

Ultrasound Assessment of Diaphragmatic Thickness in Chronic Obstructive Pulmonary Disease Patients as a Predictor for Disease Severity

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Abstract:

Background and objectives: COPD patients usually had an imbalance in the load/capacity ratio of the respiratory muscles. This study aimed to use of ultra-sonographic (U/S) techniques for the assessment of diaphragmatic thickness of the diaphragm (TD) at different lung volumes in COPD patients, and its relation with severity of the disease.

Methods A Case control study conducted on 100 subjects at outpatient clinics of Benha University Hospitals and Kafrelsheikh University Hospitals during the period from March, 2020 to December, 2020; 80 patients with clinically stable chronic obstructive pulmonary disease (COPD), were diagnosed and classified into four groups according to GOLD 2020: Group A COPD): 20 cases, Group B COPD): 20 cases, Group C COPD): 20 cases, Group D COPD): 20 cases. U/S was used for assessment of diaphragmatic thickness (TD) and diaphragmatic thickness fraction (TF) at different lung volumes in COPD subgroups, and correlated with severity of the disease and 20 apparent healthy control group. **Results:** In total 4 potentially relevant publications were included, the studies showed decrease in diaphragmatic thickness,

thickness fraction and excursion in copd patients in comparison with normal subjects specially groups B and D COPD. **Conclusion:** Ultrasound is a non-invasive, simple and available bedside diagnostic tool for outpatient clinic examination of COPD patients for severity detection.

Key words: ultrasound, diaphragmatic thickness, COPD

Introduction:

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by incomplete reversible airflow limitation (1). COPD results from a complex interaction between genes and the environment. Cigarette smoking is the leading environmental risk factor for COPD (2). Dyspnea and exercise intolerance might result from an imbalance in the load/capacity ratio of the respiratory muscles in COPD patients.

Chronic airflow limitation imposes a load on respiratory muscles, flattening of the diaphragm and reducing its ability to generate tension. Various other factors can impair respiratory muscle function in COPD patients, including activation of proteases, oxidative stress, malnutrition, ageing, and comorbidity-related systemic factors; however, changes in chest wall geometry and diaphragm position are the most commonly recognized and studied mechanisms contributing to respiratory muscle dysfunction. (3), the impairment of diaphragm is suggested to be an important factor, which is associated with alterations in the principal pulmonary function parameters such as FEV1. (4)

The use of ultra-sonographic (U/S) techniques for the assessment of diaphragmatic thickness (TD) and thickness fraction (TF) at different lung volumes in healthy and diseased individuals was proposed (5), to assess the

diaphragmatic function in COPD patients and its relation with severity of the disease.

Subjects and methods:

A Case control study conducted on 100 subject at outpatient clinics of Benha University hospitals and Kafrelsheikh University hospitals during the period from March, 2020 to December, 2020; (80) patients with clinically stable chronic obstructive pulmonary disease (COPD), during their follow up in the outpatient clinic of Chest Department of Benha and Kafrelsheikh University Hospitals and 20 healthy volunteers with age and sex matched included as a control group.

These COPD group's patients were diagnosed and classified into four groups according to GOLD 2020 as following:

- Group A COPD): 20 cases
- Group B COPD): 20 cases
- Group C COPD): 20 cases
- Group D COPD): 20 cases

Inclusion criteria: Confirmed cases of stable COPD diagnosed according to GOLD 2020 (1) in different stages of severity through the following:

1. Full history taking including,
2. General and local chest examination
3. Simple spirometry to confirm COPD based on GOLD, 2020 : COPD

patients are confirmed by spirometry (post bronchodilator forced expiratory volume 1 (FEV1)/ forced vital capacity (FVC) < 0.70)

-The severity of the COPD was based on **GOLD, 2020** report depends on:

A- PFT: spirometry with measuring of (FEV1, FEV1/FVC, FVC)

B-Dyspnea severity according to modified British Medical Research Council scale (mMRC) and (CAT) score

C-frequency of exacerbation per year.

D-combined copd assessment (ABCD categorization tool) which combines all the above tools

4. Oxygen saturation measurement by pulse oximetry
5. Laboratory work up (CBC, Liver function, Kidney function, ABG)
6. Plain chest X- ray (posterior-anterior and lateral views).
7. Ultrasonography of the diaphragm: By Philips Hd5 Color Doppler Ultrasound Machine, 2013 with (C 2-5 MHz) curved low frequency and (L 12-3 MHz) linear high frequency probe transducers for diaphragm and for intercostal muscles using the linear one.

Measured variables: diaphragmatic thickness and thickening fraction of the diaphragm were assessed through this technique: The intercostal approach is performed with a (10–15- MHz) linear array transducer positioned in a cranio-caudal direction and perpendicular to the skin in the zone of apposition between the mid-axillary and antero-axillary line, in the 8th to 11th intercostal space (Fig. 1) (6), measuring diaphragm thickness perpendicular to its fiber direction between the pleural and peritoneal membrane, and not including the membranes (Fig. 1). The lower limit for normal diaphragm thickness is around 1.5 mm in healthy subjects. Thickening fraction of the diaphragm (TFdi) is calculated in B-mode or M-mode as the percentage inspiratory increase in diaphragm thickness relative to end-expiratory thickness during tidal breathing (TFdi) or maximal inspiratory effort (TFdi (max)): $TFdi = (\text{end-inspiratory thickness} - \text{end-expiratory thickness}) / \text{end-expiratory thickness} \times 100\%$ (Fig. 1). (7)

Exclusion criteria: Subjects were excluded from the study if they had any of the following conditions:

1. Patients with other chest diseases.
2. Patients with neuromuscular diseases or chest wall deformity.

3. Patients with systemic diseases affecting muscles function e.g. endocrine, neoplastic and metabolic disorders or on drugs causing myopathy like long-term corticosteroids.
4. Patients with any cause of increased intra-abdominal pressure
5. Patients with history of recent upper abdominal or thoracic surgery.
6. Subjects refusing to participate in the study.

Ethical approval: the study was conducted at Chest medicine department of Benha and Kafrelsheikh University Hospitals after approval of the research Ethical committee at faculty of medicine, Benha University (REC-FOMBU).

Statistical analysis: The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc. (Chicago, IL, USA).

Probability value (P-value) was interpreted as follow:

- Non-significant if the p value is > 0.05
- Significant if the p value is ≤ 0.05 .
- Highly significant if the p value < 0.001 .

The following tests were done:

- 1)** One-way analysis of the variance (One-way ANOVA) was used to compare between three or more independent

groups of normally distributed variables

- 2)** Independent samples t-test was used to compare between two independent groups of normally distributed variables

- 3)** Chi square test (χ^2) and Fisher test used to calculate difference between qualitative variables as indicated.

4) Receiver operating characteristic (ROC) analysis:

Test characteristics were estimated by ROC curve and included best cutoff value, AUC, its standard error (SE), and *P*-value. In addition, to assess the effectiveness of the test, estimates as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated at the optimal cutoff.

Results

The total number of studied COPD group was 80 patients 70 male and 10 female, their age ranged from (49-76) with mean \pm SD (59.86 \pm 6.53) (table 1)

The smoking index of the studied groups was ranged from (17 to120) with Mean \pm SD 60.65 \pm 23.06 and there were (56.25%) current smoker, (36.25%) ex-smoker and (7.5%) patients were nonsmoker. (Table 2)

Current smoker patients were higher in-group C and D in comparison to other groups (37%) and (33%) patients respectively. In addition, ex-smoker patients more in groups A (33%) and B (45%) and non-smoker were more in-group A COPD. (Table 2).

Groups B and D copd patients showed more reduction in FEV1 than other subgroups .In addition, mMRC scale grading was increased with increasing COPD severity as shown in group D mMRC (grade 2 was 3 cases (15%),grade 3 was 12 cases(60%)and grade 4 was 5 cases (25%). While CAT scale was, significantly higher in groups B, D, which is compatible with COPD classification of severity (table 3).

There was a statistical significance difference between COPD group (80 patients) and control group as regard diaphragmatic thickness at (TLC and FRC), diaphragmatic thickness fraction (TF) (p value < 0.001) (table 4).

In this study ultra-sonographic assessments of diaphragmatic thickness at (TILC (mm), FRC (mm)) and diaphragm thickness fraction, there was a statistically significant reduction in diaphragmatic thickness in (TILC (mm), FRC (mm), TF) within COPD subgroups with most reduction in groups B and D (P value<0.001).(Table 5) While in a

comparison between copd subgroups and control group, there was no statistical significant difference between group A and control in measured parameters' p value (P1=0.922).

However, other groups B, C and D showed decrease in diaphragmatic thickness in (TILC (mm), FRC (mm), TF) with increasing severity which more obvious in group D copd (P value<0.001).(table 5)

In a statistical comparison between different ultra-sonographic parameter to differentiate between control & all COPD patients (No.80), the cut-off point to differentiate between copd groups and control group as regard to thickness fraction was 0.927 cm with sensitivity 75% and specificity 80%.(Table 6),(figure 2)

In addition, for each group separately as shown in (table 7), group A showed no statistical difference (P value =0.839) with sensitivity 70% and specificity 40%. (Figure 3)

While group B was significant (P value < 0.001) with sensitivity 95% and specificity 95%. (Figure 4).Group C was statistically significant (P value < 0.001) with sensitivity 60% and specificity 95%. (Figure 5) and finally group D showed statistical difference (P value < 0.001) with specificity 100% and selectivity 100%.(figure 6) (table 7)

Table (1): Demographic data of the cases included in the study

Items		Cases (n= 80)
Age (years)	Mean \pm SD	59.86 \pm 6.53
	Median (min-max)	59 (49-76)
BMI (kg/m ²)	Mean \pm SD	26.25 \pm 3.39
	Median (min-max)	25.9 (20- 33)
Sex		
Males		70 (90%)
Females		10 (10%)

Table (2): Classification of COPD according to severity of obstruction

	Control group [N=20]	Group A [N= 20]	Group B [N=20]	Group C [N= 20]	Group D [N=20]	Test of Sign.
Age (years)	46.60 \pm 12.35	56.15 \pm 6.31	62.95 \pm 8.30	60.75 \pm 4.13	59.60 \pm 5.09	F=13.553 P<0.001*
BMI (Kg/m²)	25.50 \pm 2.99	26.69 \pm 1.96	25.27 \pm 2.63	27.11 \pm 4.35	25.97 \pm 4.01	F=1.108 P=0.358
Smoking index	NA	40 (17-90)	66 (26-90)	68 (34-76)	77.5 (34-120)	F=55.023 P<0.001*
Smoking						
Current smoker	None	7 (15%)	6 (13%)	17 (37%)	15(33%)	$\chi^2=95.749$ P<0.001*
Ex-smoker		10 (34%)	13 (45%)	1 (3%)	5 (17%)	
Non smoker	20 (100%)	3 (50%)	1(17%)	2(33%)	0(0%)	

BMI (body mass index).

Table (3): Classification of COPD according to severity of obstruction as regard FEV1, exacerbation per year, mMRC and CAT.

	Group A [N= 20]	Group B [N=20]	Group C [N= 20]	Group D [N=20]	Test of Sig.
FEV1 (L)	2.45 \pm 0.12	1.67 \pm 0.44	2.27 \pm 0.14	1.22 \pm 0.22	F=93.044 P<0.001*
exacerbations in past year					
Non exacerbations	5 (25%)	4 (20%)	0 (0%)	0 (0%)	FET=5.308 P=0.045*
1 time	15 (75%)	16 (80%)	15 (75%)	0 (0%)	FET=23.624 P<0.001*
2 times	0 (0%)	0 (0%)	5 (25%)	11 (55%)	FET=16.227 P<0.001*
3 times	0 (0%)	0 (0%)	0 (0%)	7 (35%)	FET=6.132 P= 0.029*
4 times	0 (0%)	0 (0%)	0 (0%)	2 (10%)	FET=0.648 P= 0.754
mMRC					
Grade 1	20 (100%)	0 (0%)	20 (100%)	0 (0%)	FET=46.384 P<0.001*
Grade 2	0 (0%)	16 (80%)	0 (0%)	3 (15%)	FET=27.347 P<0.001*
Grade 3	0 (0%)	4 (20%)	0 (0%)	12 (60%)	FET=21.573 P<0.001*
Grade 4	0 (0%)	0 (0%)	0 (0%)	5 (25%)	FET=5.648 P= 0.041*
CAT	7.95 \pm 1.05	21.60 \pm 4.60	8.35 \pm 0.81	28.35 \pm 3.72	F=221.808 P<0.001*

FEV1(forced expiratory volume), mMRC (modified medical research council),CAT (COPD Assessment Test)

Table (4): Comparison between studied groups as regard to diaphragmatic thickness, thickness fraction and diaphragmatic excursion.

	COPD group [N= 80]	Control group [N=20]	Test of Sig.
Diaphragmatic thickness TLC(mm)	4.45 \pm 0.60	5.36 \pm 0.42	t=6.373 P< 0.001*
Diaphragmatic thickness FRC(mm)	2.50 \pm 0.23	2.71 \pm 0.24	t=3.652 P< 0.001*
Diaphragm thickness fraction (TF)	0.79 \pm 0.21	1.02 \pm 0.15	t=4.050 P< 0.001*

Table (5): Comparison between studied groups as regard to diaphragmatic thickness and thickness fraction.

	Control group [N=20]	Group A [N= 20]	Group B [N=20]	Group C [N= 20]	Group D [N=20]	Test of Sig.
diaphragmatic thickness TLC(mm)	5.36±0.42	5.16 ±0.19	4.18 ±0.50	4.45 ±0.39	3.97 ±0.46	F=45.181 P<0.001* P1=0.922 P2=0.001* P3<0.001* P4<0.001*
diaphragmatic thickness FRC(mm)	2.71±0.24	2.57 ±0.16	2.32 ±0.23	2.37 ±0.15	2.30 ±0.33	F=5.507 P<0.001* P1=0.515 P2<0.001* P3<0.001* P4<0.001*
diaphragm thickness fraction (TF)	1.02 ±0.15	0.98±0.10	0.66 ±0.13	0.87 ±0.09	0.58 ±0.11	F=55.037 P<0.001* P1=0.998 P2<0.001* P3=0.032* P4<0.001*

P= Represents differences within the COPD subgroups

P1= Represents differences between control group and Group A

P2= Represents differences between control group and Group B

P3= Represents differences between control group and Group C

P4= Represents differences between control group and Group D

Table (6): statistical comparison between different ultra-sonographic parameter to differentiate between control & all COPD patients.

	Diaphragmatic Thickness fraction
AUC	0.811
Cut off point	0.927
Sensitivity	75.0%
Specificity	80.0%
PPV	93.7%
NPV	44.4%
P value	< 0.001*

PPV: positive predictive value; NPV: negative predicted value

Table (7): Diaphragmatic thickness Roc curve for all groups

	Cutoff point	sensitivity	Specificity	PPV	NPV	<i>P value</i>
Group A	0.98	70%	40%	48%	76%	0.839
Group B	0.87	95%	95%	95%	90%	< 0.001*
Group C	0.88	60%	95%	90%	85%	< 0.003*
Group D	0.83	100%	100%	100%	100%	< 0.001*

PPV: positive predictive value; NPV: negative predicted value

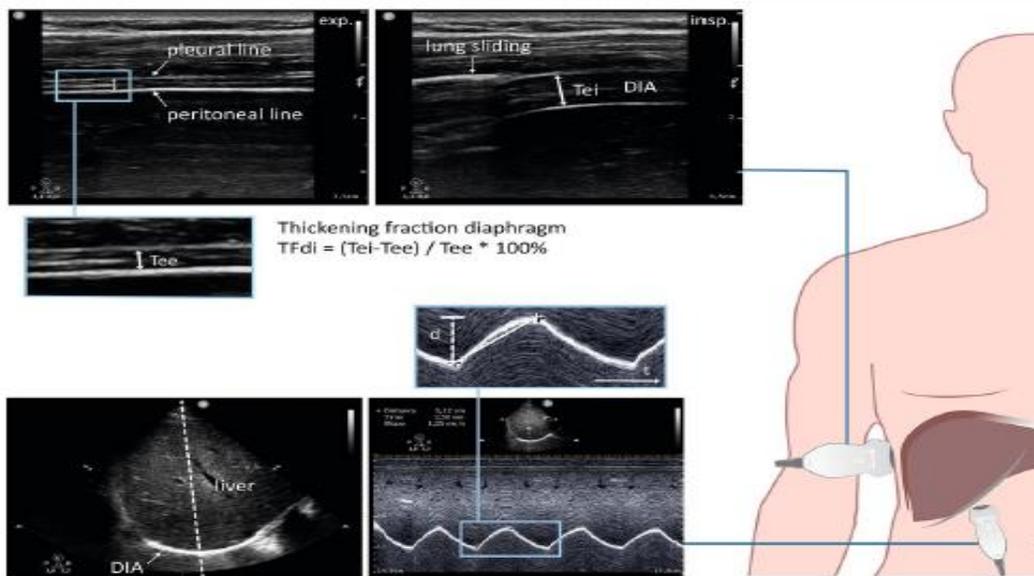


Fig (1)

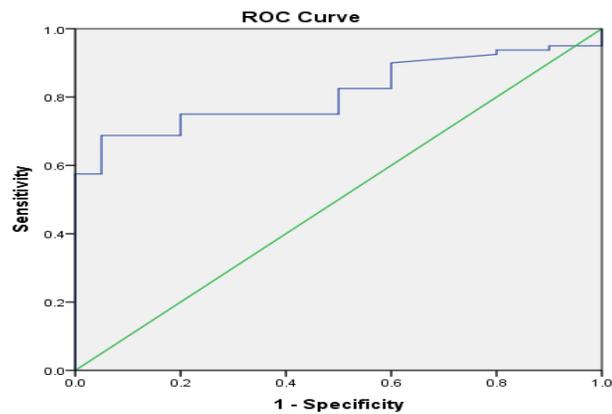


Fig (2): Roc curve of diaphragmatic thickness fraction for COPD patients.

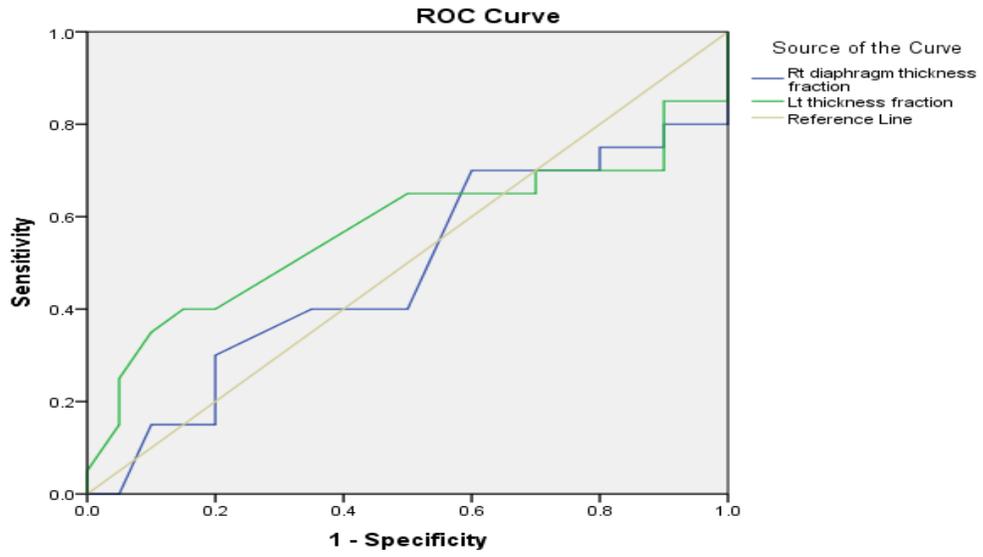


Figure (3): Roc curve group A copd (diaphragmatic thickness fraction)

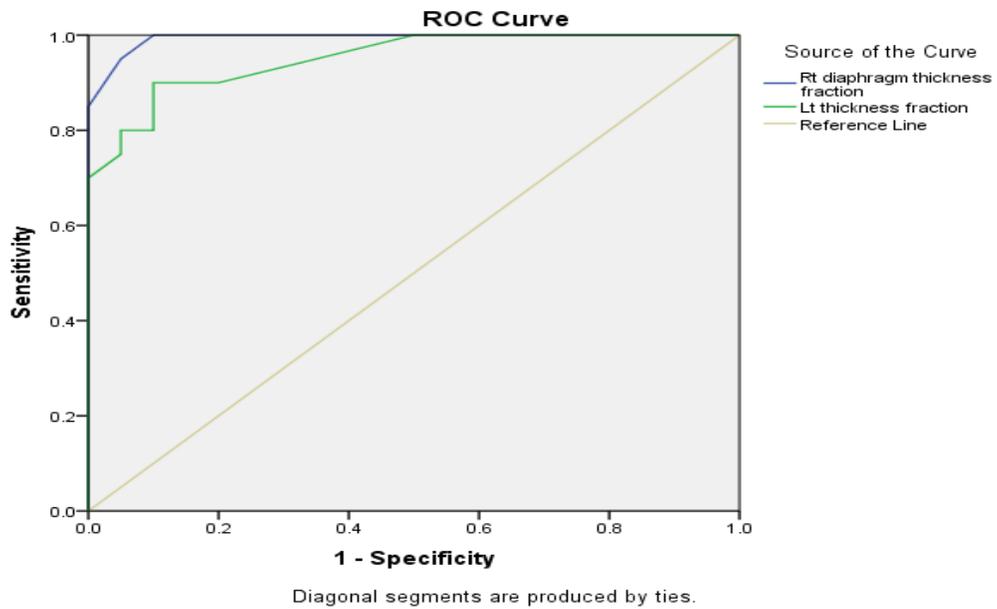


Figure (4): Prediction of ability of Diaphragm thickness fraction to differentiate between control & group B

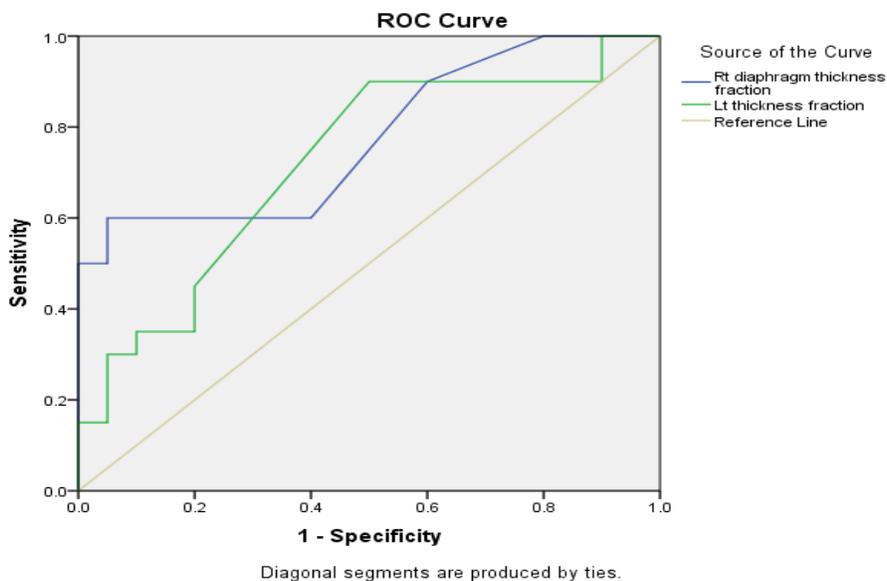


Figure (5): Prediction of ability of Diaphragm thickness fraction to differentiate between control & group C

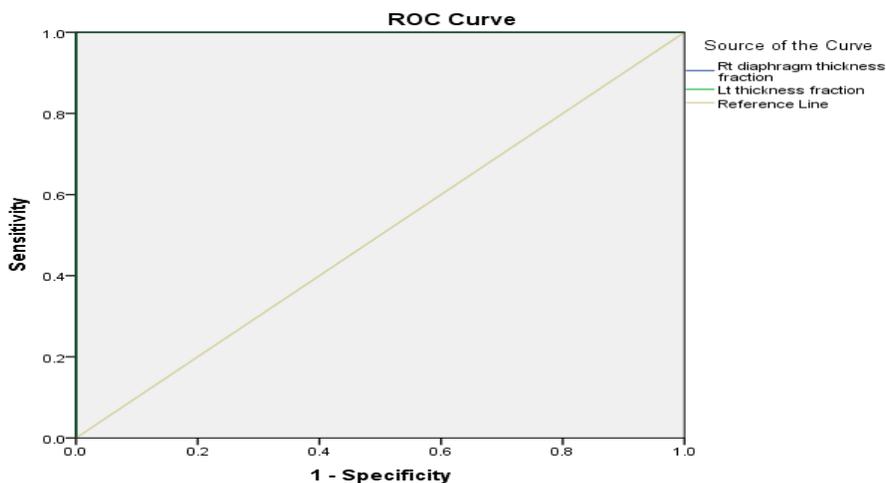


Figure (6): Prediction of ability of Diaphragm thickness fraction [on the left and right side] to differentiate between control & group D

Discussion

The use of ultrasound to evaluate the respiratory muscle pump function is relatively new; Diaphragm ultra-sonographic evaluation provides an important first step towards improving the detection of diaphragm dysfunction as well as a protective and supportive strategy for its management (8).

The diaphragm may present normal function; reduced mobility or weakness; or loss of function or paralysis. Different ultrasound methods can be used to monitor diaphragm function – excursion, and thickness, and the use of one method does not exclude the use of another (9). With recent advent of portable

ultrasound machines, which is available, bedside technique, safe, and relative cheap, ultrasound has become an important tool for assessment copd severity in chest outpatient clinics (10).

In current study and in a comparison between all COPD patients and control subjects as shown in table (1) ,there was a statistical significance difference between COPD group (80 patients) and control group(20 subjects) as regard diaphragmatic thickness at (TLC and FRC) , diaphragmatic thickness fraction (TF),tidal excursion and max excursion (P value < 0.001*)

This was in agreement with **several studies that reported** the ultra-sonographic measurement of diaphragmatic movement was useful and reliable in demonstrating diaphragmatic dysfunction in patients with COPD. (11) Similarly, **another studies** observed reduced diaphragmatic mobility in patients with COPD compared to healthy controls. Patients with lower diaphragmatic mobility were more dyspneic and had shorter 6-min walk distances. (12)

In contrast, **other studies were against this study** as measured diaphragmatic thickness by ultrasonography in 50 COPD patients and 150 healthy controls and reported the absence of a significant difference in diaphragmatic thickness between the COPD patients and the

controls. This study did not investigate the relationship of diaphragmatic thickness with clinical characteristics. (13)

In addition, **similar studies** did not identify a significant difference between diaphragmatic thickness fraction and disease severity, symptom severity, frequency of episodes, FEV1 value, and BMI. (14)

In current study for assessment of diaphragmatic function in each COPD subgroup, diaphragmatic thickness at TILC (mm), FRC (mm), and diaphragmatic thickness fraction, were a statistically significant different compared to control group except for group A, moreover, COPD subgroups A, B, C and D showed significant reduction compared to each other associated with increased reduction with severity increasing which was more obvious in group D (P <0.001).

These results were in agreement with **similar one** who reported a significant reduction in US-measurements of diaphragmatic thickness in patients with COPD compared with healthy subjects. (15), **also another** explained that defective diaphragmatic thickness in ultrasound mostly secondary to hyperinflation that could be owing to worsening of the length-tension relationship decreased length of the zone of opposition, flattening of the

diaphragm with decrease in its curvature, which is more in moderate, and severe COPD patients. (16)

On other hand, these results were against those who found no correlation between diaphragmatic thickness in patients with COPD and pulmonary function tests except for FEV1% of predicted in patients with mild COPD, and no correlations between diaphragmatic muscle thickness and symptom scores. However, there study did not include a control group and Radiologists performing B-Mode US was blind to the patient groups. (17)

In addition, studies reported increased diaphragm thickness in patients with COPD compared with healthy subjects at baseline (0.22 ± 0.07 (cm) vs 0.26 ± 0.06 (cm), $p=0.03$) with no significant link between rate of diaphragmatic thinning and COPD diagnosis ($p=0.36$) and reported no significant difference in diaphragm thickness between patients with COPD and healthy subjects; However, all of their patients were in Groups C and D, moderate and severe COPD patients, and most of them had clinical/radiological evidence of hyperinflation. (18)

In a statistical comparison between different ultra-sonographic parameter to differentiate

between control & all COPD patients as shown in table (6), the cut-off point to differentiate between copd groups and control group as regard to thickness fraction was 0.927 cm with sensitivity 75% and specificity 80%.(figure 2)

In this study, the cut-off point of TF in-group A was 0.89 with sensitivity 70% and specificity 40%, while the cut-off point of TF in-group B was 0.87 with sensitivity 95% and specificity 95%, the cut-off point of TF in-group C was 0.83 with sensitivity 100% and specificity 100%, and the cut-off point of TF in-group D was 0.88 with sensitivity and specificity 100%.

Similar study evaluated various methods to assess the diaphragm, diaphragmatic thickness, side-to-side variation, and diaphragmatic velocity. In their study, they used cut-off value of less than 0.2 cm of diaphragm thickness, measured at the end of expiration, to define diaphragmatic atrophy. (19)

Conclusion

TUS (transthorathic ultrasound) is an non invasive, simple and available bedside diagnostic tool for examination in outpatient clinic and RCU patients. TUS has a better diagnostic performance for diagnosis of

diaphragmatic dysfunction in copd patients and its relation to severity.

Measuring diaphragmatic thickness fraction is more accurate than measuring diaphragmatic thickness alone for evaluation of diaphragm in copd patients. For sure, assessment of diaphragmatic function, measuring of diaphragmatic excursion should be included.

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