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Original Article

Diagnostic Value of Radiographic Characteristics of Mediastinal and Hilar Lymph Nodes in Sarcoidosis

Olcay Ayçiçek[1], Yılmaz Bülbül[1], Funda Öztuna[1], Tevfik Özlu[1], Selçuk Akkaya[2]

[1]Department of Chest Diseases, Karadeniz Tecnichal University, Faculty of Medicine, Trabzon, Turkey
[2]Department of Radiology, Karadeniz Tecnichal University, Faculty of Medicine, Trabzon, Turkey

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Abstract

OBJECTIVE: In this study, it was aimed to investigate the diagnostic value of thorax computed tomography, which is a non-invasive method, in diagnosing sarcoidosis.

MATERIALS AND METHODS: In our Faculty of Medicine, Department of Chest Diseases between January 1, 2013, and July 1, 2019, the data of 816 patients who underwent endobronchial ultrasonography for mediastinal lymph node sampling and other sampling methods, such as mediastinoscopy, thoracotomy, etc., if the histopathological diagnosis could not be reached, were retrospectively screened and 192 patients (sarcoidosis: 62, non-sarcoidosis: 130 patients) who met the inclusion criteria were included in the study. Patients diagnosed with sarcoidosis and patients diagnosed with non-sarcoidosis were compared in terms of thorax computed tomography findings (mediastinal lymph nodes and lung parenchymal involvement).

RESULTS: Right upper paratracheal (72.6 vs. 46.9%, $P = .001$) and paraaortic lymph node involvement (79.0% vs. 60.8%, $P = .01$), hilar symmetry (88.5 vs. 58.3%, $P < .001$), and homogeneity in lymph nodes (80.6% vs. 56.9%, $P = .001$) were found to be significantly higher in the sarcoidosis group. Lymph node sizes were smaller in the sarcoidosis group and the mean density (51.3 Hounsfield unit vs. 44.1 Hounsfield unit, $P = .002$) was significantly higher. In the multivariate logistic regression analysis, the presence of homogeneity in the lymph nodes is 4.3-fold more likely to increase sarcoidosis, the presence of hilar symmetry 9.1-fold, the involvement of the right lower paratracheal lymph node 2.7-fold, the mean lymphadenopathy density >48 Hounsfield unit 4.3-fold, the maximum diameter of lymphadenopathy less than 27.5 mm 4.7-fold.

CONCLUSION: This study revealed that the localization, size, density, and homogeneity of mediastinal lymph nodes will help clinicians to diagnose patients with sarcoidosis without using invasive methods.

KEYWORDS: Sarcoidosis, mediastinal Lymphadenopathy, thorax computed tomography
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INTRODUCTION

Sarcoidosis is a multisystem granulomatous disease of unknown etiology. Lungs are most commonly involved, but any organ can be involved. The basic structure of sarcoidosis is granuloma structures without caseification necrosis.[1] In computed tomography (CT) imaging of the lung, mediastinal, and hilar enlarged lymph nodes, as well as reticulonodular infiltrates, nodules, consolidations, and perihilar conglomerate masses in the parenchyma are among the most common lesions.[2,3] The diagnosis of sarcoidosis is made by excluding other causes in addition to compatible clinical, radiological, and histopathological findings.[4,5] The most common form is stage I sarcoidosis, which is characterized by bilateral hilar lymphadenopathy.[6] Symmetrical hilar lymphadenopathy (LAP) is an important feature that distinguishes sarcoidosis from diseases such as lymphoma, fungal infection, and tuberculosis that can progress with enlargement of mediastinal and hilar lymph nodes.[7,8] Unilateral hilar LAP is seen in only 3-5% of sarcoidosis cases.[9]

Tissue biopsy is required for histopathological demonstration of granulomas without caseification necrosis.[10] However, in stage 1 patients, sarcoidosis can be diagnosed without a tissue diagnosis after other causes are excluded.[11] If other causes cannot be excluded, a biopsy should be performed. Complications such as bleeding and pneumothorax may develop due to invasive procedures such as bronchoscopy used for biopsy.[12,13] In addition, despite biopsy, it may be difficult to distinguish sarcoidosis from other granulomatous diseases.[14] Therefore, it is important to investigate whether patients can be prevented from being exposed to unnecessary invasive procedures. In this study, it was aimed to investigate the diagnostic value of thorax CT image features in the diagnosis of sarcoidosis without pathological sampling.

MATERIALS AND METHODS

The study was conducted in our Faculty of Medicine, Department of Chest Diseases between January 1, 2013, and July 1, 2019, and was carried out by screening retrospectively the patient's data who were performed with endobronchial ultrasonography (EBUS) for mediastinal lymph node sampling and in the case of nondiagnostic results, other diagnostic methods such as mediastinoscopy, thoracotomy, etc. were applied. This study was approved by Ethical committee of Karadeniz

Corresponding author: Olcay Ayçiçek, e-mail: olcayaycicek@yahoo.com

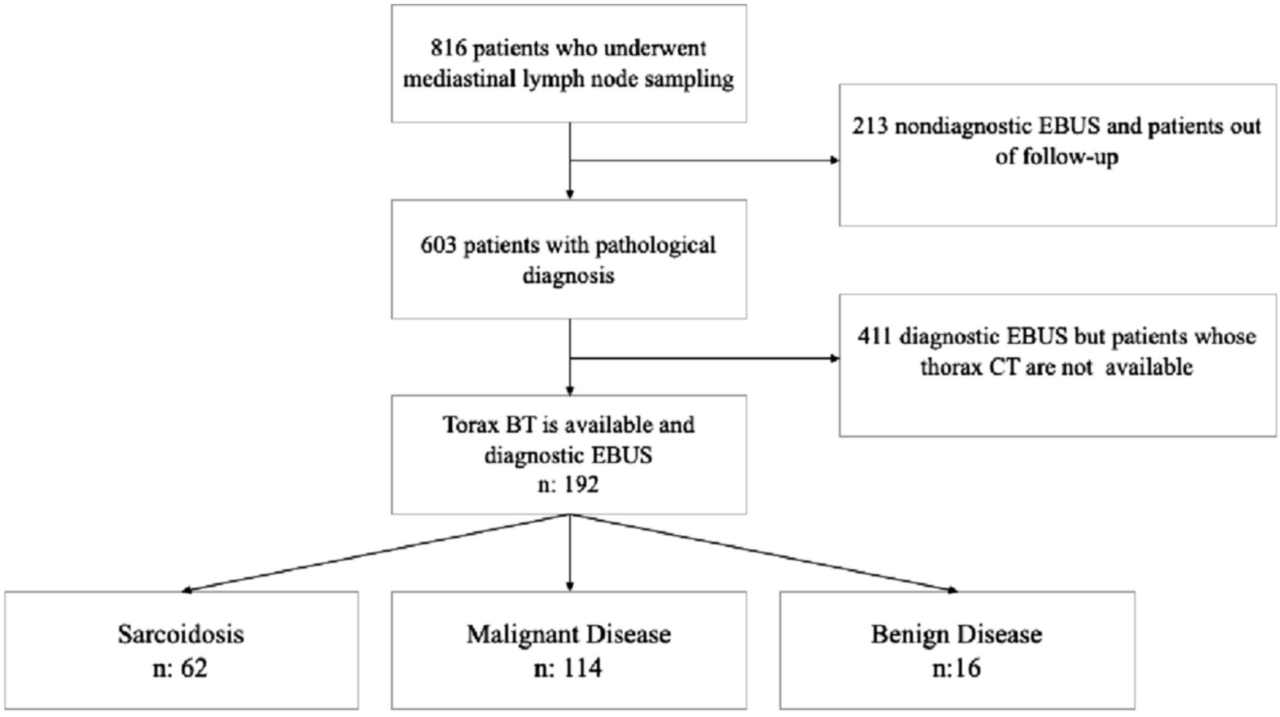

Figure 1. Inclusion and exclusion criteria.

Technical University (decision number: 2018/324, decision date: January 14, 2019). The study was initiated after the approval of the local ethics committee and only patients with a definitive histopathological diagnosis were included. Patients whose thorax CT was not in the archive of our hospital at the first admission were not included in the study (Figure 1).

Endobronchial Ultrasonography

Olympus EVIS EXERA II CV-180 device was used for EBUS imaging and sampling. An average of 2-3 biopsies were performed from each focus. Lymph node localization assessment was performed considering Wang's lymph node map (2R, 2L, 4R, 4L, etc.).

Thorax CT

All patients who were admitted to the study had thorax CT. Thorax CT mediastinal lymph nodes of the patients were evaluated in terms of features such as localization, size, density, homogeneity, necrosis, presence of calcification, and hilar symmetry. Parenchymal lesions were compared in nodules, ground glass, reticular opacity, presence of consolidation, and distribution. Somatom, Siemens, Forchhim, and Germany devices were used for CT imaging of the thorax.

MAIN POINTS

- The presence of bilateral hilar and right paratracheal lymphadenopathy on thorax computed tomography increases the possibility of sarcoidosis.
- Homogeneity of lymph nodes increases the possibility of sarcoidosis.
- The presence of necrosis in lymph nodes excludes the diagnosis of sarcoidosis.
- Lymph node density above 48 Hounsfield unit increases the possibility of sarcoidosis.

Lymphadenopathy density measurements were made by considering the largest lymph node and were made as Hounsfield unit (HU) in the rectangular area determined to touch the LAP border from 4 corners in the tomography section where lymphadenopathy showed the largest area in the axial plane. The maximum, minimum, and average densities measured in the marked region were recorded. Measurements were made by the same person in all patients (Figure 2). The absence of necrosis or calcification in lymph nodes was accepted as a homogeneity criterion.

Statistical Analysis

The Kolmogorov–Smirnov test was used to test for the normal distribution of continuous variables. Data characterized by a normal distribution were expressed as mean ± standard deviation. Student's *t*-tests were used to compare the data which had a normal distribution. The Mann–Whitney *U* test was used to compare non-normally distributed data. Discrete variables were compared by using the chi-square test. Parameters that were potential predictors of sarcoidosis

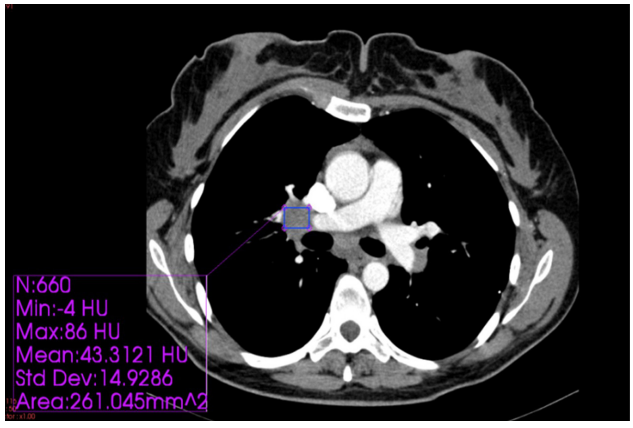

Figure 2. Measurement of lymph node density (right hilum).

were analyzed by logistic regression using. Multivariate logistic regression analysis was used as a stepwise backward LR method from predictive factors with significance ≤0.05 in the univariate analysis. Diagnostic accuracies of parameters for identifying sarcoidosis were assessed by using the area under the receiver operating characteristic (ROC) curve area under the curve (AUC). $P < .05$ was considered to be significant. Data were analyzed using SPSS statistical software (version 13.01, serial number 9069728, SPSS Inc., Chicago, Ill, USA).

RESULTS

Between the specified dates, EBUS was performed on 816 patients to investigate the etiology of mediastinal lymphadenopathy. Two hundred thirteen patients who were diagnosed with EBUS as nondiagnostic and were followed up were excluded from the study. The remaining 192 patients were included in the analysis after excluding patients who did not have a computerized tomography (shot in other hospitals) recorded in the hospital records despite the pathological diagnosis being reached with EBUS or other sampling methods. Subcarinal LN (lymph node) in 128 patients, precarinal LN in 15 patients, right hilar LN in 30 patients, left hilar LN in 21 patients, right lower paratracheal LN in 32 patients, left lower paratracheal LN in 5 patients, and right upper paratracheal LN in 1 patient were sampled with EBUS.

Because of non-diagnostic EBUS, mediastinoscopy was performed in 27 patients, thoracotomy/VATS (video assisted thoracic surgery) in 3 patients, Transthoracic fine needle aspiration biopsy (TFNAB) in 8 patients, and extrathoracic excisional LAP biopsies in 3 patients. Histopathological diagnosis was malignant in 114 patients, sarcoidosis in 62 patients, and benign diseases other than sarcoidosis in 16 patients (4 tuberculosis, 3 anthracosis, 2 hypersensitivity pneumonitis, 2 pneumoconiosis, 1 Brucella, 1 Crohn's disease, 1 Welder's lung, 1 Drug lung, 1 thymoma cases).

Sarcoidosis cases were significantly younger than non-sarcoidosis cases (51.4 ± 14.8 years vs. 63.5 ± 11.7 years) ($P < .001$). One hundred forty (72.9%) of the patients included in the study were male and 52 (27.1%) were female. Sarcoidosis in female (65.5% vs. 35.5%) and non-sarcoidosis diseases in male gender (90.8 vs. 9.2%) were found with a significantly higher rate ($P < .001$).

When the lymphadenopathy localizations were evaluated according to the computerized tomographic appearance, the right upper paratracheal (2R) and paraaortic lymph node involvement were found to be statistically significantly higher in the sarcoidosis group ($P = .001$, $P = .01$, respectively). Necrosis in lymphadenopathies was detected in 29 patients (15.1%) and was significantly higher in the non-sarcoidosis group (20.8% vs. 3.2%, $P = .002$). Hilar symmetry and homogeneity in lymph nodes were found significantly higher in the sarcoidosis group (88.5% vs. 58.3% $P < .001$ and 80.6% vs. 56.9%, $P = .001$, respectively). When evaluated in terms of parenchymal lesions (nodules, consolidation, reticulation, consolidation, and other pathological findings) according to computerized tomographic appearance, ground glass, consolidation, and other parenchymal lesions were found to be significantly higher in the non-sarcoidosis group ($P = .005$, $P = .004$, and $P < .001$, respectively) (Table 1).

The mean long LAP diameter was 27.62 ± 6.85 mm in the sarcoidosis group and 31.93 ± 12.28 mm in the non-sarcoidosis group. The mean of the shortest LAP diameter was 19.62 ± 5.05 mm in the sarcoidosis group and 23.52 ± 9.7 mm in the non-sarcoidosis group. The short and long diameters of lymphadenopathy were significantly lower in sarcoidosis cases ($P = .002$ and $P = .001$, respectively). The minimum lymph node density was 1.80 ± 19.45 HU in the sarcoidosis group, −5.35 ± 22.0 HU in the nonsarcoidosis group, the maximum lymph node density was 102.17 ± 26.61 in the sarcoidosis group, and 99.53 ± 39.32 HU in the nonsarcoidosis group. The mean lymph node density was 51.29 ± 15.05 HU in the sarcoidosis group and 44.14 ± 14.06 HU in the nonsarcoidosis group. The minimum and mean densities of lymphadenopathies were found to be significantly lower in the non-sarcoidosis group ($P = .03$ and $P = .002$, respectively).

The median age (AUC: 0.74, 95% CI: 0.667-0.818, $P < .001$), median LAP density (AUC: 0.66, 95% CI: 0.581-0.742, $P < .001$), short axis of LAP diameter (AUC: 0.61, 95% CI: 0.530-0.688, $P < .015$) and long axis of LAP diameter (AUC: 0.59, 95% CI: 0.510-0.668, $P < .047$) had the highest diagnostic accuracy for identifying sarcoidosis as measured by area under ROC curve analysis. The sensitivity and the specificity of median age for diagnosing sarcoidosis at the optimal cut-off level <61.5 years was 69.4% and 64.6%, the median LAP density at the optimal cut-off level >48 HU was 67.7% and 66.2%, the short axis of LAP diameter at the optimal cut-off level <19.5 cm was 54.8% and 60.8%, and the long axis of LAP diameter at the optimal cut-off level <27.5 cm was 56.5% and 58.5% (Table 2).

When the independent variables that were significant in the univariate regression analysis and likely to predict sarcoidosis were analyzed with the multivariate logistic regression test (backward LR method). It was determined that the presence of homogeneity in the lymph node increased the probability of sarcoidosis 4.3-fold, the presence of hilar symmetry 9.1-fold, the right lower paratracheal lymph node involvement 2.7-fold, the mean lymphadenopathy density >48 HU 4.3-fold, and the maximum diameter of the LAP less than 27.5 mm increased 4.7-fold (Table 3). Conversely, the presence of parenchymal consolidation was found to reduce the likelihood of sarcoidosis 0.3-fold. The sensitivity and specificity values of the specified parameters in diagnosing sarcoidosis are given in Table 4.

The sensitivity of the multivariate regression model in diagnosing sarcoidosis in patients was determined as 63.93% (95% CI: 50.63-75.84), specificity 91.47% (95% CI: 85.25-95.67), positive predictive value 78.00% (95% CI: 66.15-86.55), and negative predictive value was 84.29% (95% CI: 79.27-88.27).

DISCUSSION

In the study, we aimed to determine radiological findings that can distinguish sarcoidosis from other diseases and

Table 1. Demographics of the Study Population and Characteristics of the Mediastinal Lymph Nodes

		Total (n = 192)		Sarcoidosis Group (n = 62)		Non-Sarcoidosis Group (n = 130)		
		N	%	N	%	N	%	*P*
Age (Mean ± SD)		59.67 ± 13.99		51.48 ± 14.89		63.58 ± 11.71		*<.001*
Sex	Female	52	27.1	40	64.5	12	9.2	*<.001*
	Male	140	72.9	22	35.5	118	90.8	
LAP localization	Subcarinal	175	91.1	59	95.2	116	89.2	*.17*
	Hilar	176	91.7	59	95.2	117	90	*.22*
	Paraaortic	128	66.7	49	79	79	60.8	*.01*
	LR PT	158	82.3	52	83.9	106	81.5	*.69*
	LL PT	80	41.7	28	45.2	52	40	*.49*
	UR PT	106	55.2	45	72.6	61	46.9	*.001*
	UL PT	11	5.7	2	3.2	9	6.9	*.30*
LAP characteristics	Necrosis	29	15.1	2	3.2	27	20.8	*.002*
	Homogeneity	124	64.6	50	80.6	74	56.9	*.001*
	Calcification	29	15.1	7	11.3	22	16.9	*.30*
	Hilar symmetry	128	68.1	54	88.5	74	58.3	*<.001*
Parenchymal lesions	Nodule	118	61.5	43	69.4	75	57.7	*.12*
	Reticulation	30	15.6	6	9.7	24	18.5	*.175*
	Ground-glass	84	43.8	18	29	66	50.8	*.005*
	Consolidation	50	26	8	12.9	42	32.3	*.004*
	Other	145	75.5	30	48.4	115	88.5	*<.001*
Zonal Dominance	Upper lobe	38	20.5	14	25.5	24	18.5	*.28*
	Middle lobe	3	1.6	1	1.8	2	1.5	*.89*
	Lower lobe	20	10.8	8	14.5	12	9.2	*.28*
	Diffuse	38	20.4	15	26.8	23	17.7	*.15*

LAP, lymphadenopathy; PT, paratracheal.

Table 2. Comparison of Sarcoidosis and Non-sarcoidosis Patients Based on Determined Cutoff Values

	Total (n = 192)		Sarcoidosis Group (n = 62)		Non-Sarcoidosis Group (n = 130)		
	N	%	N	%	N	%	*P*
Age <61.5	82	42.7	38	61.2	44	33.8	*.001*
Density >48 HU	86	44.8	42	67.7	44	33.8	*<.001*
LAP maximum diameter <27.5 mm	99	51.6	40	64.5	59	45.4	*.014*
LAP minimum diameter <19.5 mm	85	44.2	34	54.8	51	39.2	*.015*

HU, Hounsfield unit; LAP, lymphadenopathy.

Table 3. Multivariate Logistic Regression Analysis of Parameters Likely to Predict Sarcoidosis

Variables	OR	95% CI		*P*
Lymph node homogeneity	4.333	1.741	10.785	*.002*
Hilar symmetry (bilateral hilar involvement)	9.173	3.428	24.547	*.000*
Upper right paratracheal LAP	2.769	1.133	6.771	*.026*
Parenchymal consolidation	0.373	.134	1.040	*.059*
LAP mean density >48 HU	4.302	1.935	9.568	*.000*
LAP Maximum Diameter <27.5 mm	4.770	1.969	11.554	*.001*

HU, Hounsfield unit; OR, odds ratio; LAP, lymphadenopathy.

Table 4. Univariate Sensitivity and Specificity Values of Variables in Diagnosing Sarcoidosis

	Sensitivity		Specificity		
Variables	**%**	**95% CI**	**%**	**95% CI**	***P***
Lymph node homogeneity	80.6	68.6-89.6	43.1	34.4-52.1	*.001*
Hilar symmetry (bilateral hilar involvement)	88.5	77.8-95.3	53.8	44.9-62.6	*<.001*
Upper right paratracheal LAP	72.6	59.8-83.1	52.7	43.7-61.6	*.001*
Parenchymal consolidation	12.9	5.7-23.8	67.7	58.9-75.6	*.004*
LAP mean density >48 HU	67.7	54.7-79.1	66.1	57.4-77.2	*<.001*
LAP maximum diameter <27.5 mm	56.4	43.3-69.0	58.5	49.5-67.0	*.014*

HU, Hounsfield unit; LAP, lymphadenopathy.

eliminate the need for biopsy. For this purpose, we compared thorax tomography images in patients with a pathologically definite diagnosis of sarcoidosis and diseases other than sarcoidosis.

As it is known, sarcoidosis mostly involves the hilar lymph nodes bilaterally and the accompanying right paratracheal lymphadenopathy is called lambda sign.[15,16] Our study also determined that the involvement of these foci increases the possibility of sarcoidosis. Mehrian et al[17] similar to our findings, the rate of bilateral lymph node involvement in sarcoidosis was found to be statistically significantly higher.

Lymph node sizes in sarcoidosis cases were found to be significantly lower than in non-sarcoidosis cases. Especially if the lymph node diameter was less than 27.5 mm, the probability of sarcoidosis increased 4.7-fold. When the long lymph node diameter was taken as 27.5 mm, the sensitivity and specificity of smaller lymph nodes in the diagnosis of sarcoidosis were found to be 56.45% and 58.46%, respectively. In a study conducted by Trisoloni et al[18] in which CT pattern was examined in patients with suspected sarcoidosis, the mean lymph node size was found to be 14.39 mm. In a study conducted by Lee et al.[19] in sarcoidosis and tuberculosis cases lymph nodes were compared, but contrary to our findings, lymph node diameters were found to be larger in sarcoidosis cases. Also, in the study by Jung Koo et al.[20] comparing sarcoid reaction and lymphoma, lymph node sizes were found to be higher in sarcoid-like reaction.

In our study, lymph nodes were found to be significantly more homogeneous in sarcoidosis cases. If the lymph nodes were homogeneous, the probability of sarcoidosis increased 4-fold. Similarly, if the lymph node density was above 48 HU, the probability of sarcoidosis increased 4-fold. In the diagnosis of sarcoidosis, the sensitivity and specificity of the presence of homogeneous lymph nodes and the density above 48 HU were found to be 67.74% and 66.15%, respectively. Also, in a study conducted by Jung Koo et al.[20] comparing sarcoidosis, sarcoid reaction, and malignant mediastinal lymph nodes using CT and positron emission tomography/CT; it has been reported that lymph nodes due to sarcoid reaction have significantly higher attenuation values and higher homogeneity compared to malignant lymph nodes. This finding supports our findings. In the same study, no significant difference was found between the lymph nodes due to sarcoidosis and sarcoid reaction in terms of radiological features. The high rate of necrosis in malignant lymph nodes may be a factor causing this attenuation difference. Similarly, in our study, the presence of necrosis in the lymph nodes was significantly higher in the non-sarcoidosis group, where the majority of the cases were malignant patients.

The presence of necrosis in the lymph nodes or consolidation in the lung parenchyma in sarcoidosis cases largely excluded the diagnosis of sarcoidosis. Especially if there was consolidation in the parenchyma, the probability of sarcoidosis was reduced by 0.3-fold. The sensitivity and specificity of homogeneity of lymph nodes or parenchymal consolidation in diagnosing sarcoidosis were 80.65-43.08%, 12.90-67.69%, respectively.

The presence of ground glass in the parenchyma was significantly higher in the non-sarcoidosis group. When the literature is reviewed, ground glass opacities are considered among the atypical findings for sarcoidosis.[21]

The relatively low number of sarcoidosis cases and the limited number of non-tumor cases in our study can be considered as limitations of the study. Due to the low distribution of cases according to the sarcoidosis stages, a comparison between the stages could not be made. Likewise, due to the low number of non-tumor cases, comparisons mostly consisted of comparing sarcoidosis and tumor cases. However, due to the limited number of studies on this subject, we believe that our findings are significant.

Consequently, our study revealed that on CT, the presence of symmetric bilateral hilar lymphadenopathy and right paratracheal lymphadenopathy, a lymph node size less than 27.5 mm and a homogeneity lymph node, and also a lymph node density over 48 HU, are associated with sarcoidosis. Conversely, the presence of necrosis in the lymph nodes and low lymph node density, and also the presence of ground glass and consolidation in the parenchyma were found to be associated with diseases other than sarcoidosis.

Ethics Committee Approval: This study was approved by Ethics committee of Karadeniz Tecnical University (Approval No: 2018/324).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – O.A., Y.B.; Design – O.A., Y.B.; Supervision – Y.B., T.Ö.; Funding – O.A., S.A.; Materials – O.A., Y.B.; Data Collection and/or Processing – O.A., S.A.; Analysis and/or Interpretion – O.A., S.A.; Literature Review – O.A., F.Ö; Writing – O.A., F.Ö; Critical Review – O.A.,T.Ö.

Declaration of Interests: The authors have no conflict of interest to declare.

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