Diaphragm Ultrasound Distinguishes Exacerbation From Stable Status in Chronic Obstructive Pulmonary Disease

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Abstract

**Background:** The importance of evaluating the diaphragm muscle in chronic obstructive pulmonary disease (COPD) is widely accepted. However, the role of diaphragm ultrasound (DUS) in COPD is not fully understood. We set this study to evaluate the role of DUS for distinguishing the status of COPD.

**Methods:** COPD patients who underwent DUS were enrolled between March 2020 and November 2020. The diaphragm thickening fraction ($TF_{\text{max}}$) and diaphragm excursion ($DE_{\text{max}}$) during maximal deep breathing were measured. Patients were divided into exacerbation and stable groups. Demographics, lung function, and DUS findings were compared between the two groups. Receiver operating characteristic (ROC) curve and univariate/multivariate logistic regression analyses were performed.

**Results:** Fifty-five patients were enrolled. The exacerbation group had a lower body mass index (BMI) (20.9 vs. 24.2, $p = 0.003$), lower $TF_{\text{max}}$ (94.8 ± 8.2% vs. 158.4 ± 83.5%, $p = 0.010$), and lower $DE_{\text{max}}$ (30.8 ± 11.1 mm vs. 40.5 ± 12.5 mm, $p = 0.007$) compared to stable group. The areas under the $TF_{\text{max}}$ (0.745) and $DE_{\text{max}}$ (0.721) curves indicated fair results for distinguishing exacerbation. The patients were divided into low and high $TF_{\text{max}}$ and $DE_{\text{max}}$ groups based on calculated cut-off values. Low $TF_{\text{max}}$ (odds ratio [OR] 8.40; 95% confidence interval [CI] 1.55–45.56) and low $DE_{\text{max}}$ (OR 11.51; 95% CI 1.15–115.56) were associated with exacerbation after adjusting for age, sex, BMI, forced vital capacity, and forced expiratory volume in 1 sec.

**Conclusion:** $TF_{\text{max}}$ and $DE_{\text{max}}$ distinguished exacerbation from stable status. We describe the DUS cut-off values for determining an exacerbation status in this study.

Background

Chronic obstructive pulmonary disease (COPD) is a common chronic airway disease characterized by chronic airway inflammation with persistent airflow limitation\(^1,2\). The diaphragm muscle is key in the respiration process, and it is important to understand lung exercise physiology and the mechanics of COPD\(^3,4\). Previous studies have shown that atrophy or dysfunction of the diaphragm is related to poor COPD outcomes\(^5\).

An evaluation of the diaphragm is necessary for COPD patients but is difficult to achieve. The gold standard for evaluating diaphragm function is measuring trans-diaphragmatic pressure using an electromyogram during phrenic nerve stimulation or via maximal static inspiratory pressure, which is an invasive and time-consuming technique\(^6\). By contrast, diaphragm ultrasound (DUS) is an emerging alternative technique for evaluating the diaphragm muscle\(^7-13\). It is a non-invasive, real-time, and intuitively understandable method for evaluating various aspects of the diaphragm\(^10,11\). The method and effects of DUS in COPD patients have been well described by previous studies\(^7,8\). However, few studies have compared DUS findings between patients with a stable status and those with acute exacerbation of COPD\(^9,10\). Also, there are no data about the value of diaphragm markers for distinguishing exacerbation...
from a stable status. We designed this study to analyze differences in diaphragm markers according to COPD status and identify potential exacerbation factors.

**Methods**

**Study Subjects**

COPD patients were retrospectively recruited between March 2020 and November 2020 at Yeouido St. Mary’s Hospital. They were diagnosed with COPD by pulmonologists. The patients were ≥ 40 years of age and satisfied the spirometry definition of persistent airflow limitation, such as a post-bronchodilator forced expiratory volume in 1 sec/forced vital capacity ratio (FEV₁/FVC) < 0.70.

Among them, patients who underwent DUS were enrolled. DUS was performed in the stable COPD group when they visited the outpatient clinic for a regular follow-up. DUS was performed within 48 hours of admission in patients with acute exacerbation. Exacerbation was defined by an acute change in respiratory symptoms requiring a medication change, such as a systemic steroid or antibiotics. Patients who required hospitalization had the following indications: 1) acute respiratory failure, 2) cyanosis or edema, 3) very severe symptoms, such as dyspnea at rest or mental change, 3) severe comorbidities, such as cardiovascular disease, and 4) need for refractory to acute management. Patients who did not undergo DUS or underwent DUS after 48 hours of admission were excluded. Patients with confounding factors of diaphragm function, such as hemiplegia, quadriplegia, sequelae from an abdominal or thoracic operation, or diaphragm paralysis due to phrenic nerve palsy, were also excluded. All patients enrolled in this study completed the modified Medical Research Council (mMRC) scale, COPD assessment test (CAT), and history taking for comorbidities.

**Comorbidities**

Histories of medication and comorbidities were collected during the DUS exam. Electrical medical records were reviewed to confirm the comorbidities of the patients. The modified Charlson Comorbidity Index (mCCI), in which the chronic pulmonary disease categories are removed, was calculated to predict prognosis and mortality based on the ICD-10 diagnosis for the COPD patients.

**Diaphragm ultrasound protocol**

All DUS exams were performed with a single high-resolution ultrasound machine (Affiniti 70, Phillips, Inc., Best, the Netherlands). The exams were conducted by a respiratory physician who specializes in DUS. DUS findings are well established in many studies. Patients were placed in a supine position, and the tests were performed at the right hemidiaphragm. A linear ultrasound probe (5–12 MHz) was used to measure the thickness of the diaphragm. Diaphragm excursion was measured with a convex ultrasound probe (1–5 MHz). B-mode was used to measure the thickness of the diaphragm (DT), and diaphragm
excursion (DE) was measured in M-mode. These measurements were repeated three times in the same position and the mean value was used as the representative value.

Diaphragm thickness and diaphragm excursion

DT was measured in the zone of opposition in the right hemithorax over the mid-axillary line between the eighth and eleventh intercostal spaces in longitudinal intercostal view. DT was defined by the distance between the diaphragmatic pleura and the peritoneal membrane. First, it was measured at the end of expiration, which is correlated with functional residual capacity. Then, it was measured at the end of the inspiration during both quiet tidal breathing and maximal deep breathing.

DE was measured at the anterior subcostal margin of the right hemidiaphragm. A convex probe was positioned below the costal margin at the mid-clavicular line. The incidence angle of the ultrasound beam was perpendicular to the posterior third of the diaphragm, or the so-called DE line. The DE was the diaphragm inspiratory amplitude during respiration measured at the DE line in M-mode. DE was measured during quiet tidal breathing and maximal deep breathing (DE$_{max}$) (see Supplemental Figure 1).

Diaphragm thickening fraction

The thickening fraction of the diaphragm (TF) has been evaluated in many studies$^{7,8,12}$. It is related to the generation of diaphragm muscle pressure. The TF was calculated with the DT value. TF was defined as the ratio of DT changes between the end of expiration and the end of inspiration. The TF equation was 

\[
\frac{(DT \text{ at end-inspiration}) - (DT \text{ at end-expiration})}{(DT \text{ at end-expiration})} \times 100.
\]

TF was also calculated during tidal breathing and maximal deep breathing (TF$_{max}$).

Statistical analyses

We used Student’s $t$ test and the Mann-Whitney $U$ test for analyzing continuous variables according to the normality test results. Pearson’s chi-square test or Fisher’s exact test were used to compare categorical variables between groups. A receiver operating characteristic (ROC) curve analysis was performed to evaluate the usefulness of the DUS findings for classifying the exacerbation group. The Youden index was used to identify the optimal cut-off value and compare the ROC curves. Binary univariate and multivariate logistic regression analyses were conducted to calculate the odds of being classified in the exacerbation group. A $p$-value $< 0.05$ was considered to indicate significance. Student’s $t$ test, the Mann-Whitney $U$ test, Pearson’s chi-square test, Fisher’s exact test, and the logistic regression analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). The ROC curve analyses, the Youden’s index, and the comparison of the ROC curves were performed using MedCalc® Statistical Software version 19.5.6 (MedCalc Software Ltd., Ostend, Belgium; https://www.medcalc.org; 2020).
Ethics approval

This study was approved by the Institutional Review Board of The Catholic University of Korea Yeouido St. Mary's Hospital (approval no. SC20RIS0181). The need for informed consent was waived due to the retrospective nature of the study.

Results

Demographics of study subject

Fifty-five COPD patients were enrolled in the study. Twenty-two were classified as having an acute exacerbation status (AE group) and the remainder had a stable status (stable group). No significant differences in age, sex, mCCI, or COPD medication were observed between the groups. The AE group had a lower BMI than the stable group (20.9 vs. 24.2 kg/m², p = 0.003). Scores of the symptom and dyspnea scales, such as the CAT (25.4 ± 8.2 vs. 13.7 ± 3.8, p < 0.001) and mMRC (3.1 ± 1.0 vs. 1.7 ± 1.2, p < 0.001), were significantly higher in the AE group than in the stable group. Smoking status and the baseline Global Initiative for Chronic Obstructive Lung Disease grouping differed between the two groups. Lung function was different between the two groups. Absolute values and predictive percentages of FVC and FEV₁ were significantly lower in the AE group than in the stable group. The air-trapping index (residual volume/total lung capacity) was higher in the AE group than in the stable group (51.7 ± 9.4 vs. 43.7 ± 8.1, p = 0.019) (Table 1).

DT at end-expiration and end-inspiration during quiet tidal breathing, and at end-inspiration during maximal deep breathing did not differ between the two groups. TF and DE during quiet tidal breathing did not differ between the AE and stable groups. TFₘₐₓ and DEₘₐₓ were significantly lower in the AE group than in the stable group compared to values during tidal breathing (94.8 ± 8.2% vs. 158.4 ± 83.5%, p = 0.010; 30.8 ± 11.1 mm vs. 40.5 ± 12.5 mm, p = 0.007, respectively) (Table 1).

Diaphragm ultrasound distinguished acute exacerbation from stable status in COPD patients well

ROC curve analyses of TFₘₐₓ and DEₘₐₓ for distinguishing the AE group were performed. The areas under the curve (AUC) for TFₘₐₓ and DEₘₐₓ were 0.745 and 0.721, respectively (Figure 1 and Table 2). The maximal Youden’s index was summarized for the maximum potential effectiveness of variables with optimal cut-off values. The TFₘₐₓ cut-off value was 93.8% (sensitivity 68.4%, specificity 78.8%) and that of DEₘₐₓ was 44.9 mm (sensitivity 95.2%, specificity 44.8%) (Table 2). No significant difference in TFₘₐₓ and DEₘₐₓ (p = 0.608) was observed when the ROC curves were compared (Figure 1).

We also conducted ROC curve analyses for the other variables, such as the absolute values of FVC, FEV₁, and BMI, because these variables are well-known exacerbation factors from previous studies. These
variables exhibited clinical significance in the ROC curve analyses (Table 2). Therefore, we conducted multiple comparisons of the ROC curves to compare the performance of the $T_{Fmax}$ (Figure 2a) and $D_{Emax}$ (Figure 2b) models with that of the others. The $T_{Fmax}$ and $D_{Emax}$ models for the AE group were non-inferior to those of FVC, $FEV_1$, and BMI (Figure 2c).

**Differences in demographics according to low or high $T_{Fmax}$ and low or high $D_{Emax}$**

We set new variables according to optimal $T_{Fmax}$ and $D_{Emax}$ cut-off values. The low $T_{Fmax}$ and high $T_{Fmax}$ groups were divided by a cut-off value of 93.8%. The low $D_{Emax}$ and high $D_{Emax}$ groups were divided by a cut-off value of 44.9 mm. No significant differences in age, sex, mCCI, BMI, CAT score, or mMRC score were observed between the two groups. The low $T_{Fmax}$ and low $D_{Emax}$ groups usually had many symptoms and exacerbation histories. Lung function was lower in the low $T_{Fmax}$ and low $D_{Emax}$ groups than in the high $T_{Fmax}$ and high $D_{Emax}$ groups. The percentage of AE patients was significantly higher in the low $T_{Fmax}$ (63.2%) and low $D_{Emax}$ (55.6%) groups than in the high $T_{Fmax}$ (23.5%) and high $D_{Emax}$ (7.1%) groups (Table 3).

**The low $T_{Fmax}$ and low $D_{Emax}$ groups were associated with acute COPD exacerbation status**

We performed multivariate logistic regression analyses to determine whether a low $T_{Fmax}$ and low $D_{Emax}$ could be used for distinguishing exacerbation status. The variables were entered into two models that included age, male sex, mCCI, and BMI. Model 1 included variables such as age, male sex, mCCI, BMI, and a low $T_{Fmax}$, and model 2 included a low $D_{Emax}$ as the variable instead of $T_{Fmax}$. In model 1 univariate analyses, a high mCCI, low BMI, and low $T_{Fmax}$ were associated with exacerbation. In the adjusted analyses, a low BMI (odds ratio [OR] 0.70; 95% confidence interval [CI] 0.56–0.88) and low $T_{Fmax}$ (OR 8.40; 95% CI 1.55–45.56) were associated with exacerbation. Similar results were observed for model 2. A high mCCI (OR 2.68; 95% CI 1.09–6.60), low BMI (OR 0.79; 95% CI 0.64–0.97), and low $D_{Emax}$ (OR 11.51; 95% CI 1.15–115.56) were associated with exacerbation after adjustment. Therefore, low $T_{Fmax}$ and low $D_{Emax}$ groups were associated with an exacerbation status (Table 4).

**Discussion**

We designed this study to analyze the association between DUS findings and COPD exacerbation status. Many significant differences in DUS findings, such as the DT fraction during maximal deep breathing ($T_{Fmax}$) and DE during maximal deep breathing ($D_{Emax}$) were observed between patients with a stable or acute COPD exacerbation status. However, no significant difference in DT was observed at end-expiration.
or end-inspiration. In this study, differences in breathing effort produced different results. The maximal effort measurements were significantly associated in the AE group, whereas those of quiet tidal breathing were not. Respiratory muscle reserve or contractile strength was related to the change of diaphragm thickness (TF) or change of length (DE), not by muscle mass itself (DT) in previous studies. These findings support the results of those articles\textsuperscript{8,9,12,13}.

The results of the ROC curve analyses suggest the usefulness of $T_{F_{\text{max}}}$ and $D_{E_{\text{max}}}$ in classifying the exacerbation and stable conditions. $T_{F_{\text{max}}}$ and $D_{E_{\text{max}}}$ were not inferior markers to each other and they have complementary roles. $T_{F_{\text{max}}}$ was highly specific (78.8%) and $D_{E_{\text{max}}}$ was highly sensitive (95.2%). Both were non-inferior to other classical factors of exacerbation, such as age, sex, FVC, FEV\textsubscript{1}, and BMI.

After dividing the patients into those with low or high $T_{F_{\text{max}}}$ and those with low or high $D_{E_{\text{max}}}$ the low $T_{F_{\text{max}}}$ and low $D_{E_{\text{max}}}$ groups exhibited poorer lung function and a higher proportion of exacerbation. After adjusting for age, sex, mCCI, and BMI, low $T_{F_{\text{max}}}$ patients were classified into the AE group 8.40-times higher than high $T_{F_{\text{max}}}$ patients, and low $D_{E_{\text{max}}}$ patients were classified into the AE group 11.51-times higher than high $D_{E_{\text{max}}}$ patients. These findings suggest that DUS findings can be used as distinguishing markers for COPD exacerbation.

These are valuable results regarding the use of DUS in patients with COPD. This study compared $T_{F_{\text{max}}}$ and $D_{E_{\text{max}}}$. We firstly showed that they were non-inferior to each other and were complementary markers for detecting an acute exacerbation status, as far as we know. No previous study has examined differences in DUS findings between quiet breathing and maximal breathing both in stable and exacerbation status. Only the maximal deep breathing findings were different between the groups and those were associated with an exacerbation status. TF and DE should be checked together during maximal breathing effort when DUS is performed on a patient with COPD.

Another interesting finding is the usefulness of the DUS findings. The results were associated with exacerbation status after adjustment, and the markers were not inferior to FVC, FEV\textsubscript{1}, and BMI for classifying exacerbation. DUS is a real-time test that can be performed immediately when exacerbation is suspected. With these results, we have identified novel markers for distinguishing patients with severe exacerbation who need hospitalization.

Several limitations of this study should be discussed. First, the cut-off value of the DUS findings reflected maximal potential efficiency only. More studies on proper cut-off values are needed. However, the cut-off values in this study were not inferior to those of conventional markers for classifying COPD status. More studies should specifically evaluate proper cut-off values. Second, we retrospectively included patients in this study. However, we compared the diaphragm marker itself without another intervention in this setting. Prospective research is required for further analyses.

**Conclusions**
This study describes the utility of DUS in COPD patients. This is the first study to report the role of DUS for distinguishing exacerbation from a stable status. We also showed the value of DUS findings with the consideration of other contributing factors, such as sex, age, and BMI. Based on the results, we suggest using DUS findings as indicators of exacerbation status in COPD patients.

**List Of Abbreviations**

COPD, chronic obstructive pulmonary disease; DUS, diaphragm ultrasound; FEV$_1$, forced expiratory volume in 1 sec; FVC, forced vital capacity ratio; mMRC, modified Medical Research Council scale; CAT, COPD assessment test; mCCI, modified Charlson Comorbidity Index; DT, thickness of the diaphragm; DE, diaphragm excursion; DE$_{\text{max}}$, diaphragm excursion during maximal deep breathing; TF, diaphragm thickening fraction; TF$_{\text{max}}$, diaphragm thickening fraction during maximal deep breathing; ROC, receiver operating characteristic; AE, acute exacerbation; AUC, area under the curve; OR, odds ratio; CI, confidence interval; BMI, body mass index; SD, standard deviation; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LABA, long-acting β agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroid; RV, residual volume; TLC, total lung capacity

**Declarations**

*Ethics approval and consent to participate:* This study was approved by the Institutional Review Board of The Catholic University of Korea Yeouido St. Mary’s Hospital (approval no. SC20RIS0181). Informed consent was waived due to the retrospective nature of the study.

*Consent for publication:* all authors agreed with the publication of this study.

*Availability of data and materials:* Researchers may request datasets which were used in this study to the corresponding author with reasonable request.

*Competing interests:* None of the authors have any conflicts of interest

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*Authors’ contributions:*

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**Tables**

Table 1. Patient demographics
|                                | Stable (n=33) | AE (n=22) | p-value |
|--------------------------------|---------------|-----------|---------|
| Age (years), mean ± SD         | 73.5 ± 8.3    | 72.6 ± 11.6 | 0.897*  |
| Male sex, n (%)                | 23 (69.7)     | 18 (81.8)  | 0.361   |
| mCCI (points), mean ± SD       | 0.7 ± 0.9     | 1.4 ± 1.6  | 0.078*  |
| BMI (kg/m²), mean ± SD         | 24.2 ± 3.8    | 20.9 ± 4.0 | 0.003   |
| CAT (points), mean ± SD        | 13.7 ± 6.9    | 25.4 ± 8.2 | < 0.001 |
| mMRC (points), mean ± SD       | 1.7 ± 1.2     | 3.1 ± 1.0  | < 0.001 |
| Smoking, n (%)                 |               |           |         |
| Never                          | 11 (33.3)     | 11 (50.0)  | 0.040   |
| Ex-smoker                      | 14 (42.4)     | 11 (50.0)  |         |
| Current smoker                 | 8 (24.2)      | 0 (0.0)    |         |
| Pack-years, mean ± SD          | 28.3 ± 24.5   | 22.3 ± 25.5 | 0.387   |
| Duration of COPD (years), mean ± SD | 5.1 ± 4.4 | 5.4 ± 6.1 | 0.839   |
| GOLD group, n (%)              |               |           |         |
| A                              | 14 (42.4)     | 0 (0.0)    | < 0.001 |
| B                              | 10 (30.3)     | 7 (31.8)   |         |
| C                              | 5 (15.2)      | 0 (0.0)    |         |
| D                              | 4 (12.1)      | 15 (68.2)  |         |
| Baseline COPD medication, n (%) |               |           |         |
| None                           | 2 (6.1)       | 2 (9.1)    | 0.255   |
| LABA or LAMA                   | 1 (3.0)       | 0 (0.0)    |         |
| ICS/LABA                       | 5 (15.1)      | 0 (0.0)    |         |
| LABA/LAMA                      | 12 (36.4)     | 7 (31.8)   |         |
| ICS/LABA/LAMA                  | 13 (39.4)     | 13 (59.1)  |         |
| DT (mm), mean ± SD             |               |           |         |
| at end-expiration              | 17.0 ± 6.0    | 18.9 ± 7.4 | 0.542*  |
| at tidal inspiration           | 24.5 ± 7.9    | 24.9 ± 11.3 | 0.862* |
| at maximal deep inspiration    | 41.8 ± 14.9   | 35.7 ± 14.1 | 0.151  |
### TF of diaphragm (%), mean ± SD

|                                | at tidal inspiration | at maximal deep inspiration | p-value |
|--------------------------------|----------------------|-----------------------------|---------|
| TF of diaphragm (%)            | 51.3 ± 51.0          | 42.3 ± 45.3                 | 0.523   |

### DE (mm), mean ± SD

|                                | at tidal inspiration | at maximal deep inspiration | p-value |
|--------------------------------|----------------------|-----------------------------|---------|
| DE (mm)                        | 19.6 ± 5.4           | 20.9 ± 8.7                  | 1.000*  |

### Lung function test, mean ± SD

|                                | FEV<sub>1</sub>/FVC (%) | FVC (L) | FVC (%) | FEV<sub>1</sub> (L) | FEV<sub>1</sub> (%) | RV/TLC (%) |
|--------------------------------|-------------------------|---------|---------|---------------------|---------------------|------------|
| FEV<sub>1</sub>/FVC (%)        | 52.5 ± 14.9             | 52.0 ± 17.4 | 0.922* |
| FVC (L)                       | 2.82 ± 0.93             | 2.11 ± 0.81 | 0.006  |
| FVC (%)                       | 73.2 ± 16.1             | 55.0 ± 18.6 | < 0.001|
| FEV<sub>1</sub> (L)           | 1.42 ± 0.52             | 1.00 ± 0.38 | 0.002  |
| FEV<sub>1</sub> (%)           | 54.6 ± 19.4             | 40.5 ± 18.1 | 0.010  |
| RV/TLC (%)                    | 43.7 ± 8.1              | 51.7 ± 9.4  | 0.019  |

SD, standard deviation; mCCI, modified Charlson Comorbidity Index; BMI, body mass index; CAT, COPD assessment test; mMRC, modified Medical Research Council; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LABA, long-acting β agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroid; DT, diaphragm thickness; TF, Thickening fraction; DE, diaphragm excursion; FEV<sub>1</sub>, forced expiratory volume in 1 sec; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity

* Mann-Whitney U test

Table 2. Results of the receiver operating characteristic curve analysis for COPD exacerbation
|            | AUC  | 95% CI       | Cut-off values | p-value | Sensitivity | Specificity |
|------------|------|--------------|----------------|---------|-------------|-------------|
| TF<sub>max</sub> | 0.745 | 0.605–0.856  | ≤ 93.8%        | 0.001   | 68.4%       | 78.8%       |
| DE<sub>max</sub> | 0.721 | 0.576–0.838  | ≤ 44.9 mm      | 0.003   | 95.2%       | 44.8%       |
| FEV<sub>1</sub>/FVC | 0.508 | 0.368–0.647  | ≤ 64%          | 0.927   | 57.1%       | 21.2%       |
| FVC                          | 0.709 | 0.570–0.825  | ≤ 1.78 L       | 0.003   | 47.6%       | 87.9%       |
| FEV<sub>1</sub>              | 0.747 | 0.610–0.855  | ≤ 1.21 L       | < 0.001 | 85.7%       | 57.6%       |
| BMI                          | 0.729 | 0.592–0.840  | ≤ 22.5 kg/m<sup>2</sup> | 0.002 | 77.3%       | 66.7%       |

COPD, chronic obstructive pulmonary disease; AUC, area under curve; CI, confidence interval; TF<sub>max</sub>, thickening fraction at maximal inspiration; DE<sub>max</sub>, diaphragm excursion at maximal inspiration; FEV<sub>1</sub>, forced expiratory volume in 1 sec; FVC, forced vital capacity; BMI, body mass index

Table 3. Clinical characteristics of COPD patients according to diaphragm ultrasound findings
|                                | tf<sub>max</sub> |                                | de<sub>max</sub> |                                |                                | p-value |                                | de<sub>max</sub> |                                | p-value |
|--------------------------------|------------------|--------------------------------|------------------|--------------------------------|------------------|--------|--------------------------------|------------------|--------------------------------|--------|
|                                | Low (n=19)       | High (n=34)                    | p-value          | Low (n=36)                      | High (n=14)      |        |                                | Low (n=36)      | High (n=14)                    |        |
| Age (years), mean ± SD         | 71.3 ± 12.9      | 74.2 ± 7.7                     | 0.315            | 72.9 ± 10.0                    | 73.9 ± 9.4       | 0.755  |                                |                  |                                |        |
| Male sex, n (%)                | 15 (78.9)        | 24 (70.6)                      | 0.746            | 25 (69.4)                      | 12 (85.7)        | 0.303  |                                |                  |                                |        |
| mCCI (points), mean ± SD       | 1.1 ± 1.5        | 0.8 ± 1.0                      | 0.411            | 0.9 ± 1.1                      | 0.5 ± 0.9        | 0.389  |                                |                  |                                |        |
| BMI (kg/m<sup>2</sup>), mean ± SD | 22.4 ± 4.9     | 22.9 ± 3.8                     | 0.689            | 22.1 ± 4.4                     | 24.3 ± 3.4       | 0.237  |                                |                  |                                |        |
| CAT (points), mean ± SD        | 20.5 ± 7.1       | 16.2 ± 9.7                     | 0.167            | 19.2 ± 9.6                     | 13.9 ± 8.2       | 0.089  |                                |                  |                                |        |
| mMRC (points), mean ± SD       | 2.7 ± 1.2        | 2.0 ± 1.3                      | 0.061            | 2.5 ± 1.2                      | 1.7 ± 1.4        | 0.055  |                                |                  |                                |        |
| Smoking, n (%)                 |                  |                                |                  |                                |                  |        |                                |                  |                                |        |
| Never                          | 9 (47.4)         | 13 (38.2)                      | 0.325            | 18 (50.0)                      | 2 (14.3)         | 0.052  |                                |                  |                                |        |
| Ex-smoker                      | 9 (47.4)         | 14 (41.2)                      |                  | 14 (38.9)                      | 8 (57.1)         |        |                                |                  |                                |        |
| Current smoker                 | 1 (5.3)          | 7 (20.6)                       |                  | 4 (11.1)                       | 4 (28.6)         |        |                                |                  |                                |        |
| Pack-years, mean ± SD          | 23.2 ± 27.5      | 25.7 ± 23.2                    | 0.727            | 23.9 ± 27.5                    | 32.3 ± 17.4      | 0.209  |                                |                  |                                |        |
| Duration of COPD (years), mean ± SD | 6.7 ± 5.9   | 4.7 ± 4.5                      | 0.190            | 5.4 ± 5.3                      | 5.1 ± 5.3        | 0.838  |                                |                  |                                |        |
| GOLD group, n (%)              |                  |                                |                  |                                |                  |        |                                |                  |                                |        |
| A                              | 1 (5.3)          | 13 (38.2)                      | 0.044            | 6 (16.7)                       | 7 (50.0)         | 0.009  |                                |                  |                                |        |
| B                              | 6 (31.6)         | 10 (29.4)                      |                  | 11 (30.6)                      | 3 (21.4)         |        |                                |                  |                                |        |
| C                              | 2 (10.5)         | 3 (8.8)                        |                  | 2 (5.6)                        | 3 (21.4)         |        |                                |                  |                                |        |
| D                              | 10 (52.6)        | 8 (23.5)                       |                  | 17 (47.2)                      | 1 (7.1)          |        |                                |                  |                                |        |
| Baseline COPD medication, n (%) |                  |                                |                  |                                |                  |        |                                |                  |                                |        |
| None                           | 0 (0.0)          | 3 (8.8)                        | 0.111            | 3 (8.3)                        | 0 (0.0)          | 0.005  |                                |                  |                                |        |
| LABA or LAMA                   | 1 (5.3)          | 0 (0.0)                        | 0.011            | 0 (0.0)                        | 1 (7.1)          |        |                                |                  |                                |        |
| ICS/LABA                       | 0 (0.0)          | 5 (14.7)                       |                  | 0 (0.0)                        | 4 (28.6)         |        |                                |                  |                                |        |
| LABA/LAMA                      | 6 (31.6)         | 12 (35.3)                      |                  | 14 (38.9)                      | 4 (28.6)         |        |                                |                  |                                |        |
| ICS/LABA/LAMA                  | 12 (63.2)        | 14 (41.2)                      |                  | 19 (52.8)                      | 5 (35.7)         |        |                                |                  |                                |        |
| Lung function test, mean ± SD  |                  |                                |                  |                                |                  |        |                                |                  |                                |        |
|                          | 53.9 ± 15.4 | 51.3 ± 16.4 | 0.569 | 51.0 ± 16.4 | 53.6 ± 15.9 | 0.619 |
|--------------------------|-------------|-------------|-------|-------------|-------------|-------|
| **FEV₁/FVC (%)**         |             |             |       |             |             |       |
| **FVC (L)**              | 2.20 ± 0.92 | 2.72 ± 0.94 | 0.060 | 2.20 ± 0.83 | 3.08 ± 0.83 | 0.002 |
| **FVC (%)**              | 55.8 ± 17.7 | 71.6 ± 18.4 | 0.004 | 59.7 ± 18.9 | 77.3 ± 14.7 | 0.003 |
| **FEV₁ (L)**             | 1.13 ± 0.50 | 1.31 ± 0.51 | 0.232 | 1.026 ± 0.32 | 1.60 ± 0.59 | <0.001 |
| **FEV₁ (%)**             | 44.6 ± 21.2 | 51.4 ± 19.7 | 0.254 | 41.9 ± 15.7 | 60.9 ± 23.2 | 0.002 |
| **RV/TLC (%)**           | 51.9 ± 10.8 | 44.8 ± 7.0  | 0.044 | 50.4 ± 8.1  | 41.5 ± 7.7  | 0.014 |
| **Exacerbation status, n (%)** | 12 (63.2) | 8 (23.5) | 0.007 | 20 (55.6) | 1 (7.1) | 0.003 |

COPD, chronic obstructive pulmonary disease; AUC, area under curve; CI, confidence interval; TF<sub>max</sub>, thickening fraction at maximal inspiration; DE<sub>max</sub>, diaphragm excursion at maximal inspiration; mCCI, modified Charlson Comorbidity Index; BMI, body mass index; CAT, COPD assessment test; mMRC, modified Medical Research Council; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LABA, long-acting β agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroid; FEV₁, forced expiratory volume in 1 sec; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity

Table 4. Logistic regression analysis for estimating exacerbation of chronic obstructive pulmonary diseases
| Model 1 | Univariate | Multivariate |
|---------|------------|-------------|
|         | p-value    | OR (95% CI) | p-value    | OR (95% CI) |
| Age     | 0.722      | 0.99 (0.94–1.05) | 0.682      | 0.98 (0.91–1.06) |
| Male sex| 0.317      | 1.96 (0.53–7.28) | 0.544      | 1.74 (0.29–10.34) |
| mCCI    | 0.049      | 1.62 (1.00–2.62) | 0.157      | 1.73 (0.81–3.70) |
| BMI     | 0.007      | 0.80 (0.68–0.94) | 0.002      | 0.70 (0.56–0.88) |
| Low TF<sub>max</sub> | 0.006 | 5.57 (1.64–18.94) | 0.014 | 8.40 (1.55–45.56) |

| Model 2 | Univariate | Multivariate |
|---------|------------|-------------|
|         | p-value    | OR (95% CI) | p-value    | OR (95% CI) |
| Age     | 0.722      | 0.99 (0.94–1.05) | 0.233      | 0.95 (0.88–1.03) |
| Male sex| 0.317      | 1.957 (0.53–7.28) | 0.393      | 2.16 (0.37–12.67) |
| mCCI    | 0.049      | 1.62 (1.00–2.62) | 0.032      | 2.68 (1.09–6.60) |
| BMI     | 0.007      | 0.80 (0.68–0.94) | 0.022      | 0.79 (0.64–0.97) |
| Low DE<sub>max</sub> | 0.011 | 16.25 (1.92–137.78) | 0.038 | 11.51 (1.15–115.56) |

mCCI, modified Charlson Comorbidity Index; BMI, body mass index; TF<sub>max</sub>, diaphragm thickening fraction during maximal deep breathing; DE<sub>max</sub>, diaphragm excursion during maximal deep breathing

**Figures**
Figure 1

Receiver operating characteristic (ROC) curve analysis for determining chronic obstructive pulmonary disease exacerbation status using diaphragm ultrasound findings. The ROC curve for distinguishing exacerbation from a stable status indicated that the outcomes were fair. The area under the curve (AUC) of the thickening fraction during maximal deep breathing (TFmax) was 0.745. The AUC of diaphragm excursion during maximal deep breathing (DEmax) was 0.721. No significant difference was observed between TFmax and DEmax for distinguishing exacerbation status (p = 0.608).

TF, thickening fraction at maximal inspiration; DE, diaphragm excursion at maximal inspiration.
Figure 2

Multiple comparative analysis of the receiver operating characteristic (ROC) curve between diaphragm thickening, diaphragm excursion, lung function, and body mass index (BMI). The ROC curve of thickening fraction of diaphragm during maximal breathing (TFmax) (a) and diaphragm excursion during maximal breathing (DEmax) (b) showed in figure 2. (c) There was no significant difference for distinguishing exacerbation both in TFmax and DEmax compared to those of forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and BMI in multiple comparative analysis of the ROC curve analysis.

**Supplementary Files**

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- Supplementarymaterials.docx