notably higher in sarcoidosis patients compared to the control group.

The relationship between radiological stage and serum CHIT levels yields varying results in the literature. In two separate studies by Bargagli et al.,¹⁴ conducted in 2008 and 2013, serum CHIT enzyme levels were found to be significantly higher in sarcoidosis patients at radiological stages 3 and 4, compared to those at stages 0 and 1. Additionally, a correlation was observed between radiological stages and enzyme levels.^{12,14} In their study, Popević et al.¹⁵ observed the highest serum CHIT levels in stage 2 disease. They discussed that the high level of CHIT enzyme in stage 3 pulmonary disease is due to the induction of overexpression of profibrotic type-2 (Th2) cytokines. Therefore, this elevation may also be observed in stage 2 disease due to the presence of active granulomas.¹⁵ However, Lopes et al.¹⁶ reported the highest serum CHIT levels in radiological stages 0, 1, and 2 disease. Harlander et al.¹⁷ did not detect any correlation between the radiological stages and serum CHIT levels.

In accordance with the aforementioned studies, no correlation was observed between the radiological stages and serum

CHIT levels in our study. This result may be attributed to the predominance of stage 1 and 2 patients, coupled with the limited number of patients in stages 3 and 4. A frequent polymorphism in the *CHIT* gene, which results in a CHIT enzyme deficiency, may occur due to a 24 bp duplication in exon 10, leading to an abnormal deletion and splicing of 87 nucleotides.¹⁸ Lee et al.¹⁹ investigated the allele frequency of this polymorphism in different populations and reported the results as 7-64%. The prevalence of this polymorphism in the Turkish population is unknown. The absence of a significant relation between the radiological stages and the serum CHIT levels in our study may be due to the *CHIT* gene polymorphism. However, a definite conclusion cannot be drawn about this phenomenon as this polymorphism has not been examined in our study.

The calculation of the AUC was conducted using ROC analysis in our study. A cutoff value of 6.7 ng/mL was established for diagnosing sarcoidosis, yielding a sensitivity of 86.51% and a specificity of 93.02%, with a 95% confidence interval. Similarly, Bargagli et al.¹⁴ calculated the sensitivity as 88.79% and the specificity as 92.86% for this biomarker. Bergantini et al.²⁰ observed that serum CHIT levels were higher in sarcoidosis patients with extrapulmonary involvement, and they stated a possible relationship between chitinase activity and the extent of systemic disease. However, in our study, significantly higher serum CHIT levels were observed in cases with ocular involvement. In the literature, Bennet et al.²¹ reported that higher CHIT levels were detected in patients with abdominal involvement. Secondly, ocular involvement followed abdominal involvement, and their study revealed that multiorgan sarcoid involvement was associated with higher CHIT levels. In our study, some patients with pulmonary sarcoidosis and ocular involvement also had arthritis. This multiorgan involvement may reflect the presence of highly active granulomas. Conversely, Harlander et al.¹⁷ reported that no notable difference exists in serum CHIT levels in sarcoidosis patients with or without extrapulmonary involvement.

The serum CHIT levels of 9 newly treated patients at the time of diagnosis were compared with their values at the 6th month of treatment. A significant decrease was detected in the CHIT levels of these patients after 6 months of treatment. This supports the possible use of CHIT as a beneficial biomarker in the evaluation of treatment efficacy. Besides, other studies have demonstrated the reduction in serum CHIT levels after corticosteroid or immunosuppressive therapies in sarcoidosis patients.^{14,22,23} The significantly reduced CHIT levels were also observed in juvenile sarcoidosis patients after oral corticosteroid treatment, compared to their levels before treatment.¹³

The low sensitivity and specificity of ACE limit its use as both a diagnostic and prognostic tool. The serum levels may also increase in granulomatous diseases such as berylliosis and silicosis.^{24,25} In addition, *ACE* gene polymorphism may affect serum ACE values, and the use of genotype-based reference values may improve interpretation.²⁶ The highest serum ACE values were reported in patients with radiological stages 0, 1 and 2 of the disease.¹⁶ Gungor et al.⁵ reported that serum ACE levels did not differ significantly between active and inactive disease, and they also determined the sensitivity and specificity of ACE to be 72% and 60%, respectively. Similar to our study,

which states that no significant difference was found between radiological stage and serum ACE levels, Rust et al.,²⁷ also reported that no relationship was detected between the initial radiological stage and serum ACE levels, as well as the clinical course of the disease. This may be related to the polymorphism in the ACE gene.

The most significant aspect of our study is that to the best of our knowledge, no similar study on sarcoidosis has been published in Türkiye. Another issue is that some studies evaluated serum CHIT only once.¹⁶ In our study, in the newly-treated group, we measured CHIT levels twice.

It would be useful to address some limitations of our study. It was a single-center study, and the number of patient admissions was very low due to the pandemic. This situation could be considered an important reason for the limited number of patients in stages 3 and 4. Furthermore, the short duration of the study limits the sample size. Despite the possible existence of CHIT and ACE variants among our patients, genotyping could not be performed due to inadequate conditions. Serial measurements could not be performed for serum CHIT levels in some groups. The measurement could only be performed once, in patient groups other than the newly-treated group. In addition to these, the small number of patients for whom treatment was started in the sarcoidosis group is also among the limitations of our study.

CONCLUSION

Our study suggests the potentially beneficial use of serum CHIT enzyme levels in the diagnosis of sarcoidosis, as well as in evaluating follow-up and treatment response. Consequently, this enzyme may be considered helpful in differentiating sarcoidosis patients from healthy individuals and in evaluating treatment response. However, its usefulness in predicting disease activity and prognosis may be limited since no significant relation was detected between the radiological stages and serum CHIT levels in our study. Multicenter studies with a larger patient population, serial CHIT measurements, extended follow-up periods, investigations of ACE and CHIT gene polymorphisms, and a more uniform distribution of disease stages will yield more conclusive results.

In conclusion, our study indicates that measuring CHIT enzyme levels may help reduce the necessity for radiological examinations when used in combination with other biomarkers like ACE. This, therefore, reduces the patient's exposure to radiation.

Ethics

Ethics Committee Approval: The study was initiated after approval from the Kocaeli University Medical Faculty Hospital Ethics Committee (project number: GOKAEK-2020/14.06, 2020/243, approval date: 20/08/2020).

Informed Consent: Informed consent was obtained.

Presented in: This study was presented as an oral presentation at the 26th Turkish Thoracic Society Congress in 2023.

Footnotes

Authorship Contributions

Concept: E.Ş., H.B., H.M.K., A.H.I., İ.B., S.A.B., Design: E.Ş., H.B., H.M.K., A.H.I., İ.B., S.A.B., Data Collection or Processing: E.Ş., H.M.K., Analysis or Interpretation: E.Ş., H.B., H.M.K., A.H.I., İ.B., S.A.B., Literature Search: E.Ş., H.B., H.M.K., A.H.I., İ.B., S.A.B., Writing: E.Ş., H.B., H.M.K., A.H.I., İ.B., S.A.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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