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Original article

Serum Creatinine/Cystatin C Ratio in Chronic Obstructive Pulmonary Disease Patients and its Correlation to Disease Severity

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Abstract

Background: Muscle atrophy is a major clinical feature of chronic obstructive pulmonary disease (COPD), and it is considered a strong predictor of mortality in COPD patients. **This study aimed to** assess the use of serum creatinine/serum Cystatin C ratio in the assessment of muscle wasting and disease severity in stable COPD patients. **Methods:** This case-control study included 70 COPD patients and 20 age and gender-matched healthy controls. Pulmonary function tests, measurement of the serum creatinine (Cr) and cystatin C (Cys-C) levels, chest high-resolution CT images (HRCT) for the assessment of low attenuation area percentage (LAA%) and Erector Spinae muscle (ESM) thickness, routine laboratory investigations and arterial blood gases (ABG), were done. **Results**: There was a significant positive correlation between serum cystatin c and severity of COPD and LAA% but there was a significant negative correlation between serum cystatin c and Erector Spinae muscle cross-sectional area (ESMCSA), forced vital capacity %predicted (FVC% predicted), forced expiratory volume in 1 second (FEV1%predicted) FEV1/FVC%, and body mass index (BMI). Moreover, there was a significant positive correlation between creatinine/Cys C ratio and BMI, ESMCSA, FVC% predicted, FEV1/ FVC % and FEV1% predicted. The cut-off points of ESMCSA and Cr/Cys C for severe COPD were 23.4 cm^2 and 0.87 respectively. **Conclusion:** The present study indicated that the Cr/Cys C ratio is an easy, inexpensive, repeatable, and promising tool that allows us to evaluate muscle wasting in COPD patients using serum markers as there is a positive correlation between the degree of muscle wasting and the severity of COPD.

Keywords: COPD; Creatinine/Cystatin C Ratio; ESMCSA; Disease Severity.

Introduction

Muscle atrophy is a major clinical feature of chronic obstructive pulmonary disease (COPD), and it is considered a strong predictor of mortality in COPD patients (1). Bioelectrical impedance analysis, dual-energy X-ray absorptiometry, magnetic resonance imaging, B-mode ultrasound, and measurement of the cross-sectional area (CSA) of skeletal muscles such as the psoas muscles, intercostal muscles, abdominal muscles, or leg muscles on computed tomography (CT) scans are widely used to quantify both total and local skeletal muscle mass, and these muscles are known to reflect patient s' physical activity levels (2).

There is a strong correlation between the area of the psoas muscles and that of the dorsal muscles, which can be assessed by chest CT scans (3), and CSA of the erector spinae muscle group (ESMCSA) measured by chest CT scans has been reported as a clinical parameter of disease severity and future prognosis in patients with COPD. However, although measurement of the area of these muscle groups could provide accurate estimates of muscle atrophy in COPD patients, it may cause problems due to cost and possible radiation exposure, and it has limited accessibility for follow-up and epidemiological surveillance (4).

The prevalence of chronic renal failure in patients with COPD is underestimated when diagnosed by serum creatinine (Cr) levels because of reduced skeletal muscle mass (5). It becomes apparent that chronic renal dysfunction is a common comorbidity of COPD when renal function is measured by the glomerular filtration rate (GFR) or serum cystatin C (CysC), a surrogate marker for the GFR (6).

Serum Cr is the most commonly used parameter of renal function in clinical practice, but the serum and urinary Cr levels are affected by muscle mass (7). Conversely, the serum Cr levels could be a useful blood biomarker that reflects muscle mass in patients with normal renal function. Currently, CysC has been receiving considerable attention as a surrogate marker for GFR, since it is not affected by muscle mass (8).

The CysC-based estimated GFR (eGFR) is thought to be more appropriate for elderly persons who are susceptible to sarcopenia and COPD (9). The Cr/CysC ratio has been considered to be a quantitative marker of residual muscle mass and adverse effects of chemotherapy in patients with lung cancer, because serum Cr levels corrected by CysC are independent of renal function and are, theoretically, correlated with the muscle mass (10).

The purpose of this study was to assess the use of serum creatinine/serum Cystatin C ratio in the assessment of muscle wasting and correlate it with erector spinae CSA and disease severity in stable COPD patients.

Patients and methods

This case-control study included 70 COPD patients and 20 age and gender-matched healthy controls. This study was carried out in the Chest Department at Banha University Hospital during the period from June 2022 to June 2023.

Informed written consent from all patients before participation was obtained. The study was approved by the Local Ethics Committee on Research involving Human subjects of Benha Faculty of Medicine **(Ms 10-7-2022)**.

Patients included in this study were suffering from COPD, with the age of > 40 years, at least a 10-pack-year history of smoking and meeting the Global Initiative for Obstructive Lung Disease (GOLD) stage criteria for COPD based on postbronchodilator spirometry and another control group without COPD.

Patients on hemodialysis for chronic renal failure, having had any cancer across the entire life span, diabetic patients, and with abnormal thyroid functions were excluded.

All studied cases were subjected to the following: Detailed history taking and clinical evaluation, pulmonary function tests (spirometry), routine laboratory investigations including KFTs, LFTs, CBC, CRP, TSH, fasting blood glucose, T3, T4, and 2 hours postprandial glucose test 2HPP) and arterial blood gases (ABG).

All pulmonary function tests were done using a digital spirometer. One flow model (Clement Clarke International; Harlow, UK). The diagnosis of COPD was made based on the clinical history, physical examination, and spirometry data, following the GOLD classification.

Blood sample collection: five milliliters of fresh venous blood were collected under complete aseptic conditions and were divided into 1 milliliter of whole blood collected into EDTA containing vacutainer and mixed well for CBC, which was performed by automated hematology system (Sysmex XE 5000; Sysmex America, Inc, Mundelein, USA). The rest of the blood was collected into the empty tube and allowed to clot for 20 minutes then centrifuged for 5 min at 5000 rpm for serum preparation. The serum was separated in Eppendorf tubes for measurement of liver and kidney function tests using Biosystem A15 autoanalyzer (Biosystem S.A, Barcelona, Spain). The rest of the serum samples were stored at <-20°c. Serum Cystatin C (Cys-C) levels were estimated using an enzyme-linked immunosorbent assay (ELISA) kit; Sunred Biotechnology company; Catalogue No. 201-12-1105, sensitivity:0.427ng/ml, assay range: 0.6ng/ml→100ng/ml. The Cr/Cys C ratio was calculated by dividing the serum creatinine value by the serum cystatin C value.

The estimated glomerular filtration rate (eGFR) was calculated based on serum Cr and serum CysC levels using the

following equations according to the guideline of the Japanese Society of Nephrology: eGFR based on serum Cr (eGFRCr) level = 194× Cr−1.094× Age−0.287 (mL/min/1.73 m2) for men and 194× Cr−1.094× Age−0.287×0.739 (mL/min/1.73 m2) for women. eGFR based on serum CysC (eGFRCys) level = (104× CysC−1.019×0.996Age) −8 (mL/min/1.73m2) for men and (104× CysC−1.019×0.996Age ×0.929) −8 (mL/min/1.73 m2) for women.

Measurement of LAA% was performed by high-resolution CT scans with a slice thickness of 2 mm. LAA% was calculated using a threshold of − 960 Hounsfield units (HU) to assess the emphysematous changes and the total lung volume using the computer software LungVisionTM version (Toshiba 16 Slice CT Scanner, Toshiba Inc., Japan).

Erector Spinae muscle (ESM) Thickness was measured by Scans which were obtained using 2.0-mm thick sections of contiguous images from the apex to the base of the lung using (Toshiba 16 Slice CT Scanner, Toshiba Inc., Japan). Images were captured at a window setting of−600 HU (level) and 1500 HU (width). Chest CT images were reconstructed using the mediastinal setting and used for the ESM quantitative analysis. The area of the ESM on the cross-sectional CT image (ESMCSA) was measured at the level of the lower margin of the 12th thoracic vertebra. In brief, the left and right ESMs were identified and manually shaded, the cross-sectional areas of both ESMs were calculated, and the ESMCSA was presented as the sum of the right and left muscles.

Statistical analysis

Statistical analysis was done by SPSS v26 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). Quantitative variables were presented as mean and standard deviation (SD) and compared between the two groups utilizing Student's t-test. Qualitative variables were presented as frequency and percentage (%) and were analyzed utilizing the Chi-square test. Z-test for percentage used to compare the percentage of outcome between the two groups. Correlation analysis assesses the strength of the association between two quantitative variables. The ROC Curve (receiver operating characteristic) provides a useful way to evaluate the sensitivity and specificity of quantitative diagnostic measures. Logistic and linear regression analyses were used to predict risk factors when the dependent variable is categorical. A two-tailed P value < 0.05 was considered statistically significant.

Results

There was no significant difference between control, stage 1 COPD, stage 2 COPD, stage 3 COPD, and stage 4 COPD groups regarding age, sex, and pack-year smoking while there were significant differences between control,

stage 1 COPD, stage 2 COPD, stage 3 COPD, and stage 4 COPD groups regarding BMI as it was lower in the sever than the non-severe and control group. There was a significant difference between control, mild COPD, moderate COPD, and severe COPD groups regarding CRP, serum cystatin c, creatinine, Cr/Cys c ratio, eGFRCr, eGFRCys, PCO2, and HCO3, while there was no significant difference between control, mild COPD, moderate COPD, severe COPD groups regarding PH. There was a significant difference between control, mild COPD, moderate COPD, and severe COPD groups regarding FVC% predicted, FEV1/FVC%, and FEV1% predicted. It was lower in the severe than the non-severe and control groups. Also, ESMCSA significantly decreases, and LAA% significantly increases as the disease severity increases. (**Table 1) Fig. 1 &2**

There was a significant difference between stages 3 and 4 COPD, as regard BMI, CRP, serum cystatin, Cr/ Cys c ratio, eGFRCr, HCO3, FVC% predicted, FEV1/FVC%, FEV1% predicted, ESMCSA, and LAA%. There was a significant difference between stages 1 and 2 versus stages 3 and 4 COPD as regards BMI, creatinine, Cr/ Cys c ratio, eGFRCr, Pco2, FEV1/FVC%, FEV1% predicted, ESMCSA, FVC %predicted and LAA%. (**Table 2)**

In the bivariate analysis, it was found that age, FEV1%predicted, ESMCSA, and LAA% remained independent factors affecting Cr/ Cys C ratio. (**Table 3)**

There were significant positive correlations between Creatinine/ Cys C ratio and BMI, ESMCSA, FVC% predicted, FEV1/ FVC % and FEV1% predicted while there were significant negative correlations between Creatinine/ Cys C ratio and LAA%, and severity of COPD. Significant positive correlations were found between serum cystatin C and severity of COPD, and LAA%. However, significant negative correlations were found between serum cystatin C and ESMCSA, FVC% predicted, FEV1/FVC%, FEV1% predicted, and BMI. (**Table 4)**

Receiver operating characteristic (ROC) curves and areas under the ROC curves (AUCs) of Cr/CysC and ESMCSA for severe COPD show that the cut-off point of ESMCSA for severe COPD is 23.4 cm^2(AUC 0.720 (95% confidence interval [CI] 0.619–0.820), sensitivity = 76.5%, specificity = 68.5%), while the cut-off point of Cr/CysC for severe COPD is 0.87 (AUC 0.741 (95% CI 0.642–0.841), sensitivity = 88.2% specificity = 72.6%). (**Table 5)**

Table 1: Demographic data, Laboratory, ABG, Pulmonary functions and radiological findings of the studied groups

	Control	Stage 1 COPD	Stage 2 COPD	Stage 3 COPD	Stage 4 COPD	P value
No. (%)	20 (22.2)	17 (18.9)	16 (17.8)	17 (18.9)	20 (22.2)	0.431
Age by Years	72.9 ± 6.04	74.9 ± 7.9	72.9 ± 5.6	75.4 ± 6.7	73.7 ± 6.7	0.725
Sex Female	4 (4.4)	5 (5.6)	7 (7.8)	3 (3.3)	3 (3.3)	0.281
Male	16 (17.8)	12 (13.3)	9 (10)	14 (15.6)	17 (18.9)	
BMI	22.9 ± 2.5	22.9 ± 2	22.5 ± 2.2	21.5 ± 2.06	19.7 ± 2.3	0.04*
pack-year smoking	54.9 ± 19.6	57.8 ± 11.3	60.6 ± 24.98	56.2 ± 33.2	64.2 ± 18.3	0.05*
Laboratory and ABG findings						
CRP (mg/dl)	0.24 ± 0.12	0.30 ± 0.18	0.51 ± 0.29	0.58 ± 0.41	0.99 ± 0.86	< 0.001*
S.Cys c (mg/L)	0.78 ± 0.11	0.85 ± 0.12	0.87 ± 0.06	0.85 ± 0.08	0.91 ± 0.07	0.002*
Cr (mg/dl)	0.89 ± 0.18	1.02 ± 0.18	0.84 ± 0.08	0.73 ± 0.08	0.69 ± 0.06	< 0.001*
Cr/Cys c ratio	1.15 ± 0.25	1.21 ± 0.24	0.97 ± 0.09	0.85 ± 0.02	0.76 ± 0.06	< 0.001*
$eGFR_{Cr}$ (mL/min /1.73m2)	67.21 ± 14.2	56.78 ± 10.3	69.06 ± 6.34	80.37 ± 9.55	86.14 ± 7.56	< 0.001*
$eGFR_{Cys}$ (mL/min /1.73m2)	93.72 ± 15.4	84.46 ± 15.6	82.01 ± 6.44	83.13 ± 9.59	77.91 ± 6.1	< 0.001*
PH	7.41 ± 0.013	7.41 ± 0.014	7.41 ± 0.011	7.41 ± 0.018	7.40 ± 0.013	0.159
Pco2 (mmHg)	40.12 ± 8.35	44.66 ± 6.45	46.82 ± 6.44	57.43 ± 5.34	57.06 ± 4.83	< 0.001*
Hco3 (mEq/L)	26.24 ± 2.32	25.05 ± 4.07	25.21 ± 4.27	32.32 ± 3.60	37.46 ± 3.22	< 0.001*
Pulmonary functions and radiological findings in control and case groups						
FVC % predicted. (Mean ±SD).	100.05 ± 10.3	92.28 ± 3.84	85.1 ± 2.72	68.38 ± 3.74	51.7 ± 4.16	< 0.001
FEV1/FVC, % (Mean ±SD).	81.18 ± 3.32	65.65 ± 2.1	52.44 ± 6.65	39.81 ± 6.93	30.28 ± 6.72	< 0.001
FEV1% predicted. (Mean ±SD).	97.31 ± 9.41	93.11 ± 9.55	67.37 ± 5.83	42.38 ± 4.08	25.34 ± 3.14	< 0.001
ESMCSA (cm2) (Mean ±SD).	41.07 ± 5.73	29.38 ± 4.67	26.84 ± 2.80	21.91 ± 1.23	19.44 ± 0.77	< 0.001
LAA% (Mean ±SD).	8.29 ± 3.41	10.62 ± 5.63	14.97 ± 5.80	24.74 ± 4.51	34.71 ± 3.21	< 0.001

Note: Data represented as Mean ±SD or frequency (%), *: statistically significant as P value <0.05.

COPD: Chronic obstructive pulmonary disease, BMI: body mass index, CRP: C reactive protein, Cr: creatinine, CysC: cystatin C, eGFRCr: estimated glomerular filtration rate based on Cr, eGFRCys: estimated glomerular filtration rate based on CysC, FVC % predicted: Forced Vital Capacity % predicted, FEV1% predicted: Forced Expiratory Volume in 1 Second % predicted, LAA: Low attenuation area, ESMCSA: cross-sectional area of erector spinae muscles.

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Table 2: Demographic data, laboratory findings, ABG, and radiological findings of stages 3 and 4 COPD, of stages 1 and 2 versus stages 3 and 4 COPD

		Stage 3 COPD	Stage 4 COPD	P value
Age by Year		75.4 ± 6.7	73.7 ± 6.7	0.456
Sex	**Female**	3 (3.3)	2 (18.18%)	0.828
	Male	17 (18.9)	9 ((81.8%)	
BMI (kg/m²)		21.5 ± 2.06	19.7 ± 2.3	0.015*
pack-year smoking		56.2 ± 33.2	64.2 ± 18.3	0.366
CRP (mg/dl)		0.58 ± 0.41	0.99 ± 0.86	0.001*
S.Cys c (mg/L)		0.85 ± 0.08	0.91 ± 0.07	0.043*
Cr (mg/dl)		0.73 ± 0.08	0.69 ± 0.06	0.064*
Cr/Cys c ratio		0.85 ± 0.02	0.76 ± 0.06	< 0.001*
$eGFR_{Cr}$ (mL/min /1.73m2)		80.37 ± 9.55	86.14 ± 7.56	0.048*
$eGFR_{Cys}$ (mL/min /1.73m2)		83.13 ± 9.59	77.91 ± 6.1	0.052*
PH		7.41 ± 0.018	7.40 ± 0.013	0.291
Pco2 (mmHg)		57.43 ± 5.34	57.06 ± 4.83	0.827
Hco3 (mEq/L)		32.32 ± 3.60	37.46 ± 3.22	< 0.001*
FVC, % predicted		68.38 ± 3.74	51.7 ± 4.16	< 0.001*
FEV1/FVC, %		39.81 ± 6.93	30.28 ± 6.72	< 0.001*
FEV1, % predicted		42.38 ± 4.08	25.34 ± 3.14	< 0.001*
ESMCSA (cm2)		21.91 ± 1.23	19.44 ± 0.77	< 0.001*
LAA%		24.74 ± 4.51	34.71 ± 3.21	< 0.001*
		Stages 1 + 2 COPD	**Stages 3 + 4 COPD**	
Age by Year		73.97 ± 6.85	74.49 ± 6.85	0.754
Sex	**Female**	12 (36.36)	6 (16.22)	0.054
	Male	21 (63.64)	31 (83.78)	
BMI (kg/m²)		22.72 ± 2.07	20.53 ± 2.35	< 0.001*
pack-year smoking		58.85 ± 22.16	60.51 ± 26.11	0.776
CRP (mg/L)		0.54 ± 0.35	0.62± 0.68	0.570
S.Cys c (mg/L)		0.86 ± 0.09	0.88 ± 0.08	0.305
Cr (mg/dl)		0.93 ± 0.17	0.71 ± 0.07	< 0.001*
Cr/Cys c ratio		1.09 ± 0.22	0.80 ± 0.06	<0.001*
$eGFR_{Cr}$ (mL/min /1.73m2)		62.74 ± 10.49	83.49 ± 8.90	<0.001*
$eGFR_{Cys}$ (mL/min /1.73m2)		83.27 ± 11.95	80.31 ± 8.21	0.227
pH		7.41 ± 0.01	7.40 ± 0.02	0.310
PCO2 (mmHg)		45.71 ± 6.44	57.23 ± 5.00	<0.001*
Hco3 (mEq/L)		25.55 ± 4.87	35.10 ± 4.24	0.160
FVC, % predicted		88.80 ± 4.91	58.90 ± 8.84	<0.001*
FEV1/FVC, %		59.24 ± 8.24	34.66 ± 8.26	<0.001*
FEV1, % predicted		80.63 ± 15.24	33.17 ± 9.32	<0.001*
ESMCSA (cm2)		28.15 ± 4.03	20.57 ± 1.60	<0.001*
LAA%		12.73 ± 6.04	30.13 ± 6.32	<0.001*

Note:Data represented as Mean ±SD or frequency (%), *: statistically significant as P value <0.05.

COPD: Chronic obstructive pulmonary disease, BMI: body mass index, CRP: C reactive protein, Cr: creatinine, CysC: cystatin C, eGFRCr: estimated glomerular filtration rate based on Cr,eGFRCys: estimated glomerular filtration rate based on CysC, FVC % predicted: Forced Vital Capacity % predicted, FEV1% predicted: Forced Expiratory Volume in 1 Second % predicted, LAA: Low attenuation area, ESMCSA: cross-sectional area of erector spinae muscles.

Table 3: Bivariate Logistic Analysis to assess independent factors affecting Cr/Cys C

	OR (95% CI)	P value
Age in years	0.81 (0.69–0.94)	**0.007**
FVC, % predicted	0.96 (0.86–1.07)	**0.44**
FEV1, % predicted	1.1 (1.01–1.18)	**0.02**
FEV1/FVC, %	1.09 (0.95–1.22)	**0.15**
ESMCSA in cm2	0.77 (0.64–0.93)	**0.006**
LAA%	0.84 (0.72–0.98)	**0.029**
CRP in mg/L	0.59 (0.04–8.17)	**0.69**
BMI (kg/m²)	1.02 (0.73-1.42)	**0.899**

Note: p value >0.05: nonsignificant, p value <0.05 significant.

FVC % predicted: Forced Vital Capacity % predicted, FEV1% predicted: Forced Expiratory Volume in 1 Second % predicted, LAA: Low attenuation area, ESMCSA: cross-sectional area of erector spinae muscles, BMI: body mass index, CRP:C reactive protein.

Table 4: Correlation between Cr/Cys ratio and other variables and between S. Cys c and other variables in COPD patients

Variable		Creatinine/ cys ratio	S.Cys C
ESMCSA in cm2	r	0.543	-0.389
	P	< 0.001	< 0.001
LAA%	r	-0.635	0.302
	P	< 0.001	0.004
Age in years	r	-0.194	0.038
	P	0.067	0.719
Pack year smoking	r	-0.194	0.030
	P	0.068	0.782
CRP (mg/L	r	-0.139	0.156
	P	0.193	0.141
FVC,% predicted	r	0.625	-0.353
	P	< 0.001	< 0.001
FEV1/ FVC,%	r	0.677	-0.365
	P	< 0.001	<0.001
severity of COPD	r	-0.700	0.379
	P	< 0.001	< 0.001
FEV1,% predicted	r	0.722	-0.349
	P	< 0.001	< 0.001
BMI (Kg/m²)	r	0.279	-0.209
	P	0.008	0.048

COPD: Chronic obstructive pulmonary disease, ESMCSA: cross-sectional area of erector spinae muscles, LAA: Low attenuation area, CRP: C reactive protein, FVC % predicted: Forced Vital Capacity % predicted, FEV1% predicted: Forced Expiratory Volume in 1 Second % predicted, BMI: body mass index.

Table 5: ROC curve analysis of ESMCSA and Cr/Cys ratio

Variable(s)	Area	Sensitivity	Specificity	Cut off value	CI 95%	
					Lower	**Upper**
ESMCSA in cm2	0.720	76.5	68.5	23.4	0.619	0.820
Cr/Cys c ratio	0.741	88.2	72.6	0.87	0.642	0.841

ESMCSA: cross-sectional area of erector spinae muscles, Cr: creatinine, CysC: cystatin C.

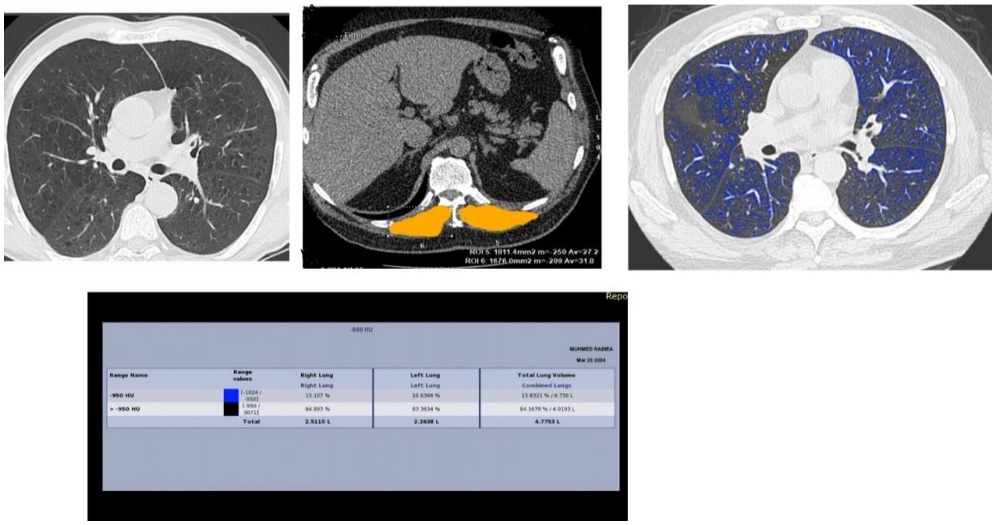

Fig. (1): Representative chest computed tomography (CT) image used to measure the cross-sectional area of erector spinae muscles (ESMCSA). The manually selected area (yellow) is used to measure ESMCSA using the computer software and the table shows the low attenuation area percentage (LAA%) in a mild COPD case.

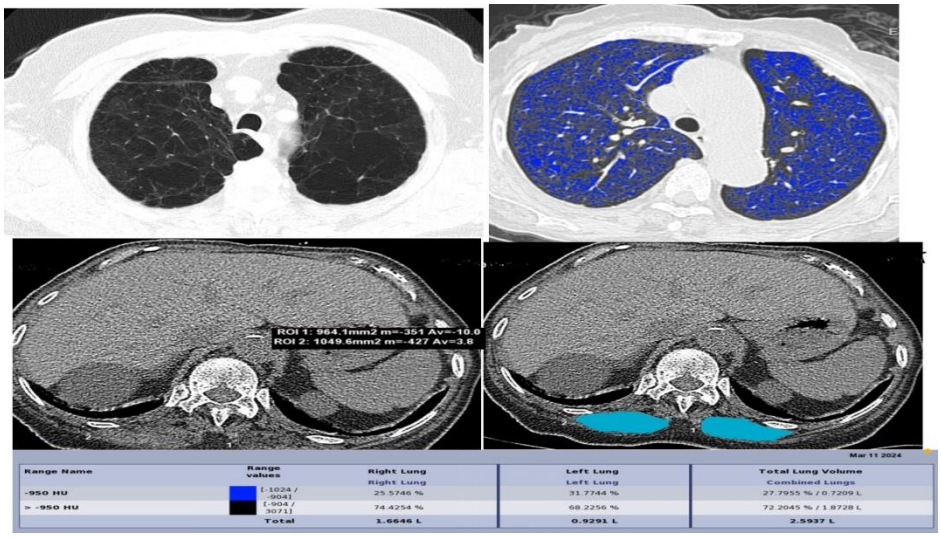

Fig. (2) Representative chest computed tomography (CT) image used to measure the cross-sectional area of erector spinae muscles (ESMCSA). The manually selected area (blue) is used to measure ESMCSA using the computer software and the table shows the low attenuation area percentage (LAA%) in a severe COPD case.

Discussion

As regards demographic data of the studied groups, there was no significant difference between control, stage 1 COPD, stage 2 COPD, stage 3 COPD, and stage 4 COPD groups regarding age, sex, or pack-year smoking index while there were significant differences between them regarding BMI as it was lower in the severe than the non-severe and control group.

There was a significant difference between control, mild COPD, moderate COPD, severe COPD, and very severe groups regarding CRP, serum cystatin c; as there were higher in stage 4 COPD, while creatinine and Cr/Cys c ratio were higher in stage 1 COPD than the other groups.

Regarding eGFRCr, it was higher in stage 4 COPD than the other groups, but eGFRCys was higher in control than in case groups.

PCO2 and HCO3 were more in stage 3,4 COPD than the other groups. (p-value <0.05), while there was no significant difference between the control, Mild COPD, Moderate COPD, and severe COPD groups regarding pH (p-value>0.05).

In the study done before (11), there were no significant differences between mild, moderate, or severe COPD groups in terms of age, sex, or smoking history. The LAA% was significantly higher in the severe COPD group than in the mild and moderate COPD groups ($p < 0.01$). C-reactive protein (CRP) was significantly higher in the severe COPD group compared to the moderate COPD group ($p < 0.01$). There were no significant differences in serum CysC between groups; however, serum Cr was significantly decreased in the severe COPD group compared with the mild COPD group ($p < 0.05$), and the serum Cr/CysC was considerably reduced in the severe COPD group compared with the mild and moderate COPD groups ($p < 0.05$). The BMI was significantly lower in the severe COPD group than the mild COPD group ($p < 0.05$) (11).

In this study, regarding the Pulmonary functions and radiological findings in control and case groups, there was a significant difference between control, mild, moderate, severe, and very severe COPD groups regarding %predicted, FEV1/FVC%, FEV1% predicted, It was lower in the severe (stage 3,4) than the non-severe (stage 1,2) and control group. It was also found that ESMCSA significantly decreased and LAA% significantly increased as the disease severity increased. While there was a significant difference between groups (stages 3 and 4 COPD) as regard BMI, CRP, serum cystatin, Cr/ Cys c ratio, eGFRCr, HCO3, FVC% predicted, FEV1/FVC%, FEV1% predicted, ESMCSA, and LAA%.

These results disagreed with Huang et al., in which 32 patients with stable

COPD and 72 patients with AECOPD were enrolled in their study. no differences between groups were found in terms of age, weight, BMI, smoking history, or FEV1/FVC, CysC, (all P > 0.05), Compared with the stable COPD group, the AECOPD group had lower FEV1, FVC, FEV1%pred (percent of forced expiratory volume in 1 second), HGS (handgrip strength), Cr/CysC ratio, and serum Cr (all P < 0.05) (12).

Regarding the difference between non-severe (stages 1 and 2) and severe (stages 3 and 4) COPD, there was significant difference between groups as regard BMI, Cr, Cr/Cys c ratio, eGFRCys, FVC, FEV1/FVC, FEV1, ESMCSA as they were higher in non-severe than in severe COPD, While CRP and S.Cys c, eGFRCr, Pco2, Hco3 and LAA% were higher in severe than non-severe COPD. In a study by Nishiki and his colleagues, the Cr/CysC ratio in patients with COPD was significantly inversely related to age. This ratio was also weakly positively correlated with BMI and weakly inversely correlated with LAA%. FEV1 and FVC values were also significantly correlated with the Cr/CysC ratio, and FEV1%, %FEV1, and %FVC were weakly correlated with this ratio (13).

While in He et al., study, the Cre/Cys C ratio was significantly associated with age (P = .000); weight (P = .000;), BMI (P = .007), FEV1/FVC ratio (P = .074) and predicted FVC% (P = .009). The results showed that the most significant predictors of the Cre/Cys C ratio were age (P = .007), weight (P = .000), BMI (P = .000), and predicted FEV1 (P = .000) (14).

In the bivariate analysis including age, FEV1%predicted, ESMCSA, and LAA%, it was found that these factors were independent factors affecting the Creatinine/ Cys ratio.

Binary logistic analysis was performed in Nishiki et al., study with age, BMI, CRP, %FVC, FEV1%, % FEV1, LAA%, ESMCSA, and Cr/Cys C, respectively. They found that sex and FEV1% predicted affected the Cr/Cys C ratio (13).

While in Kawasaki et al., regression analysis was performed to evaluate the association between clinical parameters measured in their study and respiratory disease-related mortality, the FVC percent predicted value (p < 0.01), FEV1/FVC (p < 0.05), FEV1 percent predicted value (p < 0.01), LAA% (p < 0.0001), serum Cr/CysC (p < 0.01), ESMCSA (p < 0.0001), and BMI (p < 0.001) were significantly associated with mortality. Subsequently, multivariate Cox regression analysis was conducted to examine the independent contributions of these factors to mortality. The serum Cr/CysC remained a significant predictor of mortality, regardless of age or airflow limitations p < 0.05). Similarly, the ESMCSA (p < 0.01) and BMI (p < 0.01) were also independently associated with mortality (11).

There was a significant positive correlation between Creatinine/ Cys C ratio and BMI, ESMCSA, FVC% predicted, FEV1/ FVC %, and FEV1% predicted. Also, there was a significant negative correlation between Creatinine/ cys ratio and LAA%, and the severity of COPD. In a similar study by Huang et al., they observed that the Cr/Cys C ratio was positively correlated with BMI ($r = 0.469$, $P<0.01$), weight ($r = 0.469$, $P < 0.01$), HGS ($r = 0.388$, $P < 0.01$), FEV1 ($r = 0.246$, $P = 0.037$), FVC ($r = 0.332$, $P < 0.01$), and FEV1%pred ($r = 0.244$, $P = 0.039$). Serum CysC showed no correlations with the above indicators except weight ($r =-0.242$, $P = 0.041$), while Cr was positively correlated with only BMI, weight, and FEV1%pred ($r = 0.307$, $r = 0.241$, $r = 0.287$, respectively, $P<0.05$) (12).

In another study, in the high Cre/Cys C ratio group, the moderate COPD group had a significantly elevated BMI compared with the mild, severe, and very severe groups ($P = .041$). There were no significant differences in other parameters (14).

In the current study, there was a significant positive correlation between serum cystatin c and severity of COPD and LAA% but there was a significant negative correlation between serum cystatin c and ESMCSA, FVC% predicted, FEV1/FVC%, FEV1%predicted, and BMI.

These results were in agreement with the study in which the sarcopenia index (Creatinine/Serum Cystatin c ×100) was calculated in 18 healthy control subjects and 65 stable COPD outpatients, COPD patients had a lower SI than controls and concluded that the ratio serum creatinine\serum cystatin C correlates with several COPD characteristics, and it can be used to predict COPD hospitalization (15).

In a study published in 2021, serum Cr\Cys C was significantly correlated with handgrip strength ($p<0.01$) and muscle mass ($p<0.01$) and concluded that serum creatinine\serum cystatin C ratio can be used accurately, inexpensively, and easily to evaluate sarcopenia in COPD patients (16).

In another study published in the same year, 2021, the serum Cr levels in all patients were not correlated with ESMCSA, but the serum Cr level in patients with normal serum CysC levels (CysC < 0.95 mg/L) was significantly correlated with the ESMCSA. Furthermore, the serum Cr/CysC ratio was significantly correlated with the ESMCSA in all patients in their study (13).

Receiver operating characteristic (ROC) curves and AUC of Cr/CysC and ESMCSA for severe COPD, showed that the cut-off point of ESMCSA to detect severe COPD is 23.4 (AUC 0.720 (95%) confidence interval [CI] 0.619–0.820), sensitivity = 76.5%, specificity = 68.5%), it also detects cut-off value of Cr/CysC to detect severe COPD is 0.87

(AUC 0.741 (95% CI 0.642–0.841), sensitivity = 88.2% specificity = 72.6%).

According to that former study (13), the researchers found that the cut-off points of ESMCSA and Cr/CysC for severe COPD were 24.7 (AUC 0.705 [95% CI 0.625–0.785], sensitivity = 59.3%, specificity = 76.5%) and 0.885 (AUC 0.688 [95% CI 0.616–0.760], sensitivity = 81.8%, specificity = 51.4%), respectively (13)

As in Chen et al., a study that was done on patients with AECOPD (n = 597) were retrospectively enrolled. The patient's clinical characteristics and laboratory tests, including serum cystatin C and creatinine, were reviewed. The prediction value of the CCR (creatinine/cystatin C) ratio was evaluated using the area under the receiver operating characteristic curve (AUC) values. Factors potentially impacting in-hospital mortality were investigated using univariate and multivariate logistic regression analyses, they detected that the mortality rate during hospitalization was 10.05%. CCR was lower in non-surviving vs. survived patients (41.67 vs. 61.52, P<0.001). The AUC value for CCR for in-hospital mortality prediction was 0.79 (17).

Conclusion

We concluded that the serum Cr/CysC ratio is associated with age, ESMCSA, LAA% and FEV1%predicted, which remain independent factors affecting creatinine / Cys C ratio.

The present study indicated that the Cr/Cys C ratio is an easy, inexpensive, repeatable, and promising tool that allows us to evaluate muscle wasting in COPD patients using serum markers.

Additionally, this ratio could be used in estimating muscle mass in different settings, including retrospective cohort studies, if the serum of the patients is properly stored.
Additional studies will be necessary to confirm the clinical value of this ratio in assessment of the COPD patients.

List of abbreviations

COPD: Chronic obstructive pulmonary disease ,PFT: pulmonary function tests, FVC % predicted: Forced Vital Capacity % predicted, FEV1% predicted: Forced Expiratory Volume in 1 Second % predicted, BMI: body mass index, CRP: C reactive protein, ABG: arterial blood gas, CT: computed tomography Cr: creatinine, CysC: cystatin C, eGFRCr: estimated glomerular filtration rate based on Cr, eGFRCys: estimated glomerular filtration rate based on CysC, GFR: glomerular filtration rate, LAA%: Low attenuation area percentage, ESMCSA: cross-sectional area of erector spinae muscles, GOLD: Global Initiative for Obstructive Lung Disease, HRCT: high resolution computed tomography, HU: Hounsfield units, ROC: Receiver operating characteristic, AUCs: areas under the curves ,SI: Sarcopenia Index, AECOPD: acute exacerbations of chronic obstructive pulmonary disease, HGS :handgrip strength, CBC: complete blood count, 2HPP:2-hour postprandial glucose, KFT: kidney function tests, LFT: liver function tests ,TSH :thyroid-stimulating hormone,

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