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ORIGINAL ARTICLE

AGE-RELATED THORACIC LYMPHADENOPATHIES AND DISEASE PROGRESSION IN PATIENTS WITH MODERATE-TO-SEVERE ASTHMA: AN EVALUATION OF CLINICAL AND IMAGING FINDINGS

Abstract

Introduction: Asthma is a prevalent chronic respiratory disease affecting individuals of all ages. Thoracic lymphadenopathies, commonly observed in computed tomography scans of elderly patients, may reflect lymphatic and immune changes. However, their relationship with asthma is not well understood. This study aims to explore the impact of age on thoracic lymphadenopathies' characteristics in patients with moderate-to-severe asthma and their associations with clinical and imaging findings.

Materials and Method: In this retrospective study, 114 adult patients with moderate-to-severe asthma underwent multi-slice computed tomography. Lymph node size and number were analyzed alongside demographic data, pulmonary function test results, asthma control test scores, and clinical parameters. Statistical analyses assessed correlations between thoracic lymphadenopathies, and these factors.

Results: Enlarged lymph nodes were identified in 19.2% of patients, predominantly in stations 4R, 7, and 5. Lymph node size and number positively correlated with age, smoking, prolonged asthma duration, frequent attacks, female gender, and elevated CRP levels, while negatively correlating with forced expiratory volume in 1 second and forced vital capacity ($p < 0.05$).

Conclusions: Thoracic lymphadenopathies in asthma patients are closely associated with age, inflammation, and disease progression. In elderly patients, increased number of thoracic lymphadenopathies may result from immunosenescence and chronic inflammation. These findings emphasize the need to evaluate lymphatic changes in asthma, particularly in older adults, to improve clinical management and therapeutics.

Keywords: Asthma; Aging; Lymph Nodes.

INTRODUCTION

Asthma is a chronic, heterogeneous inflammatory disease affecting over 300 million people worldwide, with significant clinical and pathological variations observed in older populations due to age-related physiological changes (1). Aging alters immune and inflammatory responses, potentially modifying the severity, progression, and structural manifestations of asthma (2). These changes, driven by chronic inflammation, include airway remodeling, subepithelial fibrosis, airway narrowing, and stiffening, all of which exacerbate asthma symptoms and increase the disease burden (3).

To date, few studies have explored the relationship between the lungs and the lymphatic system. Over the past decade, however, research on this topic has gained momentum, revealing close associations between pulmonary diseases and the lymphatic system. The lymphatic system plays a crucial role in modulating lung inflammation and immune responses (4).

Li et al. were the first to investigate the relationship between asthma and the lymphatic system. They demonstrated increased lymphangiogenesis and vascularization in the bronchial mucosa of asthmatic animal models, suggesting potential lymphatic involvement in asthma pathophysiology (5). Subsequent studies have revealed a more complex picture. While allergic sensitization in asthma is associated with increased lymphangiogenesis, severe or fatal cases are often characterized by impaired lymphatic circulation, indicating a multifaceted relationship between the lymphatic system and asthma (6). Animal models further demonstrated that inflammation-related lymphangiogenesis in the lungs may persist even when steroid treatment is delayed, although newly initiated lymphangiogenesis is inhibited by such treatment. Studies have also suggested that asthma may be linked to decreased lymphangiogenesis (7).

Molecular studies and preclinical research have undoubtedly shed light on the impact of the lymphatic system in asthma, reducing the uncertainties surrounding this relationship. However, for clinicians, the management of asthma becomes increasingly challenging as patients grow older, especially with the rising prevalence of comorbidities. The need to better understand chronic inflammation and its manifestations is paramount. Thoracic lymphadenopathies may serve as a valuable indicator of chronic inflammation when evaluating asthma patients, especially in diagnostic imaging.

Chronic inflammation has been linked to increased lymphangiogenesis, which can contribute to thoracic lymph node enlargement. Multi-slice computed tomography (MSCT) is widely used to assess structural airway changes and differentiate benign from malignant causes of lymph node enlargement, particularly in the hilar and mediastinal regions (8). Although prior research has correlated airway and parenchymal changes with asthma severity (9), the relationship between thoracic lymph node size and asthma remains unexplored.

Thoracic lymphadenopathies are frequently observed in individuals of advanced age, often reflecting systemic immune dysregulation and chronic inflammation (10). In asthma, chronic airway inflammation and immune activation may synergize with immunosenescence to exacerbate lymphatic remodeling and lymph node hypertrophy. However, the precise role of these changes in thoracic lymphadenopathy in asthma remains poorly understood.

This study aims to evaluate the size and diameter of thoracic lymph nodes in asthmatic patients and to investigate their relationship with aging and the lymphatic system. By focusing on the interplay between asthma, age, and lymphatic adaptations, this research seeks to provide new

insights into the role of lymphatic changes in the pathophysiology of asthma and its implications for clinical management.

MATERIALS AND METHODS

Study Population

This retrospective study included 114 adult patients with moderate-to-severe asthma who were followed up in our outpatient clinic for 2 years. All participants had undergone MSCT imaging of the lungs for reasons such as uncontrolled asthma or suspicion of potential comorbidities (e.g., hemoptysis, emphysema, or bronchiectasis). Patients referred to our clinic from other institutions were also included if their up-to-date MSCT records were available and if they met the inclusion criteria.

The study resumed with renewed focus, emphasizing the effects of aging on thoracic lymph node changes in asthma patients. Written informed consent for the utilization of clinical data was obtained from all participants at the time of their initial evaluation.

Inclusion and Exclusion Criteria

The patients included in this study were adults diagnosed with moderate-to-severe asthma, as defined by the Global Initiative for Asthma (GINA) guidelines (1), with no evidence of alternative lung diseases. Individuals were excluded if they had a history of malignancy or recent thoracic lymphadenopathy (within the last three months) due to conditions such as pneumonia or other diseases that could potentially cause thoracic lymphadenopathy, including interstitial lung diseases, pneumoconiosis, chronic obstructive pulmonary disease (COPD), heart failure, or sarcoidosis. Patients with acute lower respiratory tract infections or insufficient data in their medical records were also excluded.

To ensure that the study focused on the association between aging and thoracic lymph node characteristics, patients with confounding factors, such as fatal asthma requiring oral corticosteroids during severe exacerbations, were excluded. The final analysis concentrated on the size, diameter, and characteristics of thoracic lymph nodes, with particular attention given to their relationship with age.

Data Collection and Imaging Analysis

Demographic and clinical data, including age, sex, asthma severity, and comorbidities, were collected from the medical records. The MSCT scans were evaluated by two radiologists blinded to the patient's clinical data. Thoracic lymph nodes were assessed for size, diameter, and distribution with measurements obtained from mediastinal and hilar stations. Additional lung parenchymal changes and airway abnormalities were recorded but were not the primary focus of this study.

Clinical and Functional Analyses

Asthma was diagnosed by a pulmonologist based on the most recent version of the GINA guidelines at the time of diagnosis (1). Patients were categorized as having moderate or severe asthma. All patients were treated with inhaled corticosteroids, long-acting or short-acting beta-agonists, or leukotriene receptor antagonists according to their asthma severity.

Demographic and clinical data were retrospectively collected from the patients' files. These data included age, sex, smoking status (pack-years), duration of asthma, frequency of asthma exacerbations, serum C-reactive protein (mg/L), and total serum IgE (kU/L) levels. Body mass index (BMI) was calculated as weight (kg)/height squared (m^2) and recorded. The presence or absence of obstructive sleep apnea syndrome (OSAS) was also documented. Patients with mild OSAS symptoms

(e.g., snoring only) were classified as OSAS1, while those with both snoring and apnea were classified as OSAS2.

Pulmonary function tests (PFTs) were performed using a ZAN 100 spirometry device (ZAN 100, Messgeraete Gmbh, Munich, Germany) in a sitting position. Forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, and peak expiratory flow (PEF) values were calculated. Symptom control was evaluated using the Asthma Control Test (ACT), which assesses the patient's clinical condition during the preceding 4 weeks (3).

Computed Tomography Imaging and Lymph Node Assessment

All patients underwent computed tomography (CT) scans using the PHILIPS MX 16-Slice CT scanner. Glazer et al. described 10 mm as the upper reference limit for the short axis of mediastinal lymph nodes depending on the regional nodal station (11). In this study, lymph node analyses were performed from at least two reconstruction planes (typically axial and coronal). The lymph node map published by the American Thoracic Society (ATS) was used as a reference for nodal classification (11).

The features of mediastinal and hilar enlarged lymph nodes (ELNs) were characterized on MSCT by two radiology specialists. Correlations between the number, diameter, and location of ELNs and asthma-related factors were analyzed. Based on these findings, patients were divided into two groups according to a threshold diameter: the "control lymph nodes" group (short axis < 10 mm in the mediastinum; 92 patients) and the "ELN" group (short axis > 10 mm in the mediastinum; 22 patients). Since the largest lymph node in this study was in station 7, the upper limit threshold for the short axis was set at 15 mm for station 7 and 10 mm for all other locations.

Statistical Evaluation

Statistical analyses were performed using SPSS version 17.0 (IBM, Armonk, NY, USA). Nominal and ordinal parameters were described with frequency analyses, while quantitative parameters were summarized using means and standard deviations. The Kolmogorov-Smirnov test was used to evaluate the normality of the scale parameter distributions. The independent samples *t*-test was used for normally distributed scale parameters, while the Mann-Whitney U test was applied for non-normally distributed parameters. Chi-squared tests were employed to analyze the differences in nominal and ordinal parameters between the groups. Spearman's rho correlation coefficients were calculated to evaluate directional relationships between scale parameters (Tables 1 and 3). All analyses were conducted at a 95% confidence level, with *p*-values below 0.05 considered statistically significant.

One of the closest studies to the current research, conducted by Taile et al. (2016), reported an effect size of 0.6430260 (12). Using this effect size, a power analysis was conducted using the GPower 3.1.9.2 program. With a 95% confidence interval and a 0.05 margin of error, the minimum sample size required was 28 patients.

RESULTS

ELNs were detected in 22 of 114 patients. The majority of the patients were female (83.7% in the control group and 86.4% in the ELN group). The mean age was 47.41 ± 10.95 years in the control group and 53.77 ± 7.84 years in the ELN group. A total of 154 lymph nodes were classified as ELNs across 114 CT scans. Eight patients (7%) had no detectable lymph nodes (7 females, 1 male). Lymph node diameters were less than 7 mm in 11 patients, and completely calcified lymph nodes were identified in 3 patients. Six patients had ELNs only in the 2R region, with no ELNs detected in the other regions.

Table 1. Baseline characteristics, FEV1, FVC, PEF, OSAS, and biomass differences between patient groups

	Control (n=92)	ELN* (n=22)	P
Gender, n (%)			
Male	15 (16.3)	3 (13.6)	0.754a
Female	77 (83.7)	19 (86.4)	
Age(years), mean ± SD	**47.41±10.95**	**53.77±7.84**	**0.012b**
Asthma Control Test Score, mean ± SD	15.99±5.09	15.23±4.58	0.577b
Disease duration(years), mean ± SD	8.23±9.69	10.76±9.20	0.061c
Number of attacks(per year), mean ± SD	4.21±6.48	5.45±5.47	0.120c
Number of cigarette(pack/year), mean ± SD	3.09±6.72	3.95±7.99	0.710c
IgE(kU/l), mean ± SD	98.31±229.58	73.14±100.63	0.975c
CRP(mg/L), mean ± SD	**6.47±7.23**	**12.99±25.30**	**0.043c**
BMI(kg/m2), mean ± SD	31.39±5.66	33.84±4.89	0.070b
FEV1, mean ± SD	**2.05±0.45**	**1.32±0.58**	**<0.001b**
FEV1 percent, mean ± SD	78.89±16.45	66.00±25.32	0.053b
FVC, mean ± SD	**3.09±4.78**	**1.63±0.60**	**0.000c**
FVC percent, mean ± SD	**80.64±15.51**	**69.17±19.08**	**0.009b**
FEV1/FVC, mean ± SD	79.62±4.33	76.20±4.44	0.176b
FEV1/FVC percent. , mean ± SD	84.54±10.76	86.50±15.34	0.885c
PEF, mean ± SD	**4.40±1.16**	**2.88±1.00**	**<0.001b**
PEF percent, mean ± SD	**71.68±20.47**	**58.41±22.90**	**0.021b**
OSAS1, mean ± SD	200.96±0.28	200.94±0.24	0.842c
OSAS2, mean ± SD	202.42±1.00	202.67±1.21	0.479c
Biomass, mean ± SD	18.90±9.94	22.86±14.39	0.393b

a. Chi-Square Test, b. Independent Samples T-Test, c. Mann Whitney-U Test, SD: Standard Deviation.
*ELN: Patients with enlarged lymph nodes
FEV: Forced expiratory volume, FVC: Forced vital capacity, PEF: Peak expiratory flow,
OSAS: obstructive sleep apnea syndrome, Ig:Immunoglobulin, CRP: C-reactive protein, BMI: Body mass index

The average number and diameter of lymph nodes were higher in females than in males; however, this difference was not statistically significant. The mean age and CRP levels were significantly higher in the ELN group compared to the control group ($p < 0.05$). No statistically significant differences were observed between the control and ELN groups in terms of gender, ACT score, disease duration, number of attacks, smoking (pack-years), IgE levels, or BMI (Table 1).

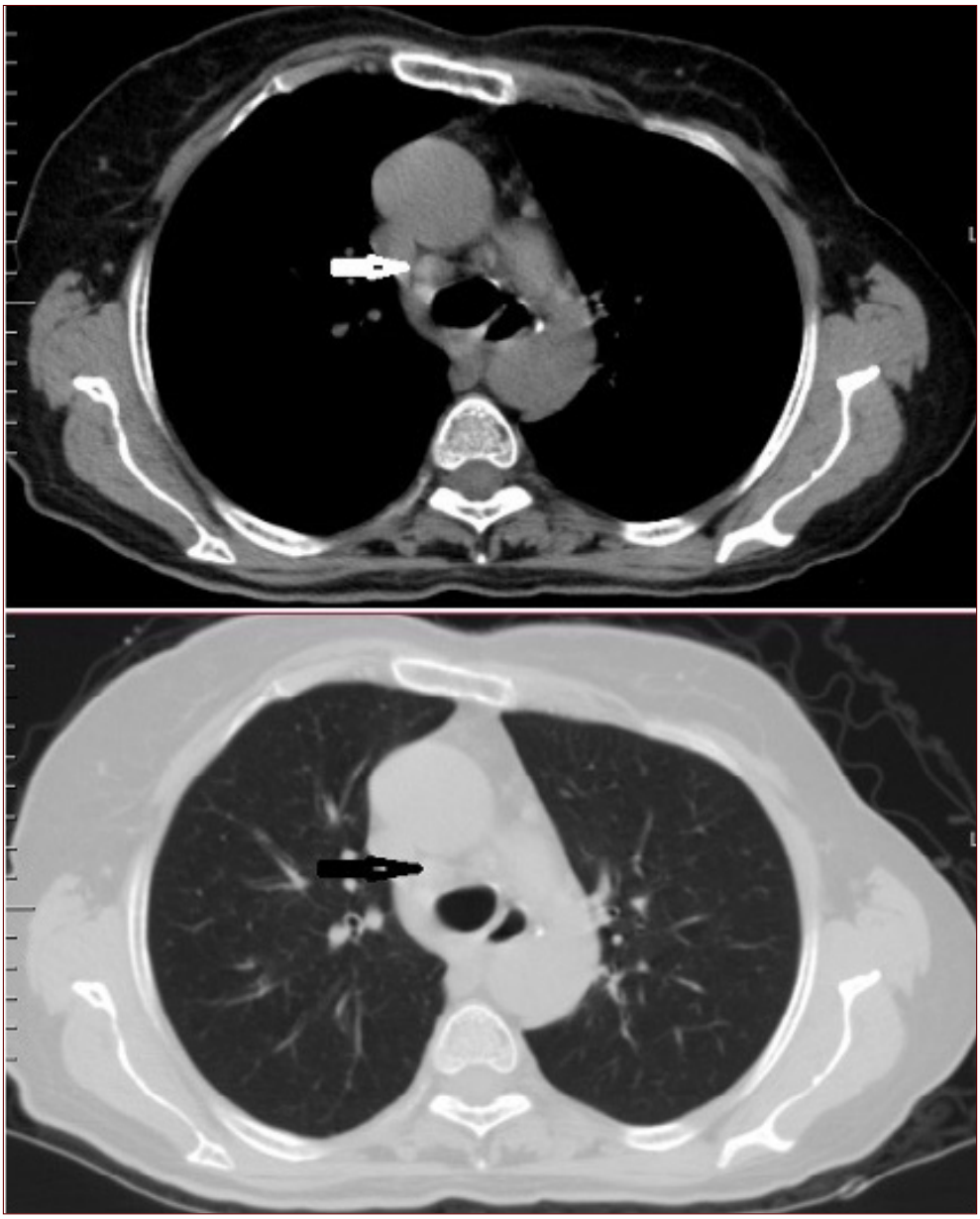

Figure 1. Multislice helical chest CT scan of a 49-years old woman with asthma. In the mediastinal and lung windows of CT scan, black and white arrows are showing the enlarged lymph node in the station 4R.

A positive correlation was found between the number and diameter of lymph nodes in asthmatic patients. Enlarged lymph nodes were most prominent in stations 4R, 7, and 5 (Figure 1). An increased number of lymph nodes was also primarily detected in these regions. The increase in ELN number and diameter was significantly associated with PFT findings, ACT scores, smoking, disease duration, number of attacks, and CRP levels ($p < 0.05$).

Table 2. Lymph node properties and difference analysis results based on lymph node regions

	Control (n=92) Mean	S.D	ELN* (n=22) Mean	S.D.	p
Short2R	-	-	10.00	4.55	p<0.05
Short4R	6.06	1.79	9.39	2.68	<0.001a
Short4L	6.22	1.39	8.25	2.55	0.056a
Short5	4.75	1.86	6.82	2.60	0.016a
Short7	5.79	1.27	9.83	2.73	<0.001b
Short10R	6.50	1.00	9.00	3.00	0.158a
Short11L	6.00	0.01	9.00	1.41	0.333a
Long2R	-	-	13.75	2.87	p<0.05
Long4R	10.13	2.50	13.06	3.49	0.000a
Long4L	10.78	2.95	12.13	3.00	0.366a
Long5	10.95	3.58	13.27	4.31	0.119a
Long7	11.58	2.50	16.11	5.16	0.002a
Long10R	12.00	2.58	12.20	2.59	0.911a
Long11L	9.00	0.01	11.50	3.54	0.667a
C2R	-		11.88	3.50	p<0.05
C4R	8.10	1.93	11.22	2.93	0.000a
C4L	8.50	1.77	10.19	2.53	0.129a
C5	7.85	2.46	10.05	3.27	0.043a
C7	8.68	1.66	12.97	3.57	<0.001a
C10R	9.25	1.71	10.60	2.63	0.407a
C11L	7.50	0.01	10.25	2.47	0.531a

a. Independent Samples T-Test, b. Mann Whitney-U Test, SD: Standard Deviation.

*ELN: Patients with enlarged lymph nodes

The mean FEV1, FVC, FVC%, PEF, and PEF% values were significantly higher in the control group compared to the ELN group ($p < 0.05$). In contrast, no significant differences were observed between the groups in terms of FEV%, FEV1/FVC, FEV1/FVC%, OSAS1, OSAS2, and biomass parameters (Table 1). In the ELN group, the short-axis diameters of stations 4R, 5, and 7; the long-axis diameters of stations 4R and 7; and the coronal axis diameters of stations 4R, 5, and 7 were significantly larger compared to the control group ($p < 0.05$) (Table 2).

The effects of aging and its relationship with lymph node characteristics were analyzed in detail. In the control group, the diameter of station C4R was negatively correlated with FEV1 ($r = −0.331$, $p < 0.05$) and FVC% ($r = −0.350$, $p < 0.05$). The diameter of station C7 was positively correlated with BMI ($r = 0.373$, $p < 0.05$) (Table 3). In the ELN group, the number of asthma attacks was positively correlated with the diameter of station C7 ($r = 0.620$, $p < 0.01$) (Table 3) In the control group, FVC was positively correlated with the number of lymph nodes ($r = 0.301$, $p < 0.05$) (Table 4).

Table 3. The relationship between clinical and laboratory parameters and the size of lymph nodes

Parameters	Control (n=92)				ELN* (n=22)			
	C4R	C4L	C5	C7	C4R	C4L	C5	C7
Asthma Control Test	-0.256	-0.075	0.047	-0.238	-0.267	-0.610	0.437	0.339
Disease duration	-0.115	-0.189	0.290	-0.108	-0.462	-0.258	-0.559	-0.169
Number of attacks	0.223	0.367	-0.091	0.028	0.230	0.194	0.082	**0.620****
Smoking	0.179	0.003	0.001	-0.070	-0.375	0.380	-0.049	0.094
FEV	-0.200	0.045	-0.064	-0.227	-0.108	-0.618	0.135	0.333
FEV percent	**-0.331***	-0.642	-0.057	0.013	-0.175	-0.271	0.163	0.337
FVC	-0.310	0.608	-0.029	-0.187	-0.203	-0.708	0.108	0.167
FVC percent	**-0.350***	-0.566	0.098	0.019	-0.246	-0.338	0.192	0.276
FEV/FVC	-0.600				0.500		-0.916	0.826
FEV/FVC percent	-0.090	0.013	0.287	0.354	0.286	0.015	0.250	0.330
PEF	0.165	0.621	-0.559	0.048	-0.069	-0.502	0.218	0.523
PEF percent	-0.197	-0.340	-0.511	0.023	-0.041	0.002	0.090	0.367
IgE	-0.026	0.133	-0.174	0.116	0.362	0.261	-0.072	-0.230
CRP	0.120	-0.248	0.065	-0.054	0.388	-0.102	0.112	0.440
BMI	0.278	-0.035	0.187	0.373*	-0.201	-0.067	-0.450	0.001

p<0.05 **p<0.01

FEV: Forced expiratory volume, FVC: Forced vital capacity, PEF: Peak expiratory flow, Ig: Immunoglobulin, CRP: C-reactive protein, BMI: Body mass index

*ELN: Patients with enlarged lymph nodes

Table 4. The association between clinical and laboratory parameters and the number of lymph nodes

Parameters	Control (n=92)	ELN* (n=22)
Asthma Control Test	-0.080	0.100
Duration	0.029	0.243
Number of attacks	-0.001	-0.130
Smoking	-0.016	-0.251
FEV	0.107	0.052
FEV percent	0.109	0.167
FVC	0.301*	0.067
FVC percent	0.087	0.088
FEV/FVC	0.091	-0.856
FEV/FVC percent	-0.184	0.061
PEF	0.070	-0.032
PEF percent	0.190	0.081
IgE	0.126	-0.346
CRP	0.114	-0.008
BMI	-0.164	0.021

*p<0.05

FEV: Forced expiratory volume, FVC: Forced vital capacity, PEF: Peak expiratory flow, Ig:Immunoglobulin, CRP: C-reactive protein, BMI: Body mass index

*ELN: Patients with enlarged lymph nodes

DISCUSSION

Aging is collectively associated with various changes in lung physiology and immune function. Termed immunosenescence can influence the clinical presentation and progression of asthma. Older adults often experience a decline in lung elastic recoil, increased chest wall rigidity, and reduced respiratory muscle strength, all of which can exacerbate asthma symptoms and complicate disease management (13). Additionally, immunosenescence may promote chronic low-grade inflammation, known as inflammaging, further contributing to respiratory conditions such as asthma in the elderly (14).

A key finding of this study is the marked enlargement and increased number of TLNs in patients with moderate-to-severe asthma over time, with these changes showing a strong correlation with disease severity. The size and count of TLNs were significantly correlated with CRP levels, frequent asthma exacerbations, reduced PFT values, and prolonged disease duration, highlighting their potential role as markers of disease progression. A particularly noteworthy finding was the significant correlation between age and the presence of ELNs in asthma patients. ELNs were detected in 19.2% of the patients, with a higher prevalence among older individuals. The number and size of these lymph nodes increased with age, suggesting that advancing age may contribute to lymph node enlargement in asthma patients.

The presence of ELNs in older asthma patients may reflect an amplified inflammatory response due to age-related immune changes. Chronic inflammation in asthma leads to airway remodeling and lymphangiogenesis, processes that may be more pronounced in the elderly due to the cumulative effects of aging and prolonged disease duration. This is supported by studies indicating that, even after the resolution of inflammation, lymphangiogenesis can persist, potentially contributing to sustained lymph node enlargement (15,16,17).

Incidental mediastinal ELNs are observed in 1% of the general population and are associated with various clinical conditions. These lymph nodes are frequently linked to benign or, more commonly, malignant diseases (18). For instance, lymphoma is the most common cause of mediastinal ELNs, while benign disease causes include granulomatous diseases, tuberculosis, silicosis, and heart failure. Evison et al. (2014) reported that the size of hilar or mediastinal lymph nodes is a strong predictor of etiology, with sizes of 15 mm or less suggesting reactive nodes, and sizes larger than 25 mm associated with pathological etiologies (19). In our study, the largest lymph node in asthma patients was detected at station 7. Therefore, the upper limit threshold for the short axis of the lymph nodes was set at 15 mm for station 7 and 10 mm for all other locations. Station 7 was identified as the most common site for lymph node enlargement. Following station 7, the greatest increase in lymph node number and size was observed at stations 4R and 5, which were found to be associated with asthma-related factors. Our study revealed that the degree, number, and localization of ELNs in asthma patients are significantly associated with worse pulmonary function, a more severe disease course, and increased inflammatory markers. Therefore, ELNs can be utilized as prognostic factors in patients with asthma. In moderate and severe asthma patients who do not respond adequately to treatment and do not exhibit the expected improvement in pulmonary function tests, increased systemic inflammation, as indicated by elevated inflammatory markers and ELNs, may be the primary reason for worsening pulmonary function.

Kirchner et al. conducted a similar study in patients with COPD, comparing the size, diameter, and localization of mediastinal and hilar ELNs according to COPD stages, and demonstrated a relationship between the clinical severity of the patients and ELN characteristics (20). Another study mentioned COPD as a benign disease leading

to ELNs. Recently, Grecuccio et al. reported the prognostic value of mediastinal lymph node enlargement in chronic interstitial lung disease (21). They found that enlarged mediastinal lymph nodes predict survival in patients with idiopathic pulmonary fibrosis (IPF) and nonspecific interstitial pneumonia, and that ELNs were associated with greater frequency of hospitalization, poor lung function, and more severe fibrosis. They also reported that the presence of ELNs could be related to a hyperplastic reaction in response to chronic inflammation in IPF. Chronic inflammation, as the cause of ELNs and a worsening clinical course, has recently been recognized as a major entity in many diseases, including COPD and asthma (22).

One of the most significant findings of this study was the relationship between pulmonary function tests and the number and size of lymph nodes. Among asthma-related factors, the strongest association with lymph node enlargement was observed with FVC, followed by FEV1. Chronic inflammation in asthmatic patients leads to airway remodeling, resulting in reduced FVC and FEV1 values (1). Notably, this study highlights the association between pulmonary function test parameters and the number of ELNs. Persistent inflammation and the increased lymphatic network surrounding the small airways in asthma patients cause pressure on the airways, leading to edema, increased airway resistance, and reduced airflow. This, in turn, explains the observed decline in FVC and FEV1 levels (3).

Animal studies on asthma models have shown that lymphangiogenesis can continue for up to a year, even after inflammation subsides (23). This could explain why some patients with asthma-triggering infections experience persistent symptoms even after the infection has been treated. In older asthma patients, the enlargement of lymph nodes may contribute to worsening lung function by exerting pressure on the airways, increasing resistance, and reducing airflow, thereby exacerbating respiratory symptoms. Furthermore, the decline in pulmonary function, as evidenced by the reduced FEV1 and FVC values, was more pronounced in the older patients with ELNs in this study.

It is also important to note that older adults with asthma often have comorbidities, such as chronic obstructive pulmonary disease (COPD), which can further complicate their condition. The overlap between asthma and COPD, known as asthma-COPD overlap syndrome (ACOS), presents unique diagnostic and therapeutic challenges (24). The presence of ELNs in this population may reflect the combined inflammatory processes of both conditions, further contributing to airway obstruction and decreased pulmonary function.

The ACT is an easy and practical test that is widely applied in clinical practice. It has good clinical accuracy in identifying patients with poor asthma control and in detecting clinically meaningful changes in asthma control over time (1). Here, the increased number and diameter of ELNs were significantly associated with ACT scores, disease duration, and the number of attacks.

Studies have shown that mediastinal lymph nodes may grow in the presence of chronic bronchitis due to smoking (25). Kirchner et al. also reported ELNs in COPD patients, particularly in those with chronic bronchitis. In our study, there was a positive association between smoking and lymph node size; however, no such correlation was observed between smoking and the number of ELNs. No study has yet explored these relationships in patients with asthma. Since smoking has a pro-inflammatory effect and smokers have increased levels of angiogenic factors, such as vascular endothelial factor (VEGF) and angiotensin-2, it may not be possible to determine whether the lymphangiogenic effect is due to smoking alone or to asthma, or both (26). The fact that smoking is commonly observed in the patients examined in this study may also suggest that patients may have concurrent COPD development. To explain the effect of smoking on the lymphatic system, a

study including only people who smoke and do not have any other comorbid pulmonary diseases can be conducted. As other contributing factors, female gender and advanced age were also among the risk factors for increased lymph node count and diameter, which may both contribute to ongoing inflammation.

Factors such as BMI, OSAS1, OSAS2, and gender were also analyzed. Female patients had larger lymph node diameters than males, possibly reflecting gender differences in immune and inflammatory responses. Intermittent hypoxia in OSAS can promote systemic inflammation, perhaps resulting in the enlargement of mediastinal lymph nodes (12). The study revealed no significant difference in lymph-node size between patients with snoring simply and those with snoring + apnea. This might be due to restricted sample size and subjective categorization of symptoms, advocating for larger studies to elucidate the link between OSAS and lymphadenopathy.

This study has several limitations. The retrospective and single-center nature of the study limits the generalizability of the findings. Additionally, the benign or malignant nature of the observed TLNs was not confirmed through histopathological analysis or PET imaging. The inclusion of smokers may have introduced confounding variables unrelated to asthma. The oldest patient in our study was 68 years old. When it comes to aging, it would be necessary to observe the changes in older patients; however, advanced anatomical disorders in the lungs due to aging, changes due to heart diseases, and the effects of other systemic diseases on the lungs would make it challenging for us to classify the patients as asthma patients who meet the inclusion criteria of this study. Finally, the lack of longitudinal data prevents an understanding of the dynamic changes in TLNs and systemic inflammation over time. Future multi-center, prospective studies are necessary to address these limitations and validate the findings.

CONCLUSION

This study highlights the significant relationship between TLNs and age, systemic inflammation, and lung function in asthma patients. Evaluating TLNs, particularly in older individuals, provides valuable insights into disease progression and severity. Future studies should assess the functional consequences of TLN enlargement, particularly regarding lymphatic drainage efficiency and systemic inflammation. Additionally, examining the molecular pathways linking immunosenescence, inflammaging, and lymphangiogenesis could help identify therapeutic targets to mitigate disease progression in older adults. These insights could inform tailored interventions aimed at improving the outcomes and quality of life of elderly asthma patients.

Conflict of Interest: The authors declare no potential conflicts of interest.

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