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The benefit of expiratory-phase quantitative CT densitometry in the early diagnosis of chronic obstructive pulmonary disease

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PURPOSE
We aimed to compare the inspiratory and expiratory quantitative computed tomography (CT) densitometric data of healthy volunteers, individuals with chronic obstructive pulmonary disease (COPD) risk, and COPD patients to aid in the early diagnosis of COPD.

MATERIALS AND METHODS
Of the study patients, 14 were healthy volunteers (Group I), 12 were patients at risk for COPD (Group II), and 13 were COPD patients (Group III). The high-resolution CT was performed at three levels (the upper, middle, and lower parts of the lungs). All images were evaluated with a specific program for the segmentation of pulmonary parenchyma. The mean lung density (MLD) was measured, and the emphysema index (EI) was calculated using this program.

RESULTS
Both MLD values and calculated EI ratios showed significant differences between Groups I and III, and Groups II and III in both expiratory and inspiratory phases ($P < 0.05$). However, in the comparison of healthy volunteers and patients at risk for COPD (Group I and II), only expiratory-phase MLD values showed statistically significant difference ($P < 0.001$).

CONCLUSION
In patients at risk for COPD, expiratory-phase MLD measurements can be used as an early diagnostic method.

Key words: • chronic obstructive pulmonary disease (COPD) • early diagnosis • CT densitometry • expiratory phase

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As a progressive illness, chronic obstructive pulmonary disease (COPD) is a public health problem that significantly increases the rate of mortality and morbidity and is one of the leading causes of death (1). Chronic air flow limitation in COPD is caused by a mixture of a small-airway disease (obliterative bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person (2). A pulmonary function test (PFT) is the method most commonly used to detect airway obstruction (3). However, PFT is usually inadequate for the prompt diagnosis of people at risk for COPD (2). Inflammatory markers are also insufficient for diagnosis (4).

Currently, computed tomography (CT) scanning is accepted as a method that is more sensitive than PFT for use in diagnosing changes in the pulmonary parenchyma, particularly emphysematous changes in a person with COPD (3, 5). In the literature, the quantitative CT densitometry evaluation is preferred to visual assessment (6) and is accepted as a COPD diagnostic method (7, 8) that can be used to help differentiate COPD phenotypes (emphysema-predominant, airway-predominant, and mixed) (3).

The previous studies were inconclusive as to whether inspiratory CT or expiratory CT is better for evaluating the severity of COPD and whether one or the other was better at identifying emphysematous changes (9, 10).

We aimed to compare the inspiratory and expiratory quantitative CT densitometry data of healthy volunteers, patients with COPD risk, and COPD patients to investigate the contribution of quantitative CT densitometry in the early diagnosis of COPD.

Materials and methods

In this study, we evaluated 14 healthy male volunteers (Group I, control group), 12 male patients at risk for COPD (Group II), and 13 male COPD patients (Group III). COPD was diagnosed according to the criteria established by the Global Initiative for Chronic Obstructive Lung Diseases (GOLD) (2) and by the use of spirometry testing, consistent with irreversible expiratory airflow obstruction. The inclusion criteria were male sex, age of 40 to 60 years, and a body mass index (BMI) below 30 kg/m^2. The inclusion criterion for the control group was a forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) of >70%.

Written informed consent was obtained from all participants before the procedure. The experimental protocol was approved by the Ethical Committee of Zonguldak Karaelmas University.

Patients with non-COPD pulmonary diseases, such as clinically-diagnosed or suspected cardiac history, bronchial asthma, bronchiectasis, collagen tissue disease, acute infection, and malignancy were excluded from the COPD group. Participants were excluded from Groups I and II if they were known to have pulmonary disease and if their forced

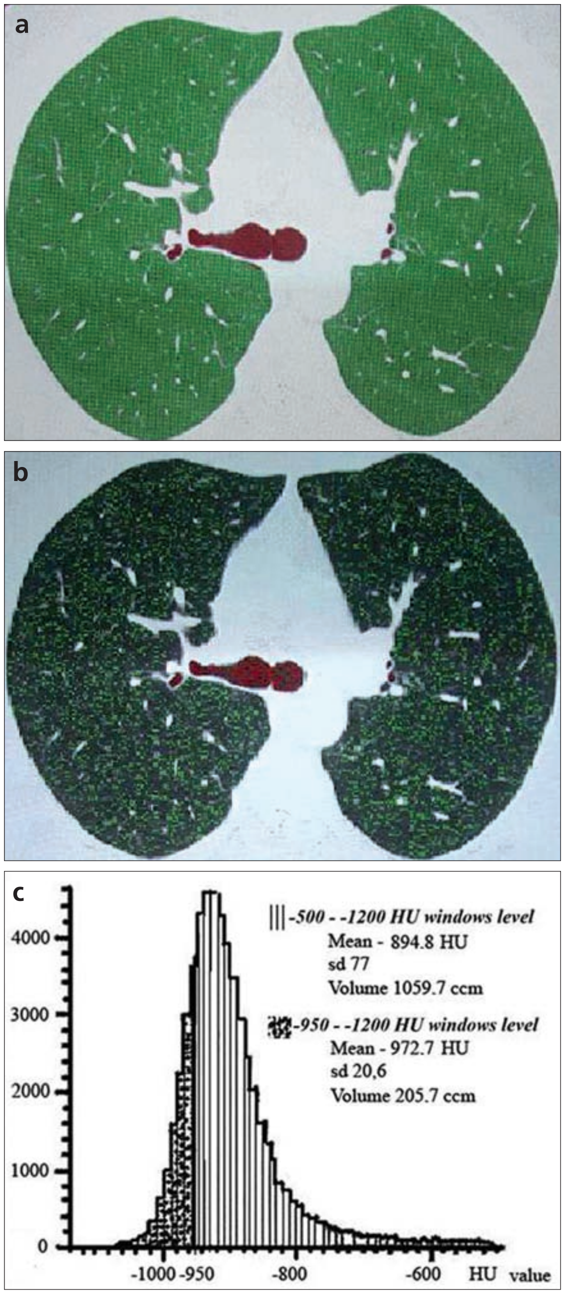

Figure 1. a–c. Color map of transverse CT images at the level of the carina demonstrate segmentation of the lungs in total lung parenchyma (-500 to -1200 HU intervals) **(a)** and emphysematous lung areas (-950 to -1200 HU intervals) **(b)**. Mean lung density (MLD) measurements were presented with the numerical measurement histogram analysis for the two threshold values **(c)**. sd, standard deviation; ccm, cm^3.

maximal mid-expiratory flow (MMEF) rate was below 50%. MMEF rate below 50% was considered to be an indicator of small-airway obstruction. Patients with COPD (in a stable period) and participants in the healthy control group were evaluated with PFT by means of a spirometer computing system (Jaeger Master Screen, MS Pneumo, Erich Jaeger GmbH, Hoechberg, Germany). PFT was measured by the same trained technician and the PFT results were evaluated by the same chest physician. FEV_1, FVC, FEV_1/FVC, and MMEF were measured. FEV_1, FEV_1/FVC, and MMEF values were used to determine air flow disruption. The PFT results were evaluated according to GOLD criteria updated in 2009 (10). The study groups were defined as follows:

Group I: Healthy volunteers with normal PFT (FEV_1/FVC ≥70% and FEV_1 ≥80% [predictive]) were classified as the control group.

Group II: Patients with chronic cough and sputum production symptoms and normal PFT (FEV_1/FVC ≥70% and FEV_1 ≥80% [predictive]) were classified as being at risk for COPD.

Group III: COPD patients as determined by FEV_1/FVC <70% and FEV_1 <80% (predictive) measurements.

All subjects were evaluated with high-resolution CT (HRCT) within one week after administration of the PFT. Before the HRCT procedure, all of the subjects rested. Respiratory exercises were then taught and applied to ensure that each of the participants was able to sufficiently inhale and exhale during the HRCT procedure. The adequacy of inspiration and expiration were determined by an experienced radiologist. The criteria for adequate inspiration and expiration were determined according to the diameter of the participant's trachea and bronchia. The HRCT scan was performed by Philips Secura CT (Philips Medical Systems, Best, the Netherlands), which was calibrated regularly with water and air phantoms. Inspiratory and expiratory HRCT scans were obtained at three levels, namely, the aortic arch, the carina, and the inferior pulmonary vein (IPV) levels, to represent the upper, middle, and lower parts of the lungs. A total of six slices were acquired in each patient. All images were obtained with the patient in the supine position using 120 kVp, 200 mAs, and 1-mm slice thickness. The inspiratory-phase images were obtained at suspended inspiration, and expiratory images were obtained during end-expiration with the same parameters. The images were reconstructed using routine adult thorax and a 512×512 matrix.

Segmentation of the pulmonary parenchyma was performed at a workstation terminal (Easy Vision, Version 5.1.1.2, Philips Medical Systems, Best, the Netherlands) using a histogram analysis program for all slices. The lung parenchyma was automatically segmented according to the predefined upper and lower threshold limits. Dual threshold values (-500 to -1200 Hounsfield unit [HU] intervals for the total lung parenchyma in one slice and -950 to -1200 HU intervals for the emphysematous lung areas in the same slice) were selected according to previous literature (9, 11, 12). All images below or above the threshold values were excluded from the measurement. In addition, the trachea; main bronchus; right and left upper, middle, lower bronchi; and hilar blood vessels were excluded manually in every slice. The histogram method was used to obtain numerical measurements for the two segmented window levels (Fig. 1). The mean lung density (MLD) was measured with this method. The emphysema index (EI) is calculated as an emphysematous lung volume between intervals of -950 and -1200 HU, divided by total lung volume, which is measured between intervals of -500 and -1200 HU for each slice (13). The -950 HU value used to calculate the EI was adapted from studies that used a similar technique and which had the best correlation with pathological assessment (9, 12). In this study, -1200 HU was used as the lowest threshold unit, similar to a previous report (11). Thus, MLD, EI ratios, the average MLD values, and the average EI ratios were calculated at three levels for three lung segments.

All analyses were conducted with a commercially available software (Statistical Package for Social Sciences, version 17, SPSS Inc., Chicago, Illinois, USA). The statistical differences between Groups I, II, and III were examined using the Kruskal-Wallis H test and the Mann-Whitney U test. P values < 0.05 were considered to be significant.

Results

All of the participants were between the ages of 42 and 60 years with mean ages of 49.07±5, 54.54±5.2, and 51.55±6.47 years, in Groups I, II, and III, respectively. The mean BMI for Groups I, II, and III was 26.61±2.21, 25.59±5.3, and 25.45±2.89 kg/m^2, respectively. No statistical difference was found between groups for age (P = 0.068) and BMI (P = 0.484).

The PFT results are summarized in Table 1. The PFT results of Groups I and II were normal according to GOLD 2009 criteria (10). The PFT results showed significant differences among the three groups. The PFT results of Group III were significantly different from those of Groups I and II.

All of the MLD values and the EI ratios were significantly different between the groups (P < 0.05) except for the inspiration phase assessment of the IPV levels (Tables 2 and 3) in the quantitative CT densitometry assessment. The results of the quantitative CT densitometry assessment for inspiration and expiration phases are presented in Figs. 2 and 3. For the inspiratory and expiratory phase of the quantitative CT densitometry assessment, the MLD values for Group I were higher than the MLD values for Groups II and III. However, a statistically significant difference between Groups I and II was found only in the expiratory phase of the quantitative CT densitometry assessment. These significant differences were not observed in the inspiratory phase quantitative CT densitometry assessment. The MLD values for the inspiratory phase and the expiratory phase were significantly higher for Group

Table 1. The pulmonary function test results as mean±standard deviation among the study groups

	Group I (n=14)	Group II (n=12)	Group III (n=13)	P^a
FVC	105. 44±10.15	100.52± 14.16	88.71±8.6	0.002
FEV_1	107.29±12.03	94.06±12.42	66.01±6.95	< 0.001
FEV_1/FVC (%)	82.58±3.8	76.05±3.49	59.96±5.33	< 0.001
MMEF (%)	95.42±19.05	62.63±11.15	28.47±6.1	< 0.001

[a]Kruskal-Wallis H test
FVC, forced vital capacity; FEV_1, forced expiratory volume in the first second of expiration; FEV_1/FVC, ratio of FEV_1 to FVC; MMEF, maximal mid-expiratory flow rate.

Table 2. The mean (±standard deviation) lung density according to quantitative CT densitometry among the study groups

	Group I (n=14)	Group II (n=12)	Group III (n=13)	P^a
Inspiratory phase				
Aortic arch	-868.60±15.17	-876.08±25.59	-900.06±22.47	< 0.001
Carina	-870.14±13.3	-871.58±20.18	-888.48±26.18	0.01
IPV	-866.94±16.17	-866.07±21.37	-876.60±23.07	0.093
Average	-868.56±14.73	-871.24±20.71	-888.38±20.69	0.014
Expiratory phase				
Aortic arch	-749.80±27.47	-779.17±45.15	-844.81±48.23	< 0.001
Carina	-750.26±36.13	-782.85±26.8	-830.78±40.58	< 0.001
IPV	-744.38±38.88	-785.94±30.99	-820.89±31.84	< 0.001
Average	-748.14±33.03	-782.65±28.42	-832.16±38.18	< 0.001

[a]Kruskal-Wallis H test.
IPV, inferior pulmonary vein.

Table 3. The emphysema index (mean±standard deviation) according to quantitative CT densitometry among the study groups

	Group I (n=14)	Group II (n=12)	Group III (n=13)	P^a
Inspiratory phase				
Aortic arch	16.96±05.04	20.25±12.37	31.00±13.14	0.001
Carina	16.73±4.63	16.25±7.85	24.69±11.74	0.031
IPV	15.20±4.74	14.83±6.56	19.39±7.15	0.153
Average	16.34±4.65	17.17±8.58	25.08±9.94	0.009
Expiratory phase				
Aortic arch	5.13±2.44	7.92±10.21	19.08±15.23	0.002
Carina	3.50±1.7	5.67±5.93	12.77±9.11	0.001
IPV	3.48±1.89	5.17±3.13	10.08±5.48	0.003
Average	4.08±1.93	6.33±5.96	13.92±9.22	0.001

[a]Kruskal-Wallis H test.
IPV, inferior pulmonary vein.

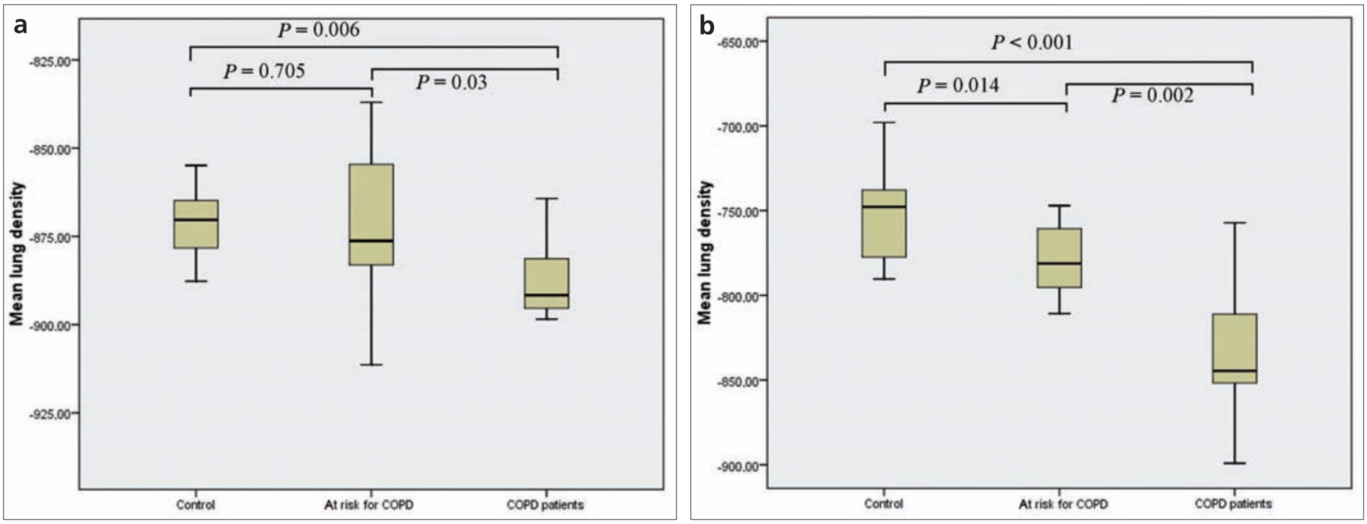

Figure 2. a, b. Box plots (minimum–maximum, median, and 25th–75th percentiles) showing the mean lung density (MLD) results at inspiration **(a)** and expiration **(b)**. There was statistically significant difference between Groups I and II only in the expiratory phase. The MLD values of Group III were significantly different from those of the other groups. COPD, chronic obstructive pulmonary disease.

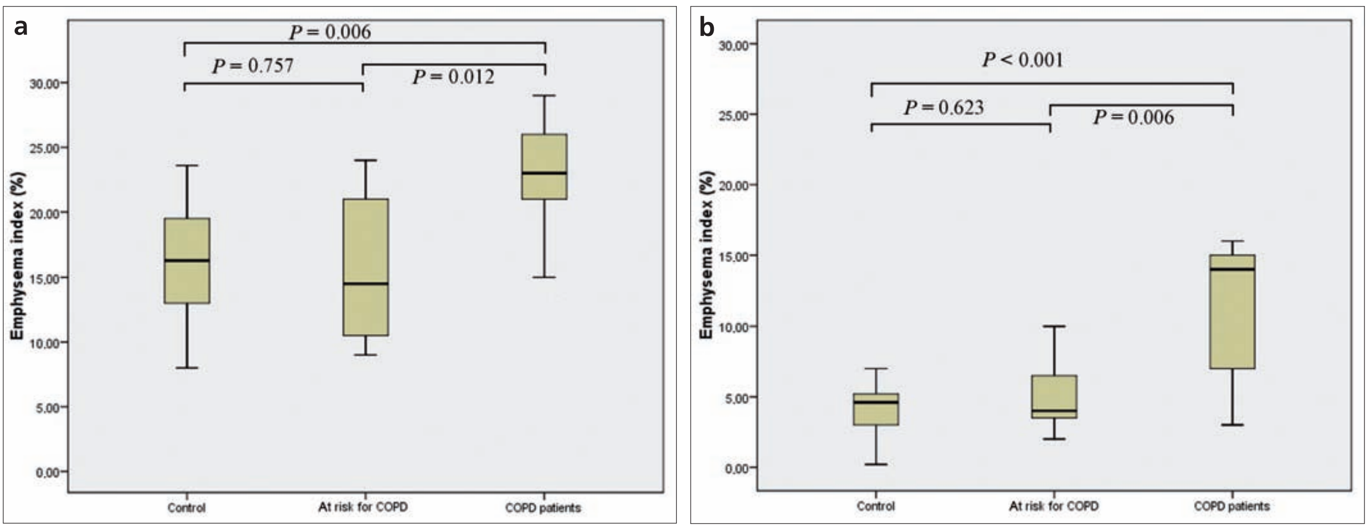

Figure 3. a, b. Box plot (minimum–maximum, median, and 25th–75th percentiles) showing the emphysema index (EI) ratios at inspiration **(a)** and expiration **(b)**. There was no statistically significant difference between Groups I and II. The EI ratios of Group III were significantly different from the other groups. COPD, chronic obstructive pulmonary disease.

II than for Group III (Fig. 2). The EI ratios for Group I were lower than the EI ratios for Groups II and III in the inspiratory and expiratory phase quantitative CT densitometry assessments. However, no statistically significant differences were found in the EI ratios between Groups I and II. The inspiratory and expiratory phase EI ratios were significantly lower in Group II than they were in Group III (Fig. 3).

Discussion

Emphysema, chronic bronchitis, or a combination of the two, underlies COPD, which is one of the leading health problems related to mortality, morbidity, and economic burden (14). New medicines and methods are being developed to treat this illness, and new methods are being developed for its early diagnosis (12).

The morphometric estimation at pathological examination represents the gold standard for the evaluation of pulmonary emphysema; the pathophysiological hallmark of COPD is expiratory flow limitation (6, 15). Treatment guidelines note that PFT is the preferred method for the diagnosis of COPD (2, 3). Radiological studies, such as HRCT and CT densitometry, are frequently used to evaluate the extent and severity of parenchymal destruction (6, 16). The destructive changes in the alveolar walls distal to the terminal bronchioles result in an increased amount of air per unit area of lung parenchyma, which, in the HRCT, is visualized as areas of lower attenuation. Furthermore, in normal, healthy individuals, a general increase is observed in the density of the lung tissue after expiration. However, in patients with emphysema, this increased amount of air per unit of area of the lung tissue is less than expected due to air trapping in the damaged parenchyma (7, 12, 17).

Quantitative CT densitometry is based on the detection of air trapping. Air trapping indicates the retention of excess gas, and this air is detected as decreased attenuation in an expiratory

CT as compared to an inspiratory CT. Moreover, in COPD patients, decreased attenuation also denotes the presence of emphysema (18). Cavigli et al. (6) revealed that quantitative CT densitometry is a method that should be preferred to visual assessment because it enables a more reproducible evaluation of the extent of pulmonary emphysema. In 1997, Gierada et al. (19) found a high correlation between quantitative CT densitometry scan values and preoperative physiologic values in 46 patients who underwent lung volume reduction surgery for palliation for severe emphysema. Gierada et al. (19) also found a high correlation between quantitative CT densitometry scan values and outcome measures in those study participants. Quantitative CT densitometry of emphysema is highly valuable in the assessment of pulmonary functions, in the planning of surgical treatment, and in the application of pharmacotherapy methods (17, 20). Furthermore, a research study conducted by Stolk et al. (21) revealed that, in a 30-week follow-up of COPD patients, CT densitometries varied more than PFTs.

The literature stated that an examination of the HRCT images of healthy individuals, taken at the inspiratory phase, show that their MLDs are usually between -700 HU and -900 HU and that they are relatively homogenous (12). In our study, we found that, for healthy individuals, the full lung average MLD value was -868.56 HU in the inspiratory phase and -748.14 HU in the expiratory phase. For patients at risk for COPD, the average MLD value was -871.24 HU in the inspiratory phase and -768.65 HU in the expiratory phase. MLD values for COPD patients were -888.38 HU for the inspiratory phase and -832.16 HU for the expiratory phase. Kauczor et al. (12) reported that the mean MLD of the control group was -806 HU in the inspiratory phase and -703 HU in the expiratory phase, whereas in the group diagnosed with obstructive disease, the mean MLD was -833 HU in the inspiratory phase and -781 HU in the expiratory phase. Temizoz et al. (22) reported that the mean MLD of the inspiratory phase was -898 HU in patients with emphysema and -825 HU in the control group.

Furthermore, for healthy individuals in our study, the average EI ratio was 16.34% in the inspiratory phase and 4.08% in the expiratory phase. In patients at risk for COPD, the average EI ratio was 17.17% in the inspiratory phase and 6.33% in the expiratory phase. In COPD patients, this ratio was 25.08% in the inspiratory phase and 13.92% in the expiratory phase. Kauczor et al. (12) reported that, in the control group, the mean EI ratio was 2% in the inspiratory phase and 0.3% in the expiratory phase; in patients with obstructive disease, the authors calculated the mean EI ratio to be 12.7% in the inspiratory phase and 10.1% in the expiratory phase. In a study conducted by Gevenois et al. (23), which evaluated patients who underwent surgery due to pulmonary cancer and/or emphysema, the mean EI ratio was found to be 8.5% at the -950 HU threshold value in the inspiratory phase and 9.8% at the -910 HU threshold value in the expiratory phase. In emphysematous patients, Zaporozhan et al. (24) found that the EI ratio was 54% in the inspiratory phase and 43% in the expiratory phase.

Although the inspiratory and expiratory phase MLD values and the EI ratios calculated in the inspiratory and expiratory phases of healthy volunteers and COPD patients in our study were generally similar to those in the literature, some of the values differed from the findings reported by others (12, 23, 24). Some of the reasons for this difference might be that the age span in the previous studies was very wide, and the BMI and gender of the participants were not taken into consideration. Moreover, those studies used different threshold values. We suggest that part of the differences might also originate from the technical parameters used in the CT scanning, such as mAs, slice thickness, matrix, and the threshold values used for segmentation. Researchers have stated that a correlation occurs between the age and densitometry measurements as the age of healthy individuals increases (25, 26). Goodpaster et al. (27) reported a strong correlation with increased fat ratios and decreased attenuation values in CT scans. Furthermore, Lazarus et al. (26) reported that BMI correlated negatively with FVC and positively with FEV_1 and FEV_1/FVC. Collins et al. (28) reported a negative correlation between the BMI and the FVC. Although Gevenois et al. (25) did not find a correlation between age and MLD measurements in the studies they conducted with healthy individuals; they did find a distinctive correlation between age and EI ratios. Kauczor et al. (12) performed their study on individuals between the ages of 18 and 86 years without considering gender. By taking these factors into consideration, our study was conducted with men between the ages of 40 and 60 years, whose BMI was below 30 kg/m^2. Therefore, we believe that most of the numerical and some of the statistical differences in our findings result from differences in the methodological approaches that were used.

Our study found a significant difference between the MLD values and the EI ratios of healthy volunteers and COPD patients in both the inspiratory and expiratory phases. This finding supports the results presented in previous literature. Additionally, the COPD patients in our study were classified as Stage II based on GOLD criteria, which is an earlier stage than the participants involved in research studies presented elsewhere (2). In the literature, a significant correlation has been reported between quantitative CT assessment and PFT (12, 22–24, 29–31). However, Kauczor et al. (12) did not compare participants based on COPD stages. Gevenois et al. (23) evaluated patients who underwent surgery due to pulmonary cancer and/or emphysema, and reported mean FEV_1 of 70% (range, 13%–112%), which reflects a wide range using a different threshold value. That study found that the inspiratory phase was more meaningful than the expiratory phase. In studies conducted by Zaporozhan et al. (24) and Akira et al. (29), researchers enrolled patients who were mostly at moderate and severe stages of COPD, according to PFT results. Akira et al. (29) found that the patient's COPD stage affected the results. They found that in patients with mild or moderate COPD, inspiratory scans reflect airflow limitation better than expiratory scans ($FEV_1 \geq 50\%$), whereas, in patients with severe COPD, expiratory scans reflect airflow limitation better than inspiratory scans ($FEV_1 < 50\%$) (29). Zaporozhan et al. (24) indicated that, in patients with severe emphysema, expiratory multidetector CT (MDCT) scans reflect PFT abnormalities better than inspiratory scans. Moreover, Temizoz et al. (22) studied patients with severe-stage emphysema, in whom the mean FEV_1 was 49%. The results showed that, in patients with emphysema, quantitative confirmation should be used in combination with other radiological methods and PFT. However, the authors did not administer a CT scan during the expiratory phase. Kauczor et al. (12) and Spiropoulos et al. (30) reported a correlation between MLD values measured in both inspiratory and expiratory phases and PFT. They found that PFT was somewhat higher in the expiratory phase. While Matsuoka et al. (31) concluded that paired inspiratory and expiratory CT could be useful for the quantitative evaluation of air trapping in COPD without the influence of emphysema, we found that expiratory CT densitometry is more useful than inspiratory CT densitometry in both COPD patients and patients at risk for COPD. Contrary to findings presented in the previous research studies conducted on patients with moderate and severe stages of COPD, our study examined patients at risk for COPD and patients who had Stage 2 COPD, as determined by the GOLD criteria. With the exception of Kauczor et al. (12) and Temizoz et al. (22), the other studies did not include any healthy controls. To the best of our knowledge, this study is the first in the literature designed to evaluate the results of quantitative CT densitometry as used to distinguish normal individuals from individuals at risk for COPD. In previous studies, researchers usually revealed only the correlation between PFT and quantitative CT densitometry assessment in determining the severity of COPD. Furthermore, our study showed that quantitative CT densitometry assessment, especially with regard to MLD values obtained during the expiratory phase, is superior to PFT for the early diagnosis of COPD risk in individuals whose PFT results fall within the normal ranges.

We also found that the MLD values obtained during inspiratory quantitative CT densitometry were similar between healthy volunteers and patients at risk for COPD (Table 2). We think that this is due to the expiratory flow limitation present in people with COPD (15). Therefore, no significant difference was found during the inspiratory-phase quantitative CT densitometry assessment. Additionally, both the MLD value and the EI ratio showed no significant difference at the IPV levels during the inspiratory-phase quantitative CT densitometry assessment (Tables 2 and 3). We think that prominent vascular and bronchial tissue at the IPV level may have caused this result.

This study has some limitations. First, our study groups were small; however, our results were statistically significant. Second, while X-ray exposure is an important problem in radiologic diagnostic methods, low-dose CT may be a clinically acceptable and diagnostically adequate technique for the CT quantification of emphysema. We tried to minimize the radiation dose by taking only three levels of scans, and the quantitative CT densitometry was evaluated using only six slices. Third, the volumetric MDCT studies for COPD have been studied, and significant results were reported recently (18, 29, 32). Volumetric MDCT studies are representative of the entire lung. However, the technical properties of our device were not conducive to whole-lung volumetric measurements. Therefore, we chose three lung levels, which were representative of the upper, middle and lower parts of the lungs. Fourth, no pathological correlations for the evaluation of pulmonary emphysema were applied in our COPD patients. However, similar to previous studies that used different thresholds for quantification, we preferred to use the -950 HU value, which has the best correlation with pathological assessment (9, 12). In spite of these limitations, our study contributes to the literature because it utilized partially homogenous groups. Data were categorized according to age, gender, and BMI parameters, which influenced the resulting MLD values and EI ratios.

In conclusion, the early diagnosis of COPD is necessary and is an important issue for preventing serious mortality, morbidity, and economic burden. Our study demonstrated that quantitative CT densitometry assessment (especially expiratory-phase MLD measurements) is significant in COPD patients and in patients at risk for COPD. In patients suspected to be at risk for COPD, who have normal pulmonary function tests, expiratory-phase MLD measurements can be used as an early diagnostic method. Additional quantitative CT densitometry studies are needed before this test can be used as a supplementary method concurrent with clinical symptoms in the early diagnosis of COPD.

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Conflict of interest disclosure

The authors declared no conflict of interest.

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