Diagn Interv Radiol 2021; 27:329–335

CHEST IMAGING

ORIGINAL ARTICLE

Prognostic value of mediastinal lymph node enlargement in chronic interstitial lung disease

Stefano Grecuccio
Nicola Sverzellati
Elisabetta Uslenghi
Antonella Caminati
Giueseppe Pedrazzi
Maurizio Zompatori

PURPOSE
Mediastinal lymph node (MLN) enlargement detected on chest computed tomography (CT) is frequent in patients with interstitial lung disease (ILD) and is shown in approximately 70% of cases of idiopathic pulmonary fibrosis (IPF). We hypothesized that enlarged MLNs might be a predictor of poor prognosis, associated with lower survival and stronger disease severity.

METHODS
This study included patients with idiopathic pulmonary fibrosis (IPF) or nonspecific interstitial pneumonia (NSIP) from January 2009 to December 2018. Baseline chest CT scan and one-year follow-up scan of the patients were reviewed for the extent of lung fibrosis and MLNs. Two radiologists independently assessed MLN diameter and location. Patients with drug toxicity-related ILD, sarcoidosis, chronic hypersensitivity pneumonitis and other rare idiopathic interstitial pneumonias were excluded. The primary endpoint was survival. Secondary endpoints included number of hospitalizations for respiratory causes, lung function evaluated by forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO), and lung fibrosis score determined by CT scan.

RESULTS
We retrospectively reviewed the medical registries of 110 patients with chronic pulmonary fibrosis (mean age 71 years, 60.4% male). Nine participants were excluded because the CT scans were of poor diagnostic quality for the evaluation of the mediastinum or unavailable for review. The analysis of 101 patients showed that enlarged MLNs (short axis diameter ≥10 mm) were present in 50.5% (n=51) and strongly predicted survival (HR= 2.11, 95% CI 1.12–3.96, $p = 0.020$). Patients with MLN enlargement experienced greater number of hospitalizations for respiratory causes (mean 2.5 vs. 1.8, $p = 0.010$) and had significantly worse lung function parameters (FVC, 71% vs. 81%, $p = 0.018$ and DLCO, 40% vs. 50%, $p = 0.001$) and a higher lung fibrosis score (50% vs. 39%, $p = 0.001$).

CONCLUSION
In patients with IPF and NSIP, enlarged MLNs predict survival, are associated with increased number of hospitalizations, and show signs of poorer lung function and more severe fibrosis.

Predicting prognosis of patients affected by fibrotic lung diseases is challenging. Yet, it is of paramount importance for the choice of the therapeutic approach. The prognostic value of several computed tomography (CT) features and metrics of fibrotic lung disorders have been explored in the last decade (1–3). The presence of honeycombing as well as the severity of traction bronchiectasis on CT are both strong prognostic factors. However, their assessment is limited by several factors, such as interobserver variability. Quantitative analysis could replace the visual scoring, although dedicated software is not widely available and its regular use is still scarce in routine practice (4). A recent study by Adegunsoye et al. (5) reported that mediastinal lymph node (MLN) enlargement predicts transplant-free survival and hospitalization risk in patients with interstitial lung diseases (ILDs), and is correlated with decrement in plasma concentration of a key circulating soluble CD40-ligand (sCD40-L), therefore having an impact on the prognosis. The aim of the study was to confirm these recent finding and to determinate whether features of MLNs on chest CT predict clinically relevant outcomes

From the Department of Radiology (S.G. ✉ *stefano.grecuccio@studenti.unipr.it.*, N.S.), University of Parma, Parma, Italy; Department of Diagnostic Imaging and U.O. of Multi Medical Radiology IRCCS (E.U., M.Z.), Milan, Italy; U.O. of Pneumology and Semi-Intensive Respiratory Therapy (A.C.), Service of Respiratory Pathophysiology and Pulmonary Hemodynamics, San Giuseppe Multimedica Hospital, Milan, Italy; Department of Medicine and Surgery (G.P.), Unit of Neuroscience and Robust Statistics Academy, University of Parma, Parma, Italy.

Received 10 December 2019; revision requested 11 January 2020; last revision received 16 May 2020; accepted 15 June 2020.

Published online 22 April 2021.

DOI 10.5152/dir.2021.19585

You may cite this article as: Grecuccio S, Sverzellati N, Uslenghi E, Caminati A, Pedrazzi G, Zompatori M. Prognostic value of mediastinal lymph node enlargement in chronic interstitial lung disease. Diagn Interv Radiol 2021; 27:329–335

in patients with either idiopathic pulmonary fibrosis (IPF) or nonspecific interstitial pneumonia (NSIP).

Methods

Study design and patient selection

This study retrospectively reviewed clinical and CT data of 110 patients with either IPF (n=81) or NSIP (n=20) between January 2009 and December 2018. All patients obtained a multidisciplinary diagnosis. Nine participants, whose CT scans were of poor diagnostic quality for the evaluation of the mediastinum or unavailable for review, were excluded. Data regarding pulmonary function parameters, comorbidities, hospitalizations and exitus were collected from the hospital registry data.

We considered whether patients were treated with Pirfenidone or Nintedanib. Each participant was followed up until December 2018.

The study was approved by the local Ethical Committee (Protocol n. 89.2019) and all patients signed informed consent.

Data collection

We retrospectively reviewed the electronic medical record to extract clinical information from each participant, including demographic data (sex and age), history of cigarette smoking, eventual comorbidities (cardiovascular diseases, diabetes mellitus, acid reflux in patients with hiatal hernia), pulmonary function tests (forced vital capacity [FVC] and diffusing capacity of lung for carbon monoxide [DLCO]), type of treatment for pulmonary fibrosis, chest CT imaging findings (reticulations, traction bronchiectasis, honeycombing and ground glass opacity).

Main points

- Enlarged mediastinal lymph nodes (defined as short axis diameter ≥10 mm on chest CT) are frequenty observed in patients with interstitial lung disease (ILD).
- We hypothesized that enlarged MLNs might be a predictor of poor prognosis, associated with lower survival and stronger disease severity.
- In patients with idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia, enlarged MLNs predict survival, are associated with increased number of hospitalizations, and show signs of poorer lung function and more severe fibrosis.

Table 1. The GAP staging system

Stage	I	II	III
Points	0–3	4–5	6–8
Mortality, %			
1-year	5.6	16.2	39.2
2-year	10.9	29.9	62.1
3-year	16.3	42.1	76.8

The total point score is used to classify patients as stage I (0–3 points), stage II (4–5 points), or stage III (6–8 points). Model-predicted 1-, 2-, and 3-year mortality is shown by stage.
GAP, gender/ age/ pulmonary function (forced vital capacity and diffusing capacity of lung for carbon monoxide).

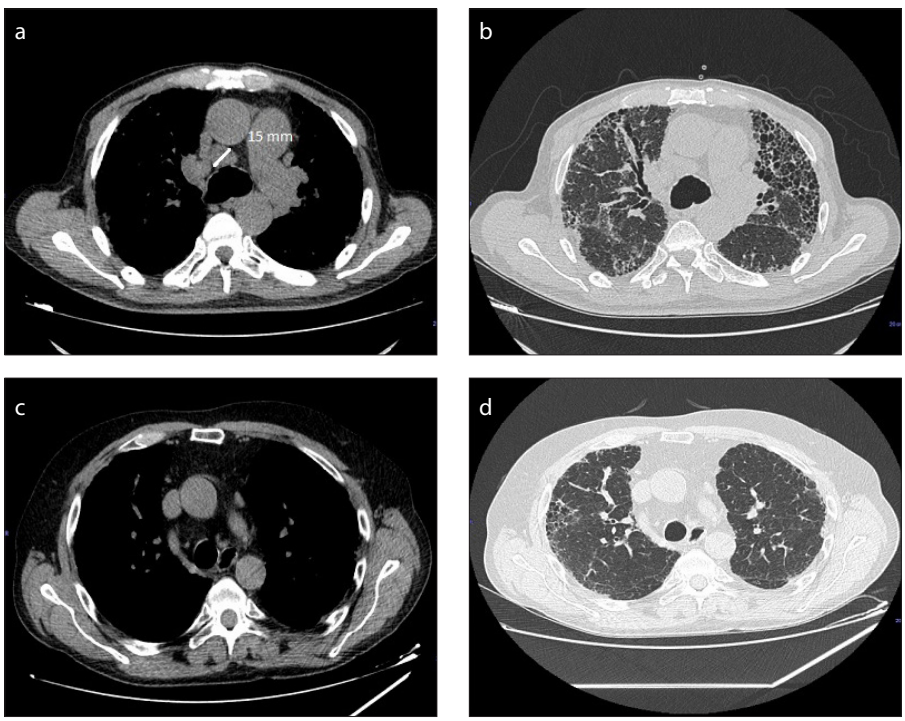

Figure 1. a–d. High-resolution CT scan (soft tissue and parenchymal windows, respectively) showing typical appearance of lung fibrosis with **(a, b)** and without **(c, d)** mediastinal lymph node (MLN) enlargement. MLN enlargement was defined as short axis diameter of greater than 10 mm in the transverse plane.

We constructed a scoring system that provides a simple screening method to determine the average risk of mortality of patients with IPF: multidimensional GAP index and staging system (gender [G], age [A], pulmonary function [P]) selected four parameters that are commonly collected in clinical practice: two patient-specific variables (sex, age) and two disease-specific variables (FVC, DLCO). Points are assigned for each predictor of the scoring system (range, 0–8) to create a point-score model. The total point score is used to classify patients as stage I (0–3 points), stage II (4–5 points), or stage III (6–8 points) and provides 1-, 2-, and 3-year mortality estimates (6) (Table 1). For three patients it was not possible to calculate the GAP index because they were unable to perform the DLCO test.

CT scans

Multidetector row CT scanners were used to acquire chest CTs. We used both 1 mm detectors to obtain high-resolution images with 1.25 mm thick sections or 2.5 mm detectors obtaining 3 mm thick sections. All CT images were reconstructed into soft tissue mediastinal window and lung window in axial and coronal planes (Fig. 1). The MLN diameter was measured in the soft tissue window; the extent of pulmonary fibrosis was assessed in the parenchymal window.

Chest CT evaluation

For each participant two CT scans were reviewed to evaluate the trend of changes in both visual and functional parameters: baseline chest CT scan (t_0) and first fol-

low-up scan (t_1), which was conducted at least one year later. Patients for whom only one CT was available or who performed the baseline CT scan and the first follow-up CT less than a year apart were excluded. Since the end of the study was established to be December 31, baseline CT scan must have been performed at least a year before. As this study objective was focused on MLNs (stations 1–9), we excluded hilar and interlobar lymph nodes (stations 10–14). In case of lymph node conglomeration, the whole station was considered as a single entity.

Two radiologists independently described the presence, size, number, and location of the lymph nodes. In particular we identified two zones: above the carina (stations 1–6) and below the carina (stations 7–9).

MLNs diameter was measured with electronic calipers using the soft tissue windows. Lymph nodes with a short axis diameter ≥10 mm were considered as enlarged (7–10). For any discrepancies the individual node measurement was averaged. Furthermore, each radiologist visually assessed the extent of parenchymal fibrosis across a quantitative CT visual score (11). Each lung was divided into 3 zones: upper (lung apex to aortic arch), middle (aortic arch to inferior pulmonary veins) and lower (inferior pulmonary veins to lung bases). The extent of lung fibrosis in each of six zones was visually scored, using a scale from 0 to 4: 0, absent; 1, 1%–25%; 2, 26%–50%; 3, 51%–75%; and 4, 76%–100% (12, 13). A mean of two radiologists' visual scores was calculated for each patient.

Table 2. Baseline variables of the study population

Variables	Total study population (n=101)	Lymph node <10 mm (n=50)	Lymph node >10 mm (n=51)	*p* (<10 mm vs. >10 mm)
Age (y), mean±SD	70.8±8.4	71.2±8.7	70.5±8.1	0.67
Gender M/F (%)	61/40 (60.4/39.6)	28/22 (56.0/44.0)	33/18 (64.7/35.3)	0.41
Tobacco, n (%)				
Non smoker	42 (41.6)	21 (42.0)	21 (41.2)	0.54
Smoker	16 (15.8)	6 (12.0)	10 (19.6)	
Ex-smoker	43 (42.6)	23 (46.0)	20 (39.2)	
FVC (% predicted), mean±SD	73.1±20.6	77.8±20.8	68.5±19.4	0.024
DLCO (% predicted), mean±SD	45.1±17.4	50.3±16.8	39.7±16.4	0.002
No. of hospitalizations				
Mean±SD	2.2±1.8	1.8±1.9	2.5±1.6	0.007
Median (IQR)	2.0 (3.0)	1.0 (3.5)	2.0 (3.0)	
PA diameter (mm), mean±SD	29.0±4.1	27.7±3.5	30.2±4.4	0.002
Mediastinal width (mm), mean±SD	83.2±14.5	78.8±12.9	87.4±14.8	0.002
Visual score (%), mean±SD	44.6±15.8	39.0±14.2	50.1±15.4	<0.001
Hiatal hernia (N/Y)	53/48 (52.5/47.5)	25/25 (50.0/50.0)	28/23 (55.0/45.0)	0.68
ILD subtype, n (%)				
IPF	81 (80.2)	40 (80.0)	41 (80.4)	1.000
NSIP	20 (19.8)	10 (20.0)	10 (19.6)	
GAP-index				
Mean±SD	4.1±1.3	3.7±1.2	4.5±1.2	0.002
Median (IQR)	4.0 (2.0)	4.0 (2.0)	5.0 (2.0)	

The diameter of MLNs is measured along the short axis.
SD, standard deviation; M/F, male/female; FVC, forced vital capacity; DLCO, diffusing capacity of lung for carbon monoxide; IQR, interquartile range; PA, pulmonary artery; N/Y, no/yes; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; NSIP, nonspecific interstitial pneumonia; GAP index, gender/age/lung function parameters of FVC and DLCO.

Follow-up and endpoint of the study

The primary endpoint of our study was overall survival (OS) defined as time from the diagnosis of chronic ILD diagnosis to death. Each patient was followed up until the end of the study period, exitus, lung transplantation, or loss to follow-up. Follow-up time was censored on December 31, 2018.

Secondary endpoints included number of hospitalizations for respiratory causes, lung function (two parameters evaluated, FVC and DLCO) and lung fibrosis score determined by CT scan.

Patients were considered to have a respiratory hospitalization when the primary cause for hospitalization was one of the following: acute respiratory worsening consisting of increased dyspnea, hypoxia, or respiratory distress, respiratory failure (requiring mechanical ventilation), acute exacerbations, pneumonia, pulmonary embolism, pulmonary hypertension, pneumothorax.

Statistical analysis

All the analyses were performed with the statistical software IBM-SPSS version 23 and R version 3.6.2. Descriptive statistics for continuous variables included arithmetic mean, 5% trimmed mean, standard error of the mean, median, standard deviation, asymmetry and kurtosis, all with their 95% confidence intervals. Categorical data were described by frequencies and percentages.

Patients were initially classified into two groups depending on the presence or absence of any enlarged MLNs. We performed Kaplan–Meier analysis with log-rank test to compare overall survival according to the presence of MLN enlargement. Cox proportional hazard regression analysis was then used to calculate hazard ratio and 95% confidence intervals, adjusting final MLN enlargement value for smoking status, age and gender. Cox model assumptions were tested by global and single covariate statistical test (cox.zph) included in the R package "survival". The proportional hazards assumption was also checked using graphical diagnostics based on the scaled Schoenfeld residuals. Non-linearity was checked by martingale residuals.

Independent t-test and the nonparametric Mann–Whitney U test were used to compare the number of hospitalizations for respiratory causes according to the presence of enlarged MLNs. Normality was checked by the Kolmogorov–Smirnov and Shapiro–Wilk test.

A paired sample *t*-test and the Wilcoxon signed-rank test were used for assessing the relationship between MLN diameter

Table 3. Lung function parameters (FVC and DLCO) at baseline evaluation and first follow-up

	Lung function parameters			
Variable	Mean (%)	SD (%)	95% CI	*p*
t_0				
FVC				
MLN <10 mm	78.6	21.2	72.3–84.9	0.024
MLN ≥10 mm	71.3	20.7	64.9–76.4	
DLCO				
MLN <10 mm	50.4	18.0	45.3–55.2	0.001
MLN ≥10 mm	39.2	16.1	34.0–44.4	
t_1				
FVC				
MLN <10 mm	81.4	24.1	73.4–87.4	0.006
MLN ≥10 mm	67.2	20.3	60.7–73.8	
DLCO				
MLN <10 mm	45.3	19.4	39.6–51.1	0.004
MLN ≥10 mm	34.1	17.4	28.5–39.7	

SD, standard deviation; 95% CI, 95% confidence interval; t_0, baseline evaluation; FVC, forced vital capacity; MLN, mediastinal lymph node; DLCO, diffusing capacity of lung for carbon monoxide; t_1, first follow-up at least one year later.

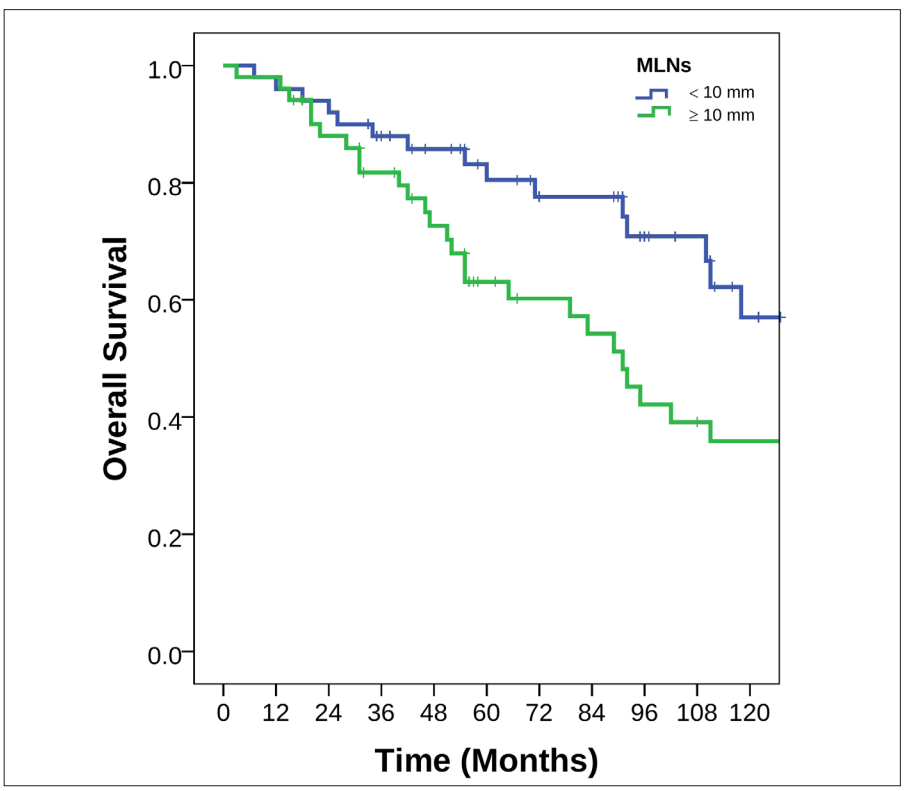

Figure 2. Kaplan–Meier survival curves during the follow-up period according to the presence of mediastinal lymph node (MLN) enlargement. The overall survival rate of subjects with MLN enlargement *(green line)* was significantly lower than that of the subjects without enlarged MLNs *(blue line)*. *p* value was obtained by log-rank test. Hazard ratio and 95% confidence interval were obtained by multivariate cox regression.

and changes in FVC and DLCO at t_0 and t_1, where t_0 is the initial evaluation and t_1 after first follow-up.

Wilcoxon signed-rank test was also used to calculate the association between MLN and visual score.

Repeated measures ANOVA (mixed models) was used to investigate the changes in mean visual scores over one year of follow-up.

p values less than 0.05 were considered statistically significant.

Results

Baseline characteristics of the 101 participants included in our study are shown in Table 2. A total of 61 subjects were male (60.4%), mean age was 70.8±8.4 years, and the mean percentage predicted FVC and DLCO were 73%±21% and 45%±17%, respectively. Fifty-nine subjects (58%) were either current (16%) or former (42%) smokers. Eighty-one subjects (80%) had classical IPF pattern and 20 (20%) had NSIP pattern on CT. Enlarged MLNs were present in 51 patients (50.5%); of these, 65% had 10–14 mm, 30% had 15–19 mm, 5% had >20 mm MLNs.

When compared with those without MLN enlargement, study subjects with MLN enlargement reported a greater number of hospitalizations (2.5 vs. 1.8), showed a greater pulmonary artery diameter (30 mm vs. 28 mm), greater mediastinal width (87 mm vs. 79 mm), and higher visual score of the extent of lung fibrosis (50% vs. 39%).

Statistically significant differences in gender, age, smoker proportion, hiatal hernia between subjects with and subjects without MLN enlargement were not detected.

The risk of death in study subjects with MLN enlargement (HR 2.11; 95% CI, 1.12–3.96; $p = 0.020$) was higher compared with patients without enlarged MLNs (Fig. 2). Patients with MLN enlargement had a 1-year survival rate of 97.9% (vs. 100% for patients without enlarged MLNs) and a 5-year survival rate of 65% (vs. 80% for patients without enlarged MLNs). The median survival times for patients with enlarged MLNs were 91 months (range, 74.3–107.7). The increased risk of death in our study participants remained statistically significant even after adjusting for covariates including gender, age and tobacco smoking (HR 2.07; 95% CI, 1.09–3.93; $p = 0.025$), but it was not significant after adjusting for GAP index (HR 1.99; 95% CI, 1.54–2.59 $p < 0.001$).

No statistically significant difference was found when enlarged MLNs were divided into three subgroups according to their size (10–14 mm, 15–19 mm, and >20 mm) and correlated with OS, neither when enlarged MLNs were divided into two subgroups according to their location above the carina (stations 1–6) and below the carina

Table 4. Fibrosis score at baseline evaluation and first follow-up

Variable	Visual score				
	Mean (%)	Median (%)	SD (%)	95% CI	*p*
Visual score					
t_0					
MLN <10 mm	39.0	35.0	14.2	34.9–43.0	<0.001
MLN ≥10 mm	50.1	50.0	15.4	45.8–54.5	
t_1					
MLN <10 mm	48.4	46.8	19.5	42.9–53.9	<0.001
MLN ≥10 mm	61.4	63.5	17.2	56.5–66.2	

SD, standard deviation; CI, confidence interval; MLN, mediastinal lymph node; t_0, baseline evaluation; t_1, first follow-up at least one year later.

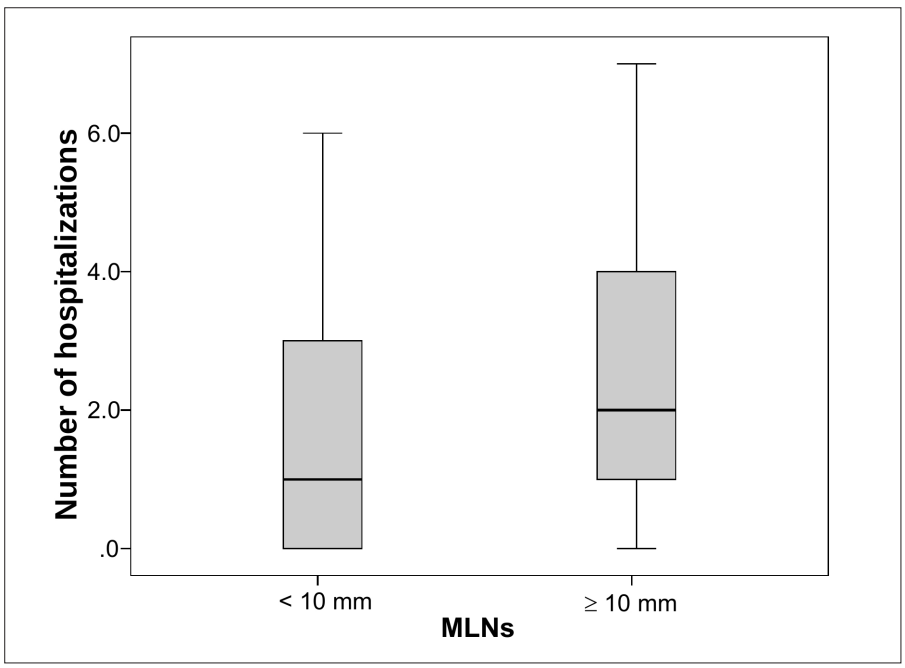

Figure 3. Mediastinal lymph node (MLN) enlargement is associated with a higher number of hospitalizations for respiratory causes.

(stations 7–9). No statistically significant correlation was found between OS and the total number of enlarged MLNs.

Subjects with MLN enlargement experienced a major number of hospitalizations for respiratory causes (mean 2.5 vs. 1.8, $p = 0.010$) (Fig. 3). Furthermore, participants with enlarged MLNs had significantly worse lung function parameters at both baseline (FVC 71% vs. 81%, $p = 0.018$; DLCO 40% vs. 50%, $p = 0.001$) and first follow-up (FVC 67% vs. 80%, $p = 0.009$; DLCO 34% vs. 45%, $p = 0.006$) (Table 3).

Enlarged MLNs correlated with disease severity (evaluated with the visual score) both at baseline CT evaluation (50% vs. 39%, $p = 0.001$) and at first follow-up (61% vs. 48%), but the worsening trend was the same for both groups (equal slope) (Table 4, Fig. 4).

Discussion

Mediastinal lymph node enlargement has a prevalence of 66% in patients with IPF, while is higher in patients with the diagnosis of NSIP (80%) (14). In 70% of cases, MLN enlargement is seen in only 1 or 2 nodal stations, more frequently caudal to the carina of the trachea; the lymph node diameter generally measures no more than 15 mm (15–17).

The reason of enlarged MLNs in chronic ILDs is still not clear. As suggested from previous studies, it could be related to hyperplastic reaction in response to a chronic inflammation (15, 18–20): cytokines released by activated alveolar macrophages would evoke the proliferation of lymphoid cells into lymphoid tissues (21). Histopathological examination of enlarged nodes has shown benign nodal hyperplasia (15, 18). The need for the inflammation to be chronic may also explain the lower prevalence of lymphadenomegaly in organizing pneumonia, in which patients present with a short history (less than ~2 months) of symptoms before diagnosis, than in other subtypes of idiopathic ILD, in which patients are usually symptomatic for at least six months (17).

Predicting prognosis of patients with lung fibrosis is fundamental for treatment strategy. However, this is challenging due to heterogeneous variables concerning diseases and patients characteristics. Previous studies have suggested that use of the GAP model, a clinical prediction tool based on gender, age, and pulmonary physiology, accurately predicted mortality in patients with chronic ILD (6).

We suggest that MLN enlargement is a very useful parameter, which could simply be detected on chest CT at the time of diagnosis and may help to refine prediction of mortality.

A recent study of Adegunsoye et al. (5) has shown a relevant association between MLN enlargement on chest CT and survival in patients with a broad heterogeneous group of ILDs; the authors suggest that MLN enlargement is supposedly linked to underlying immunologic phenomena in lung tissue, which consequently contribute to the pathophysiology of progression of pulmonary fibrosis.

This study particularly revealed differences in the plasma concentrations of multiple cytokines in subjects with enlarged MLNs. One of the most important modification was the decrement in plasma concentration of sCD40-L, which plays an important role in immune-modulatory activities (22). Targeting the CD40-L (expressed on activated antigen-specific CD4+ T cells) and CD40 (expressed on dendritic cells) pathway is a powerful means of attenuating immune responses in chronic diseases (23). sCD40-L is released as a soluble, proteolyzed form of CD40 ligand which is exposed on the surface of activated T cells and increases the stimulation of B cells (24).

The study included several subtypes of ILD, including IPF, chronic hypersensitivity

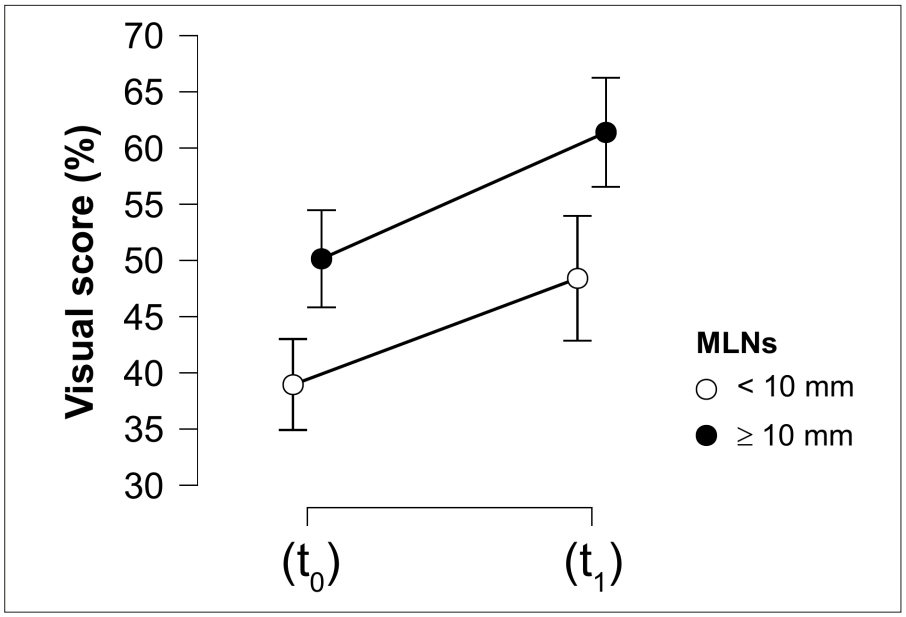

Figure 4. Descriptive plot shows worsening of diffuse parenchymal disease at first follow-up (t_1) compared with baseline CT evaluation (t_0). Enlarged MLNs correlated with a higher visual score both at baseline CT evaluation (t_0) and at first follow-up (t_1); however, the worsening trend was the same for the two groups (equal slope).

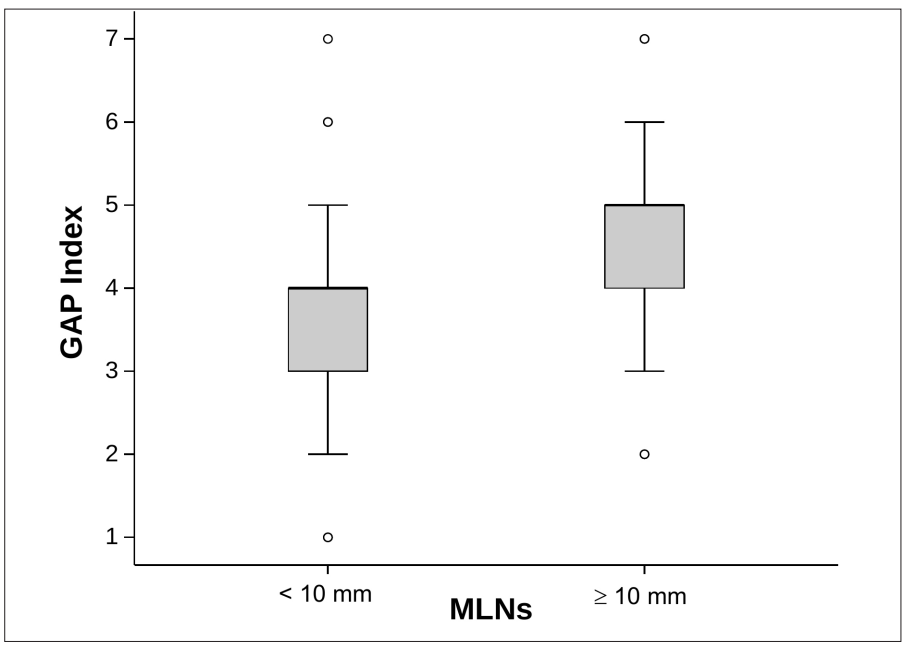

Figure 5. Mediastinal lymph node (MLN) enlargement is associated with a higher GAP (gender/ age/ pulmonary functions) index score.

pneumonitis, connective tissue disease-associated interstitial lung disease (CTD-ILD), interstitial pneumonia with autoimmune features, and unclassifiable ILD (5). Instead, we focused on both IPF and NSIP CT pattern and we added clinical and radiological parameters. Patients with enlarged MLNs experienced a major number of hospitalizations for respiratory causes (mean 2.5 vs. 1.8, p = 0.010) and had significantly worse lung function parameters (FVC 71% vs. 81%, p = 0.018 and DLCO 40% vs. 50%, p = 0.001) and a higher lung fibrosis score (50% vs. 39%, p = 0.001).

On the other hand, subgroups according to the location, size and number of enlarged MLNs did not reveal any statistically significant differences. First, we identified two zones of mediastinal lymph nodes, above the carina (stations 1–6) and below the carina (stations 7–9), and correlated each group with the OS. Enlarged MLNs were divided into three subgroups according to their size as 10–14 mm, 15–19 mm and >20 mm and correlated with OS. Finally, we counted the total number of enlarged MLNs and evaluated the associations with OS.

Furthermore, we constructed the sex / age/ physiology score (GAP index) for study participants that provided an estimation of individual risk of mortality (6). After adjusting for GAP index the most important factor was GAP index (HR 1.99; 95% CI 1.54–2.59; p < 0.001). This is because GAP index distribution is significantly different for the presence or absence of the MLN enlargement (p = 0.002) (Fig. 5).

This study has several limitations. First, our study was analyzed retrospectively. A prospective analysis is required to make precise estimates of prognostic factors. Second, in accordance with the terminology, the MLN evaluation was strictly limited to the thoracic lymph node stations within the mediastinum (superior mediastinal, aortopulmonary, subcarinal and inferior mediastinal nodal stations) as defined by the International Association for the Study Lung Cancer (IASLC) nomenclature (25). Therefore, we excluded nodes in stations 10–14 (hilar and interlobar) since they are not located in the mediastinum. Third, not all images were acquired with high-resolution CT protocols for ILDs; a small number of participants had standard chest CT scans, which are not specific to assess parenchymal abnormalities in pulmonary fibrosis. However, we ensured that all included CT scans in the study had the necessary quality for MLN evaluation. Fourth, although the GAP index is a model validated only for patients with IPF, we extended the assessment in patients with NSIP.

In conclusion, our study revealed that enlarged MLNs strongly predict mortality and clinical endpoints in patients with IPF and NSIP; thus, MLN enlargement is likely to be a useful marker that should be reported by radiologists to help clinicians manage patients with these subtypes of chronic pulmonary fibrosis.

Conflict of interest disclosure

The authors declared no conflicts of interest.

References

1. Ley B, Elicker BM, Hartman TE, et al. Idiopathic pulmonary fibrosis: CT and risk of death. Radiology 2014; 273:570–579. [Crossref]

2. Nakagawa H, Fukunaga K, Ikeda S, et al. Prognostic factors in patients with idiopathic pulmonary fibrosis; evaluation using quantitative CT analysis of fibrosis and emphysema. Eur Respir J 2019; 54(Suppl 63): Abstract 1332. [Crossref]
3. Jacob J, Bartholmai B, Rajagopalan S, et al. Mortality prediction in idiopathic pulmonary fibrosis: evaluation of computer-based CT analysis with conventional severity measures. Eur Respir J 2017; 49:1601011. [Crossref]
4. Watadani T, Sakai F, Johkoh T, et al. Interobserver variability in the CT assessment of honeycombing in the lungs. Radiology 2013; 266:936–944. [Crossref]
5. Adegunsoye A, Oldham JM, Bonham C, et al. Prognosticating outcomes in interstitial lung disease by mediastinal lymph node assessment. an observational cohort study with independent validation. Am J Resp Crit Care Med 2019; 199:747–759. [Crossref]
6. Ryerson CJ, Vittinghoff E, Ley B, et al. Predicting survival across chronic interstitial lung disease: the ILD-GAP model. Chest 2014; 145:723–728. [Crossref]
7. Udoji TN, Phillips GS, Berkowitz EA, Berkowitz D, Ross C, Bechara RI. Mediastinal and hilar lymph node measurements. comparison of multidetector-row computed tomography and endobronchial ultrasound. Ann Am Thorac Soc 2015; 12:914–920. [Crossref]
8. Walker CM, Chung JH, Abbott GF, et al. Mediastinal lymph node staging: from noninvasive to surgical. AJR Am J Roentgenol 2012; 199:W54–64. [Crossref]
9. Glazer GM, Gross BH, Quint LE, Francis IR, Bookstein FL, Orringer MB. Normal mediastinal lymph nodes: number and size according to American Thoracic Society mapping. AJR Am J Roentgenol 1985; 144:261–265. [Crossref]
10. Jacob J, Bartholmai BJ, Rajagopalan S, et al. Automated quantitative computed tomography versus visual computed tomography scoring in idiopathic pulmonary fibrosis: validation against pulmonary function. J Thorac Imaging 2016; 31:304–311. [Crossref]
11. Sánchez RP, Fabrellas EF, Samper GJ, Montañana MLD, Vilar LN. Visual HRCT score to determine severity and prognosis of idiopathic pulmonary fibrosis. Int J Respir Pulm Med 2018; 5:084. [Crossref]
12. Sverzellati N, Calabrò E, Chetta A, et al. Visual score and quantitative CT indices in pulmonary fibrosis: Relationship with physiologic impairment. Radiol Med 2007; 112:1160–1172. [Crossref]
13. Best AC, Lynch AM, Bozic CM, Miller D, Grunwald GK, Lynch DA. Quantitative CT indexes in idiopathic pulmonary fibrosis: relationship with physiologic impairment. Radiology 2003; 228:407–414. [Crossref]
14. Niimi H, Kang EY, Kwong JS, Carignan S, Müller NL. CT of chronic infiltrative lung disease: prevalence of mediastinal lymphadenopathy. J Comput Assist Tomogr 1996; 20:305–308. [Crossref]
15. Bergin C, Castellino RA. Mediastinal lymph node enlargement on CT scans in patients with usual interstitial pneumonitis. AJR Am J Roentgenol 1990; 15:251–254. [Crossref]
16. Warrick JH, Bhalla M, Schabel SI, Silver RM. High resolution computed tomography in early scleroderma lung disease. J Rheumatol 1991; 18:1520–1528.
17. Souza CA, Müller NL, Lee KS, Johkoh T, Mitsuhiro H, Chong S. Idiopathic Interstitial Pneumonias: Prevalence of Mediastinal Lymph Node Enlargement in 206 Patients. AJR Am J Roentgenol 2006; 186:995–999. [Crossref]
18. Franquet T, Gimenez A, Alegret X, Rodriguez-Arias JM. Mediastinal lymphadenopathy in cryptogenic fibrosing alveolitis: the effect of steroid therapy on the prevalence of nodal enlargement. Clin Radiol 1998; 53:435–438. [Crossref]
19. Wechsler RJ, Steiner RM, Spirn PW, et al. The relationship of thoracic lymphadenopathy to pulmonary interstitial disease in diffuse and limited systemic sclerosis: CT findings. AJR Am J Roentgenol 1996; 167:101–104. [Crossref]
20. Garber SJ, Wells AU, duBois RM, Hansell DM. Enlarged mediastinal lymph nodes in the fibrosing alveolitis of systemic sclerosis. Br J Radiol 1992; 65:983–986. [Crossref]
21. Warrick JH, Bhalla M, Schabel SI, Silver RM. High resolution computed tomography in early scleroderma lung disease. J Rheumatol 1991; 18:1520–1528.
22. Jenabian MA, Patel M, Kema I, et al. Soluble CD40-ligand (sCD40L, sCD154) plays an immunosuppressive role via regulatory T cell expansion in HIV infection. Clin Exp Immunol 2014; 178:102–111. [Crossref]
23. Daoussis D, Andonopoulos AP, Liossis SN. Targeting CD40L: a promising therapeutic approach. Clin Diagn Lab Immunol 2004; 11:635–641. [Crossref]
24. Fischer BM, Mortensen J, Hansen H, et al. Multimodality approach to mediastinal staging in non-small cell lung cancer. Faults and benefits of PET-CT: a randomised trial. Thorax 2011; 66:294–300. [Crossref]
25. Rossi DL, Vicari AP, Franz-Bacon K, McClanahan TK, Zlotnik A. Identification through bioinformatics of two new macrophage proinflammatory human chemokines: MIP-3alpha and MIP-3beta. J Immunol 1997; 158:1033–1036.