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The Role of the Mediastinal Lymph Node Density in Assessing Severity of Pulmonary Edema

Pulmoner Ödem Şiddetinin Belirlenmesinde Mediastinal Lenf Nodu Dansitesinin Rolü

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ABSTRACT Objective: Mediastinal lymph node density (MLND) on non-contrast computed tomography has shown potential as a diagnostic marker in thoracic imaging. The aim of this article is to investigate the relationship between MLND and the severity of pulmonary edema (PE). **Material and Methods:** This retrospective, double-center study was conducted on 80 patients with PE, categorized into interstitial edema (IE) group (n=40) and alveolar edema (AE) group (n=40), along with a control group of healthy individuals (n=73). IE was defined as fluid accumulation within the lung interstitium, and AE was defined as the progression of the fluid accumulation into the alveolar spaces. MLND was calculated by measuring the Hounsfield unit (HU) value within a circular region of interest. **Results:** Median MLND values were 34.0 HU (interquartile range 31.0-36.0) in healthy controls, 21.5 (20.0-24.0) in patients with IE, and 9.5 HU (6.3-13.8) in patients with AE, respectively (p<0.001). All healthy individuals had MLND at least 28 HU, and all patients with PE had MLND below 28 HU. A negative correlation was observed between MLND and PE severity, adjusted for age, sex and body-mass-index. **Conclusion:** MLND is significantly associated with the severity of PE, suggesting that it may be used for clinical evaluation of patients with PE.

Keywords: Mediastinal lymph node density; pulmonary edema; thorax computed tomography

ÖZET Amaç: Kontrastsız bilgisayarlı tomografi ile ölçülen mediastinal lenf nodu dansitesi (MLND), torasik görüntülemede potansiyel bir tanı göstergesi olarak dikkat çekmiştir. Bu makalenin amacı, MLND ile pulmoner ödem (PÖ) şiddeti arasındaki ilişkiyi araştırmaktır. **Gereç ve Yöntemler:** Bu retrospektif analiz, 80 PÖ hastası üzerinde gerçekleştirilmiştir. Hastalar, interstisyel ödem (İÖ) grubu (n=40) ve alveoler ödem (AÖ) grubu (n=40) olarak sınıflandırılmıştır. Kontrol grubu ise sağlıklı bireylerden (n=73) oluşmuştur. İÖ, akciğer interstisyumunda sıvı birikimi olarak tanımlanırken; AÖ, bu sıvı birikiminin alveoler alanlara ilerlemesi olarak tanımlanmıştır. MLND, bir dairesel ilgi alanı içinde Hounsfield birimi [Hounsfield unit (HU)] değeri ölçülerek hesaplanmıştır. **Bulgular:** Medyan MLND değerleri sağlıklı bireylerde 34,0 HU (güven aralığı 31,0-36,0), İÖ hastalarında 21,5 HU (20,0-24,0) ve AÖ hastalarında 9,5 HU (6,3-13,8) olarak ölçülmüştür (p<0,001). Tüm sağlıklı bireylerde MLND en az 28 HU bulunurken, tüm PÖ hastalarında bu değer 28 HU'nun altında kalmıştır. Yaş, cinsiyet ve beden kitle indeksi için ayarlama yapıldığında MLND ile PÖ şiddeti arasında bir ilişki gözlenmiştir. **Sonuç:** MLND, PÖ şiddeti ile anlamlı bir şekilde ilişkilidir ve PÖ hastalarının klinik değerlendirilmesinde yardımcı bir araç olarak kullanılabilir.

Anahtar Kelimeler: Mediastinal lenf nodu dansitesi; pulmoner ödem; toraks bilgisayarlı tomografi

Pulmonary edema (PE) is defined as extravascular fluid flow into the pulmonary interstititum or alveolar air spaces, due to elevated hydrostatic pressure, increased permeability, or a combination of both.[1]

Interstitial edema (IE) is described as smooth, linear opacities outlining the secondary pulmonary lobules and the absence of alveolary opcities, indicating fluid accumulation within the interstitium. It

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is also referred to as interlobular septal thickening on computed tomography (CT).[2] Similarly, the lymphatics runnig along these bundles also become expanded, leading to peribronchial cuffing appearance on CT. When fluid flows through the alveolar-capillary barrier and occupies the air spaces, alveolary edema (AE) occurs.

In early stages, ground-glass opacities are seen due to partial fluid filling, whereas in advanced stages, marked consolidation occurs as the air spaces become completely filled with fluid.[2] Although the diagnosis and severity of PE can be assessed through parenchymal findings on thorax CT, these findings may sometimes be subtle or confusing, particularly in early-stage or atypical cases. As emphasized in previous studies, including Barile, the radiological appearance of PE can vary depending on the underlying mechanism and disease phase, which may complicate interpretation in daily clinical practice.[2] In such situations, the measurement of mediastinal lymph node density (MLND) may provide an additional, objective parameter to support the diagnosis and evaluation of PE.[2]

MLND can be quantitatively measured through CT in Hounsfield units (HU).[3] It has previously been explored in conditions such as sarcoidosis and malignancies.[4-6] However, no prior studies have investigated MLND in the context of PE diagnosis as well as its severity in terms of IE and AE.

In the current study, we aimed to investigate the relationship between MLND and the severity of PE.

MATERIAL AND METHODS

STUDY PARTICIPANTS

The study was conducted in accordance with the Declaration of Helsinki. The Koç University Committee on Human Research approved the study protocol (date: January 6, 2025; no: 2025.004.IRB2.00). Written informed consent was obtained from all the subjects involved in this study.

This study was a double-center Koç University Hospital and Koç Healthcare American Hospital İstanbul retrospective evaluation of a clinical cohort between April 2021-February 2024.

Written informed consent was obtained from all patients prior to CT imaging as part of standard clinical care. Given the retrospective design and the use of anonymized data, additional consent for study participation was not required, in accordance with the approval of the institutional ethics committee.

Among the 456 adult patients who underwent thorax CT due to a preliminary or differential diagnosis of PE between April 2021-February 2024, those with co-existing pneumonia, contrast-enhanced CT scans, malignancies, interstitial lung disease, sequelae of tuberculosis, or poor-quality imaging were excluded. After applying these criteria, 80 patients were randomly selected from the remaining eligible cases across 2 centers. The diagnosis of PE was based on a combination of clinical, laboratory, and radiological findings, and the categorization into interstitial or AE was made according to CT imaging features. The selection process ensured balanced representation of both IE and AE, with 40 patients in each group. In addition, 73 healthy controls were randomly selected from the check-up list (Figure 1). To avoid potential variability in HU measurements due to the use of intravenous contrast, only non-contrast chest CT scans were included in the study.

IE was characterized by interlobular septal thickening and thickened bronchovascular bundles. AE was defined as fluid accumulation in the alveoli, presenting as ground-glass opacities and, in advanced stages, frank consolidation on CT images.[2]

Demographic characteristics, pre-existing conditions (hypertension, Type 2 diabetes mellitus), clinical symptoms, laboratory parameters and radiological findings were found from electronic health record systems.

CHEST CT PROTOCOL AND ASSESSMENT

Siemens Healthineers, Forchheim, Germany's Somatom® Definition AS 64-detector row CT was used to scan all patients without intravenous contrast administration, with patients in supine position during full inspiration. The scans were acquired using a tube voltage of 120 kVp and automatic tube current modulation (CareDose4D), with a pitch value ranging from 0.8 to 1.2 depending on patient size. The scan range extended from the lung apices to the

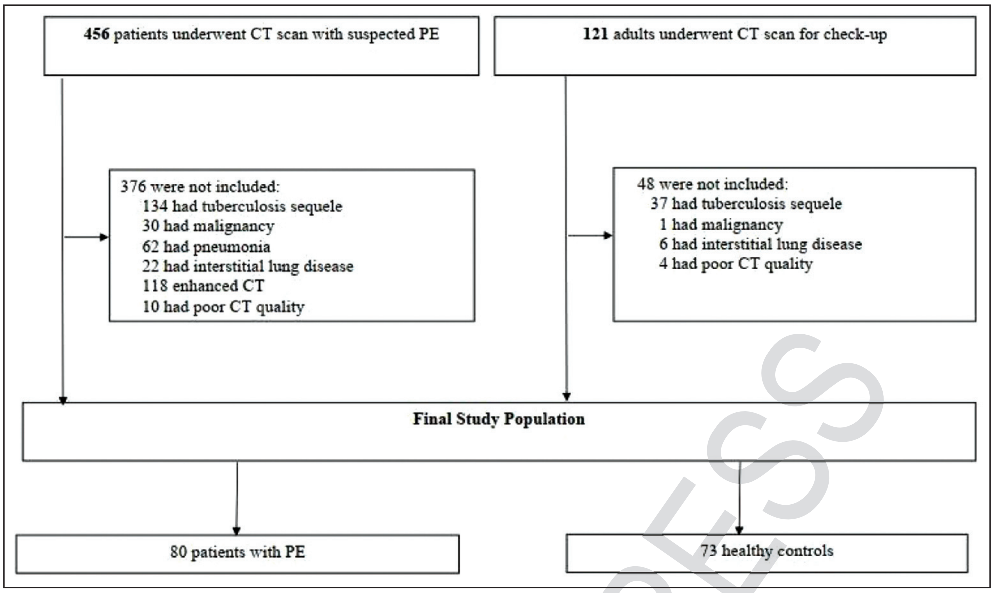

FIGURE 1: Flow-chart of the study population
CT: Computed tomography; PE: Pulmonary edema

costophrenic angles. All raw data were reconstructed using a standard soft-tissue convolution kernel (B30f), with a consistent slice thickness and reconstruction interval of 1.0 mm applied to all cases. Axial, coronal, and sagittal reformatted images were evaluated using lung and mediastinal window settings on a dedicated PACS workstation.

MLND was measured in HU using a region of interest (ROI). HU measurements were done on mediastinal window settings.

We evaluated the largest lymph nodes in the mediastinum on unenhanced CT scans. In each patient, only the largest mediastinal lymph node was selected for measurement. The density of the largest lymph node in the mediastinum was measured using a ROI size that covered approximately two-thirds of the lymph node cortex. HU values were obtained by placing circular ROIs on three separate cortical areas of the same node, and the average of these 3 measurements was used for analysis. Calcifications, vascular structures, or artifacts were excluded within the ROI. The hilum of the lymph nodes was also excluded from the measurements because the fat-containing hilum could potentially cause an inaccurately low mean HU density. All measurements were performed by an experienced radiologist at three independent time points, blinded to the clinical data and the results of previous assessments to minimize intraobserver bias. The long- and short-axis diameters and MLND values of the lymph nodes were recorded for statistical analysis. Only lymph nodes with a short-axis diameter greater than or equal to 10 mm were included in the analysis to ensure standardization and minimize measurement variability. CT scans of a healthy control, IE, and AE are illustrated in Figure 2.

STATISTICAL ANALYSIS

Baseline demographics were summarized as median with 25th and 75th percentile for the continuous variables, and as count with percentage for the categorical variables. For the continuous variables, the between groups differences was tested via Kruskal-Wallis test. For the categorical variables, chi-square test was applied. The linear regression analysis was performed to evaluate the correlation between PE severity and MLND measurements adjusted for age, sex and body mass index. Receiver operating characteristics curve analysis was not performed in this study due to the structure of the data and study design. The severity of PE classified into three predefined diagnostic categories (healthy control, IE, and

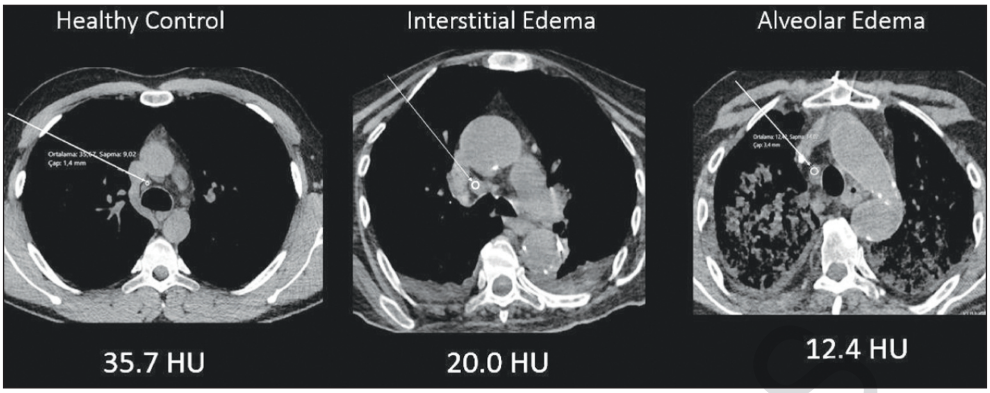

FIGURE 2: MLND measurements of a healthy control and patients with IE and AE, respectively
MLND: Mediastinal lymph node density; IE: Interstitial edema; AE: Alveolar edema; HU: Hounsfield unit

AE) based on clinical and radiological criteria, rather than being derived from a continuous variable or binary outcome that would serve as a reference standard. Moreover, MLND was used as a quantitative marker compared across these diagnostic groups, rather than as a predictive classifier against a gold standard. Thus, participants were coded as healthy controls=0, IE=1 and AE=2, respectively. The accepted significance level for all tests was set as 5%, and statistical analyses were performed using IBM SPSS 28.0 for Windows SPSS Inc., Chicago, Illinois, USA.

RESULTS

As illustrated in Figure 1, a total of 456 patients had the preliminary or differential diagnosis PE on the CT-scans, and 376 were not included due to concomitant pneumonia, interstitial lung disease, contrast enhanced CT scans, malignancy or poor CT quality. In total, 80 patients were remained for the final analysis, 40 with IE and 40 with AE. Among 121 adults undergoing CT scans for check-up, 48 were excluded due to malignancy, interstitial lung disease, tuberculosis sequele or poor CT quality, and 73 participants comprised the healthy controls.

Thus, 153 participants (47.7% females) with a median age of 65.0 (45.5-81.0) years were examined in this research. As shown in Table 1, patients in the AE group were significantly older and there was a significant difference among the study groups regarding the MLND values (Figure 3). All healthy individuals had MLND at least 28 HU, and all patients with PE had MLND below 28 HU.

There was a statistically significant difference in MLND values among the three groups ($p<0.001$, Kruskal-Wallis test).

"Post hoc" pairwise comparisons revealed a significant difference in MLND between the IE and control groups ($p<0.001$), and between the AE and control group ($p<0.001$).

TABLE 1: Baseline demographics and clinical characteristics of the study groups

	Healthy controls n=73	IE n=40	AE n=40	p value
Age, years	47.0 (38.5-58.50)	82.0 (75.8-87.0)	79.0 (64.8-85.5)	<0.001
BMI, kg/m^2	24.8 (22.0-29.2)	25.5 (21.5-27.3)	25.7 (23.8-28.8)	0.627
Male sex, %	40 (54.8)	15 (37.5)	25 (62.5)	0.068
Hypertension, %	12 (16.4)	29 (72.5)	20 (50.0)	<0.001
Diabetes mellitus, %	5 (6.8)	14 (35.0)	8 (20.0)	<0.001
MLND, HU	34.0 (31.0-36.0)	21.5 (20.0-24.0)	9.5 (6.3-13.8)	<0.001

BMI: Body mass index; MLND: Mediastinal lymph node density; HU: Hounsfield unit; IE: Interstitial edema; AE: Alveolar edema

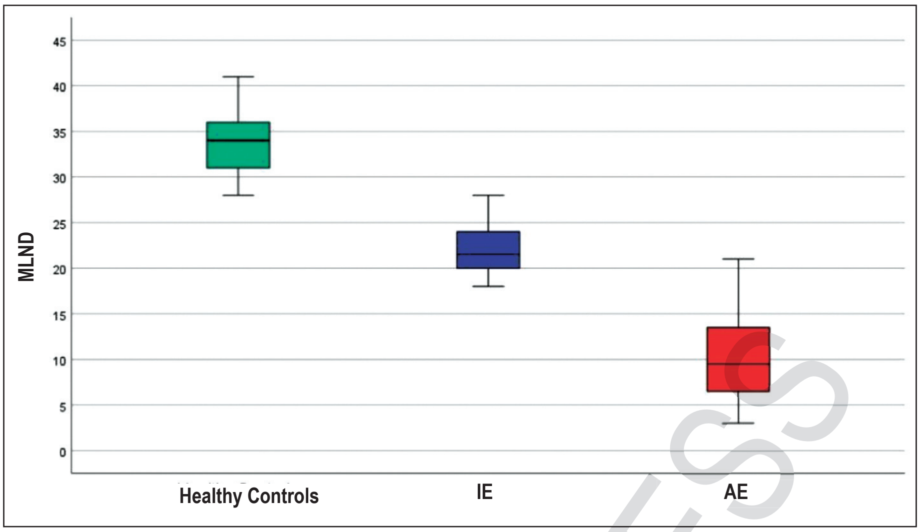

FIGURE 3: PE: Pulmonary edema; MLND: Mediastinal lymph node density; AE: Alveolar edema; IE: Interstitial edema; BMI: Body mass index

TABLE 3: Association of the severity of PE and the MLND

	Unstandardized coefficients β	95% confidence interval for β Lower	Upper	p value
AE vs IE and controls	-11.46	-12.360	-10.561	<0.001
Age	-0.020	-0.058	0.020	0.346
BMI	-0.033	-0.156	0.090	0.594
Male sex	0.453	-0.680	1.585	0.431

PE: Pulmonary edema; MLND: Mediastinal lymph node density; AE: Alveolar edema; IE: Interstitial edema; BMI: Body mass index

As shown in Table 2, only the association between MLND and PE severity was statistically significant (β=-11.46, $p<0.001$), while age, sex, and BMI did not show significant effects.

DISCUSSION

The primary result of the present research was a remarkable association between decreased MLND and the severity of PE. Patients with AE exhibited the lowest MLND values, followed by those with IE while healthy controls demonstrated the highest values. This relationship suggests that MLND may serve as a radiological indicator of PE severity.

To our knowledge, no previous study has demonstrated a measurable decline in MLND in the setting of PE. Our findings suggest that this decrease in attenuation, as observed on non-contrast CT, is not only a consistent feature of edema but also varies in relation to its severity. Specifically, MLND values were significantly lower in patients with AE compared to those with IE and healthy controls, indicating that the extent of fluid accumulation within the lymphatic structures may reflect the degree of pulmonary fluid overload.

Although parenchymal findings are routinely used to diagnose and assess the severity of PE on CT, they may not always provide clear information in early-stage or atypical cases. In such situations, MLND may serve as an additional, objective measurement to support radiological interpretation, especially when conventional signs are inconclusive.[2]

The underlying mechanism of the decrease in MLND is the lymph node enlargement in PE due to lymphatic congestion as well as increased interstitial and alveolar fluid accumulation.

When the lymphatic system is unable to compensate for this fluid shift, as often occurs in acute decompensated states, mediastinal lymph nodes may become congested with transudative fluid. This internal accumulation, rich in water content, likely results in lower density on CT imaging.

Mediastinal lymph node enlargement caused by PE has been investigated previously.[7-10] Shweihat and colleagues found that frequent occurrence of mediastinal lymph node enlargement is commonly seen in cardiac failure, and is linked to acute volume overload rather than long term congestive heart failure.[7] While their study contributed to the patterns of nodal enlargement, such as multistation mediastinal involvement, it did not address the MLND as a diagnostic parameter.

Previous researches have conducted HU measurements in cases such as sarcoidosis and in malignant lymph nodes.[4,6] These studies have shown the utility of HU thresholds in differentiating malignant from benign lymph nodes.[12-14] Future research focusing on the differentiation of malignant lymph nodes from conditions like edema may open new pathways for noninvasive diagnostic techniques. By measuring MLND in various benign conditions, future studies may contribute to a more comprehensive understanding of how imaging biomarkers can refine diagnostic accuracy and reduce unnecessary invasive procedures. MLND measurement may provide a practical, quick, and reproducible method based on routine non-contrast chest CT scans. MLND can be assessed without additional procedures and reflects both the presence and radiological severity of PE. Compared to other conventional radiological signs, MLND offers a quantitative measurement, which may enhance diagnostic confidence. In addition to its diagnostic potential, the observed difference in MLND values between alveolar and IE indicates that MLND may serve as a useful parameter for assessing the radiological severity of PE. These features support the potential role of MLND as a complementary tool in clinical decision-making and stratification of cardiogenic PE. Further large-scale studies are warranted to validate its integration into routine imaging protocols and to explore its role in diverse patient populations. Moreover, MLND measurements could complement the findings like interlobular septal thickening and the presence of ground glass opacities or pleural effusions to distinguish between IE and AE.

We should also acknowledge certain limitations in our research. The retrospective method might restrict the generalizability of the findings, and the potential for selection bias cannot be ignored. Future investigations should confirm our findings in larger cohorts and explore the effect of preexisting conditions on MLND. Although PE diagnosis was based on both imaging and clinical parameters, overlapping CT findings with other conditions, such as pneumonia, may still present a limitation. MLND HU measurements could have been influenced by minor variations in tube voltage (kVp) and current (mAs) across patients, even though a standardized CT protocol was followed. This technical variability is also a limitation. Such variations are not only limited to our patient population but may also occur across different patient groups and imaging centers. Future research should prioritize the implementation of automated exposure control systems and standardized acquisition protocols to ensure consistency and comparability of HU-based measurements in multicenter settings. Measurements were performed three times at separate time points by the same radiologist to reduce intra-observer bias; however, inter-observer variability was not assessed and remains a limitation. Another limitation is that MLND measurements can vary depending on whether the CT scan was contrast-enhanced. Since intravenous contrast may increase the attenuation of lymph nodes, we excluded all contrast-enhanced CT scans from this study to ensure consistency in HU measurements.

CONCLUSION

In conclusion, MLND may be a promising radiological parameter for assessing PE severity. However, its clinical applicability requires further validation through multicenter, prospective studies before it can be recommended for routine use.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

This study is entirely author's own work and no other author contribution.

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