Serum Creatinine to Cystatin C Ratio is an Effective Indicator for Muscle Strength Decline in Men with Acute Exacerbation of Chronic Obstructive Pulmonary Disease

Dan Huang*, Canhui Xie*, Chaoqun Sun*, Min Chen, Lian Li, Huajuan Yi, Jinyu Liao, Xuanna Zhao, Xiaoping Shen, Donglan He, Dongming Li, Dong Wu

Department of Respiratory and Critical Care Medicine, Affiliated Hospital of Guangdong Medical University, Zhanjiang, People’s Republic of China

*These authors contributed equally to this work

Correspondence: Dong Wu; Dongming Li, Department of Respiratory and Critical Care Medicine, Affiliated Hospital of Guangdong Medical University, 57th South Renmin Road, Zhanjiang, 524001, Guangdong, People’s Republic of China, Tel/Fax +867592387413, Email wudong98@126.com; 1335887835@qq.com

Purpose: This study explored the value of the serum creatinine/cystatin C (Cr/CysC) ratio in diagnosing the reduction of muscle strength in men with acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

Patients and Methods: In this study, we enrolled 72 male patients with AECOPD and 32 male patients with stable chronic obstructive pulmonary disease (COPD). We compared clinical characteristics between the AECOPD and stable COPD groups. Then, we subdivided AECOPD patients into normal muscle strength and low muscle strength groups; we compared the clinical characteristics between these two groups. We analyzed the relationships of serum creatinine (Cr), cystatin C (CysC), and Cr/CysC ratio with clinical characteristics in male AECOPD patients. We also investigated whether the Cr/CysC ratio could aid in the diagnosis of muscle strength decline via receiver operating characteristic curve and binary logistic regression analysis.

Results: We found that handgrip strength, Cr/CysC ratio, serum Cr, FEV$_1$, FVC, and FEV$_1$%pred were lower in AECOPD patients than in stable COPD patients. Among AECOPD patients, BMI, weight, FEV$_1$, FVC, FEV$_1$%pred, and Cr/CysC ratio were lower in the low muscle strength group than in the normal muscle strength group; there were more patients with ≥2 acute exacerbations within the past year in the low muscle strength group. The Cr/CysC ratio was correlated with handgrip strength, FEV$_1$, FVC, FEV$_1$%pred, BMI and weight. The area under curve for low handgrip strength was greater for the Cr/CysC ratio than for Cr. Binary logistic regression analysis showed that a Cr/CysC ratio <0.99 was a risk factor for decreased muscle strength in male patients with AECOPD.

Conclusion: The Cr/CysC ratio is a useful predictor of muscle strength decline in male AECOPD patients, while a low Cr/CysC ratio is a risk factor for muscle strength decline in male patients with AECOPD.

Keywords: muscle strength, AECOPD, male, Cr/CysC ratio, handgrip strength

Introduction

Chronic obstructive pulmonary disease (COPD) is a common chronic airway disease characterized by persistent respiratory symptoms and irreversible airflow limitation, which severely threatens human health. In 2010, there were 384 million patients suffering from COPD worldwide, with an overall prevalence of 11.7%. The prevalence of COPD is expected to gradually increase in the next 40 years; more than 5.4 million people are expected to die of COPD and related diseases each year by 2060. Patients with COPD often exhibit comorbidities such as cardiovascular disease, osteoporosis, skeletal muscle disease, lung cancer, anxiety, and depression; these additional diseases have significant impacts on mortality, frequency of acute exacerbation, hospitalization rate, and quality of life in affected patients.
Sarcopenia is a common comorbidity of COPD with clinical features that include age-related loss of skeletal muscle mass and loss of muscle strength and/or reduced physical performance. According to the most recent European Working Group on Sarcopenia in Older People, low muscle strength is a prerequisite for the diagnosis of sarcopenia; handgrip strength (HGS) measurement is a reliable alternative to complex muscle strength measurement methods, such as arm and leg strength measurement. Studies have shown that malnutrition is one of the main factors for frequent exacerbations of COPD and increased risk of death, and it is also an important contributor to sarcopenia. HGS is not only a simple method to screen for sarcopenia but also a useful tool for diagnosing malnutrition. Current studies have shown that HGS is positively correlated with forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) in COPD patients and it can be used to assess the severity of patients. Low HGS is associated with adverse events in patients with COPD; patients with low HGS also have worse quality of life, as well as increased risks of morbidity, mortality, and exacerbation.

Serum creatinine (Cr) is mainly produced by creatine via slow and stable non-enzymatic cyclization; it is then released into the blood and excreted through the kidneys. However, creatine is mainly produced by the liver and transported to the muscles; 98% of the creatine pool is stored in the muscles. Thus, the serum Cr concentration is related to muscle mass; this concentration is easily affected by renal function. Cystatin C (CysC) is a low molecular weight protein produced by all nucleated cells at a constant rate; it can be freely filtered by the glomerulus and reabsorbed, then catabolized in the proximal tubules. CysC concentration is mainly determined by the glomerular filtration rate, regardless of sex, age, and muscle mass.

Based on the physiological characteristics of serum Cr and CysC, the serum Cr/CysC ratio has been used to evaluate sarcopenia. Some studies have found that Cr/CysC ratio was a valuable indicator of muscle mass and was positively correlated with muscle mass. Cr/CysC ratio can also assess muscle strength and has been shown to be associated with decreased muscle strength in terminal cancer patients, non-dialysis chronic kidney disease patients and elderly inpatients. Cr/CysC ratio has shown a good correlation with HGS in patients with stable COPD. In addition, because of differences in physical fitness between men and women, HGS is usually higher in men than in women, and Cr/CysC ratio as an evaluation index of muscle strength corresponds to higher. A cross-sectional study including 2339 participants aged ≥40 years found that HGS and Cr/CysC ratios were higher in men than in women; moreover, the Cr/CysC ratio was positively correlated with HGS. To our knowledge, there have been few studies of the Cr/CysC ratio in patients with COPD; only one study has investigated the clinical value of Cr/CysC ratio in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

This study was performed to analyze the relationships of the Cr/CysC ratio with various clinical indicators and HGS in male AECOPD patients; it also explored the feasibility of the Cr/CysC ratio as an assessment of muscle strength decline in AECOPD patients.

Materials and Methods

Patient Population

This prospective study enrolled 72 male AECOPD patients and 32 male stable COPD patients who were treated in the Affiliated Hospital of Guangdong Medical University from November 2020 to October 2021. COPD and AECOPD were diagnosed in accordance with the Global Initiative for Chronic Obstructive Lung Disease 2020 (GLOD 2020) criteria. AECOPD were defined as an acute worsening of respiratory symptoms that result in additional therapy. Inclusion criteria included: (1) all patients met the diagnostic criteria for COPD defined by GOLD 2020: dyspnea, history of chronic cough or sputum production, and/or a history of exposure to factors for the disease, together with lung function tests showed forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) <0.70 after inhalation of bronchodilator, (2) male sex, (3) consent to participate in the study, and (4) age ≥40 years. Exclusion criteria included inability to complete spirometry and/or the presence of the following conditions: chronic kidney disease or acute kidney injury, comorbid malignancy or history of treatment for malignancy, severe respiratory disease except COPD, and/or comorbidity that affected muscle status (eg, abnormal thyroid function, orthopedic disease, or severe neuromuscular disease). Our study complied with the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects.
The study protocol was approved by the Ethics Committee of the Affiliated Hospital of Guangdong Medical University (Approval number: PJ2017066; Date: 4th Sep 2017); all participants provided written informed consent.

Subgroups
According to the Asian Working Group for Sarcopenia (AWGS) 2019 guidelines, HGS < 28 kg in men is defined as low muscle strength. In this study, the HGS was measured in all participants. Participants with HGS < 28 kg and ≥ 28 kg were included in the low muscle strength and normal muscle strength groups, respectively. All participants used an electronic handgrip dynamometer (CAMRYEH102, Xiangshan, Zhongshan, China) to perform strength measurements with their dominant hand. During the measurement, we first adjusted the dynamometer to an appropriate grip distance according to the size of the participants’ hand; Then, the participants’ body kept upright, feet were shoulder-width apart, elbows were fully extended, and the force was measured by squeezing with the dominant hand. A total of three HGS measurements were taken, and the maximum HGS value was used for subsequent analyses.

Clinical and Laboratory Measurements and Spirometry
Data were collected regarding age, sex, course of disease, height, weight, body mass index (BMI), smoking history, and exacerbation history. Serum Cr was measured by the picric acid method, and urea nitrogen was measured by urease ultraviolet absorption spectrophotometry. Serum CysC was measured by latex enhanced immune turbidimetry and the assay details were as follows: Buffer-diluted serum samples were mixed with latex covalently bound antibodies to form stable antigen–antibody complexes, resulting in a certain degree of turbidity. By measuring the absorbance of the mixture and comparing it with the calibration solution under the same conditions, the concentration of CysC in the sample could be calculated. All measurements were conducted by our hospital’s clinical laboratory. The COPD Assessment Test (CAT) was used to assess the impact of COPD on health status; the modified Medical Research Council (mMRC) dyspnea scale was used to assess the degree of dyspnea. We performed spirometry according to the guidelines for lung function tests formulated by the Chinese Thoracic Society. The procedures and diagnostic criteria in this guideline are not significantly different from the ATS/ERS guideline.

Statistical Analysis
All statistical analyses were performed using SPSS software, version 22.0 (SPSS Inc., Chicago, IL, USA). The normalities of data distributions were assessed using the Kolmogorov–Smirnov test. Independent samples t-tests were used for the comparison of normally distributed continuous variables. The Mann–Whitney U-test was used for the comparison of non-normally distributed continuous variables. Categorical variables were compared using the two-sided Fisher’s exact test or the chi-squared test. Correlations between continuous variables were assessed by Spearman correlation analysis. Receiver operating characteristic (ROC) curves were used to compare the efficacies of serum Cr and Cr/CysC ratios for predicting muscle strength decline in male AECOPD patients; they were also used to calculate the corresponding cut-off value. The risk factors in male AECOPD patients, combined with muscle strength decline, were analyzed via binary logistic regression; variance inflation factors (VIF) were computed as a collinearity diagnostic check. VIF < 10 indicates that there is no multicollinearity among the parameters, and that these parameters will be included in the binary logistic regression for statistics. Two-sided P-values <0.05 were considered to indicate statistical significance.

Results
Participant Characteristics
In total, 32 patients with stable COPD and 72 patients with AECOPD were enrolled in this study. No differences between groups were found in terms of age, height, weight, BMI and BMI stratification, smoking history, course of disease, ≥2 acute exacerbations within 1 year, FEV₁/FVC, CysC, or urea nitrogen (all P > 0.05). Compared with the stable COPD group, the AECOPD group had higher CAT and mMRC scores; it also had lower FEV₁, FVC, FEV₁%pred (percent of Forced Expiratory Volume in 1 second), HGS, Cr/CysC ratio, and serum Cr (all P < 0.05) (Table 1).
Comparison of Clinical Characteristics Between Normal Muscle Strength and Low Muscle Strength Subgroups of AECOPD Patients

Based on the normal value of HGS in men, as defined by the AWGS 2019 guidelines, patients with AECOPD were divided into normal muscle strength and low muscle strength groups. No differences between the groups were found in terms of age, height, BMI stratification, course of disease, smoking history, CAT score, mMRC score, FEV$_1$/FVC, serum Cr, CysC, and urea nitrogen (all $P > 0.05$). BMI, weight, FEV$_1$, FVC, FEV$_1$/pred, HGS, and Cr/CysC ratio were lower in the low muscle strength group than in the normal muscle strength group; there was a greater proportion of patients with ≥2 acute exacerbations within 1 year ($P < 0.05$) (Table 2).

| Table 1 Comparison of Characteristics Between Stable COPD and AECOPD Groups |
|-----------------------------|-----------------------------|-----------------------------|
| Clinical Characteristics    | Stable COPD Group (n = 32)  | AECOPD Group (n = 72)       |
|                             | Age (years)                 | 65.13±9.67                  |
|                             | Height (m)                  | 1.65±(1.62–1.69)            |
|                             | Weight (kg)                 | 55.27±7.78                  |
|                             | BMI (kg/m$^2$)              | 20.50±2.98                  |
|                             | Underweight* (n, %)         | 8(25.00%)                   |
|                             | Normal weight* (n, %)       | 20(62.50%)                  |
|                             | Overweight* (n, %)          | 4(12.50%)                   |
|                             | Smoking history (Yes/No)    | 30/2                        |
|                             | Course of disease (months)  | 48(36.00–114.00)            |
|                             | Acute exacerbations ≥2 within one year (Yes/No) | 9/23 |
|                             | HGS (kg)                    | 34.00(27.80–35.40)          |
|                             | mMRC score                  | 1.50(0.00–3.0)              |
|                             | CAT score                   | 9.0(4.0–17)                 |
|                             | FEV$_1$ (L)                 | 1.23(0.78–1.53)             |
|                             | FVC (L)                     | 2.50±0.74                   |
|                             | FEV$_1$/FVC                 | 48.71±9.33                  |
|                             | FEV$_1$/FVCpred             | 45.93±16.88                 |
|                             | Cr (mg/dl)                  | 0.94±0.19                   |
|                             | CysC (mg/L)                 | 0.89±0.18                   |
|                             | Cr/CysC ratio               | 1.08(0.91–1.23)             |
|                             | Urea nitrogen (μmol/L)      | 5.10(4.06–6.18)             |

Notes: *Underweight (BMI<18.5 kg/m$^2$); *Normal weight (18.5 kg/m$^2$ ≤BMI< 24 kg/m$^2$); *Overweight (24 kg/m$^2$ ≤BMI< 28 kg/m$^2$).

Abbreviations: COPD, chronic obstructive pulmonary disease; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BMI, body mass index; HGS, handgrip strength; mMRC, modified British Medical Research Council; CAT, COPD Assessment Test; FEV$_1$, forced expiratory volume in 1 second; FVC, functional vital capacity; FEV$_1$/FVC, forced expiratory volume in 1 second /forced vital capacity; FEV$_1$/pred, percent of forced expiratory volume in 1 second; Cr, creatinine; CysC, cystatin C; Cr/CysC, creatinine/cystatin C.

Correlations of Serum Cr, CysC, and Cr/CysC Ratio with Clinical Characteristics in Patients with AECOPD

The Cr/CysC ratio was positively correlated with BMI ($r = 0.469, P<0.01$), weight ($r = 0.469, P<0.01$), HGS ($r = 0.388, P<0.01$), FEV$_1$ ($r = 0.246, P = 0.037$), FVC ($r = 0.332, P < 0.01$), and FEV$_1$/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 FEV$_1$/pred ($r = 0.307, r = 0.241, r = 0.287$, respectively, $P<0.05$) (Table 3).

Sensitivity and Specificity of Serum Cr and Cr/CysC Ratio for Identifying Male AECOPD Patients with Decreased Muscle Strength

ROC curve analysis showed that Cr/CysC ratio at the cut-off of 0.99 yielded an area under the curve (AUC) of 0.731 for identifying male AECOPD patients with low muscle strength, with a sensitivity and specificity of 83.9% and 63.4%,
respectively. The AUC for serum Cr was 0.605; the optimal sensitivity (41.9%) and specificity (85.4%) were obtained with a cut-off concentration of 0.73 mg/dL (Figure 1).

### Analysis of Risk Factors for Muscle Strength Decline in Male Patients with AECOPD

Binary logistic regression analysis of the AECOPD group was performed with HGS as the dependent variable. In order to avoid the existence of collinearity in these variables interfering with the accuracy of the regression analysis, we performed collinearity diagnosis and found collinearity in BMI and weight, as well as FEV₁ and FEV₁%pred. Therefore, FVC, FEV₁ and weight were included in the binary logistic regression analysis as independent variables.
Cr/CysC ratio was dichotomized based on the appropriate cut-off value that was determined according to the ROC curve. The results showed that Cr/CysC ratio <0.99 (OR = 5.779, 95% CI: 1.671–19.982, \( P<0.05 \)) was identified as a risk factor for low muscle strength in male patients with AECOPD (Table 4).

### Discussion

The main causes of sarcopenia include satellite cell senescence, oxidative stress, chronic inflammation, and motor unit loss. However, the causes of sarcopenia in patients with COPD are more complex; factors such as chronic hypoxia, malnutrition, long-term glucocorticoid use, and muscle waste should be considered. The diagnosis of sarcopenia is inseparable from the measurement of muscle mass and muscle strength; low muscle strength is a key factor in the diagnosis of sarcopenia. In recent years, there has been increasing focus on muscle strength, mainly because muscle strength is more reliable than muscle mass for predicting adverse events. In a 3-year follow-up of 498 patients, Schaap et al found that the incidence of recurrent falls was associated with low HGS; it was not associated with low muscle mass. In a follow-up study with a mean interval of 4.9 years, HGS were strongly associated with mortality, while muscle mass measured by CT (Computer Tomography) or DXA (dual-energy X-ray absorptiometry) was not strongly associated with mortality. Therefore, we presumed that HGS can adequately estimate muscle strength; we used HGS to detect muscle strength in this study.

In our study, we found that HGS in male patients with stable COPD was 34 kg, similar to the value of 31 kg reported by Hirai. Moreover, HGS in AECOPD patients was 29.20 kg, lower than in stable COPD patients. In the study by Lee, the HGS in AECOPD patients was 25.3 kg, which was lower than the value in our study; this is presumably because the

### Table 4 Analysis of Risk Factors for Low Muscle Strength in Male Patients with AECOPD

| Factor         | Regression Coefficient | Standard Error | Wald  | \( P \)  | OR     | 95% CI          |
|----------------|------------------------|----------------|-------|--------|--------|-----------------|
| Cr/CysC ratio  | 1.754                  | 0.663          | 7.680 | <0.05  | 5.779  | 1.671–19.982    |
| Weight(kg)     | -0.037                 | 0.036          | 1.059 | >0.05  | 0.964  | 0.898–1.034     |
| FVC (L)        | -0.630                 | 1.134          | 0.309 | >0.05  | 0.532  | 0.058–4.920     |
| FEV\(_1\) (L)  | 0.160                  | 1.670          | 0.009 | >0.05  | 1.173  | 0.044–30.970    |

**Abbreviations:** Cr/CysC, creatinine/cystatin C; FVC, functional vital capacity; FEV\(_1\), forced expiratory volume in 1 second.
previous study included female patients. A recent study has indicated that HGS is correlated with the Cr/CysC ratio, which could help identify low HGS. Some reports have shown that Cr/CysC ratio is correlated with HGS in patients with non-dialysis chronic kidney disease or with liver disease. However, few studies have explored the relationship between Cr/CysC ratio and HGS in patients with COPD. The Cr/CysC ratio has been significantly correlated with HGS in male stable COPD patients; it is more effective than other markers (eg, CysC, Cr, and albumin) for diagnosing sarcopenia. Here, we compared the Cr/CysC ratio between stable COPD patients and AECOPD patients; we found that the Cr/CysC ratio was lower in AECOPD patients (1.08 vs 0.91). Similarly, the Cr/CysC ratio was lower in the low muscle strength group than in the normal muscle strength group (0.85 vs 1.02). These results suggested that the Cr/CysC ratio may be related to the condition of COPD and also to HGS in patients with AECOPD. Correlation analysis revealed that the Cr/CysC ratio was positively correlated with HGS in AECOPD patients, while Cr was not associated with HGS. This finding suggests that the Cr/CysC ratio can partially eliminate the influences of other factors on Cr or CysC, thereby improving the evaluation of muscle strength.

The roles of Cr/CysC in COPD are to assess sarcopenia and evaluate disease severity. The Cr/CysC ratio exhibits relationships with important clinical characteristics in COPD patients, such as FEV1, 6-minute walk test results, and fat-free body mass index; it could also be used to predict hospitalization in COPD patients. Furthermore, the Cr/CysC ratio was lower in patients with COPD than in healthy controls; it was also lower in patients with mMRC score ≥2, patients with CAT score ≥10, and patients with a high risk of exacerbation. A lower Cr/CysC ratio may be indicative of more severe dyspnea, a longer hospital stay, and worse lung function in AECOPD patients. Our results were similar to previous findings that AECOPD patients had a lower Cr/CysC ratio, which was correlated with FEV1, FVC, and FEV1%/pred. Additionally, patients with a lower Cr/CysC ratio had worse lung function.

Muscle strength is an important factor that affects lung function; there is a good correlation between HGS and respiratory muscle strength. Because the Cr/CysC ratio is a useful index for evaluating muscle strength, it can be used to evaluate respiratory muscle conditions that severely restrict airflow and affect the risks of acute exacerbation, hospitalization, and death in COPD patients. In this regard, the Cr/CysC ratio may be an important prognostic indicator. Here, calculation using the ROC curve showed that the cut-off value of the Cr/CysC ratio for predicting decreased muscle strength in male AECOPD patients was 0.99, which is greater than the value reported by Hirai (0.71). This is presumably because our predicted target was muscle strength decline, whereas Hirai et al predicted sarcopenia (ie, low muscle mass + low muscle strength). Multivariate binary logistic regression showed that a Cr/CysC ratio <0.99 was a risk factor for muscle strength decline in male AECOPD patients, which may provide insights for the diagnosis and treatment of sarcopenia patients.

Although our findings suggest that the Cr/CysC ratio can be used to predict whether patients with AECOPD exhibit comorbid muscle weakness, our study was conducted in a single center, and the sample size was limited. Therefore, further confirmatory studies are needed. Because of the higher COPD incidence in men, we only included male patients; thus, sex differences in the Cr/CysC ratio were not analyzed. We did not measure the muscle mass among participants in this study; accordingly, we could not evaluate the diagnostic value of the Cr/CysC ratio in male AECOPD patients with sarcopenia.

Conclusions

The findings in this study suggest that the Cr/CysC ratio is associated with HGS and lung function in male patients with AECOPD. When the Cr/CysC ratio was <0.99, it was a useful predictor of decreased muscle strength in male AECOPD patients. Moreover, a low Cr/CysC ratio is a risk factor for muscle strength decline in male patients with AECOPD.

Abbreviations

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; COPD, chronic obstructive pulmonary disease; Cr, creatinine; CysC, cystatin C; Cr/CysC, creatinine/cystatin C; AUC, area under the curve; HGS, handgrip strength; BMI, body mass index; FEV1, forced expiratory volume in 1 second; FVC, functional vital capacity; FEV1%/pred, percent of forced expiratory volume in 1 second; FEV1/FVC, forced expiratory volume in 1 second/forced vital capacity; GOLD 2020, Global Initiative for Chronic Obstructive Lung Disease 2020; ROC, receiver operating
characteristic; CAT, COPD Assessment Test; mMRC, modified British Medical Research Council; AWGS, Asian Working Group for Sarcopenia.

Acknowledgments
We thank all patients who participated in this study. We also thank Ryan Chastain-Gross, Ph.D., of Liwen Bianji (Edanz) for editing the English text of a draft of this manuscript.

Funding
This work was supported by the National Science Foundation of Guangdong Province (2021A1515011062), the Project of Administration of Traditional Chinese Medicine of Guangdong Province (20221211), the Project of Zhanjiang city (2020B01346, 2021A05082, 2021B01315) and the Affiliated hospital of Guangdong Medical University (LCYJ2017A003, CLP202113001, CLP2021B001, LCYJ2020B008).

Disclosure
The authors declare no conflicts of interest in this work.

References
1. Global Initiative for Chronic Obstructive Lung Disease GOLD. Global Strategy for the Diagnosis, Management and Prevention of COPD 2020. Global Initiative for Chronic Obstructive Lung Disease (GOLD); 2020.
2. Adeloye D, Chua S, Lee C, et al. Global and regional estimates of COPD prevalence: systematic review and meta-analysis. J Glob Health. 2015;5(2):020415. doi:10.7189/jogh.05.020415
3. World Health Organization. Projections of mortality and causes of death, 2016 and 2060. Available from: https://www.who.int/healthinfo/global_burden_disease/projections_method.pdf. Accessed December 26, 2021.
4. Lopez AD, Shibuya K, Rao C, et al. Chronic obstructive pulmonary disease: current burden and future projections. Eur Respir J. 2006;27(2):397–412. doi:10.1183/09031936.06.00025805
5. Smith MC, Wrobel JP. Epidemiology and clinical impact of major comorbidities in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2014;9:871–888. doi:10.2147/COPD.S40621
6. Chen LK, Woo J, Assantachai P, et al. Asian Working Group for sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment. J Am Med Dir Assoc. 2020;21(3):300–307 e302. doi:10.1016/j.jamda.2019.12.012
7. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(4):601. doi:10.1093/ageing/afz046
8. Keogh E, Mark Williams E. Managing malnutrition in COPD: a review. Respir Med. 2021;176:106248. doi:10.1016/j.rmed.2021.106248
9. Volkert D. The role of nutrition in the prevention of sarcopenia. Wien Med Wochenschr. 2011;161(17–18):409–415. doi:10.1007/s10354-011-0910-x
10. Contreras-Bolivar V, Sanchez-Torralvo FJ, Ruiz-Vico M, et al. GLIM criteria using hand grip strength adequately predict six-month mortality in cancer inpatients. Nutrients. 2019;11(9):2043. doi:10.3390/nu11092043
11. Jeong M, Kang HK, Song P, et al. Hand grip strength in patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2017;12:2385–2390. doi:10.2147/COPD.S140915
12. Shah S, Nahar P, Vaidya S, Salvi S. Upper limb muscle strength & endurance in chronic obstructive pulmonary disease. Indian J Med Res. 2013;138(4):492–496.
13. Ahmadi A, Mazloom Z, Eftekhari MH, et al. Muscle mass and function are related to respiratory function in chronic obstructive pulmonary disease. Med J Islam Repub Iran. 2021;35:34. doi:10.47176/mirjirn.35.34
14. Turan Z, Ozemisiz Taskiran O, Erdem Z, Kokturk N, Kaymak Karatas G. Does hand grip strength decrease in chronic obstructive pulmonary disease exacerbation? A cross-sectional study. Turk J Med Sci. 2019;49(3):802–808. doi:10.3906/sag-1811-22
15. Martinez CH, Diaz AA, Meldrum CA, et al. Handgrip strength in chronic obstructive pulmonary disease: associations with acute exacerbations and body composition. Ann Am Thorac Soc. 2017;14(11):1638–1645. doi:10.1513/AnnalsATS.201610-821OC
16. Holden M, Fyfe M, Poulin C, et al. Handgrip strength in people with chronic obstructive pulmonary disease: a systematic review and meta-analysis. Phys Ther. 2021;101(6). doi:10.1093/ptj/pzab057
17. Levey AS, Perrone RD, Madias NE. Serum creatinine and renal function. Annu Rev Med. 1988;39:465–490. doi:10.1146/annurev.me.39.020188.002341
18. Randers E, Erlandsen EJ. Serum cystatin C as an endogenous marker of the renal function--a review. Clin Chem Lab Med. 1999;37(4):389–395. doi:10.1515/CCLM.1999.064
19. Osaka T, Hamaguchi M, Hashimoto Y, et al. Decreased the creatinine to cystatin C ratio is a surrogate marker of sarcopenia in patients with type 2 diabetes. Diabetes Res Clin Pract. 2018;139:52–58. doi:10.1016/j.diabres.2018.02.025
20. Fu X, Tian Z, Wen S, et al. A new index based on serum creatinine and cystatin C is useful for assessing sarcopenia in patients with advanced cancer. Nutrition. 2021;82:111032. doi:10.1016/j.nut.2020.111032
21. Lin YL, Chen SY, Lai YH, et al. Serum creatinine to cystatin C ratio predicts skeletal muscle mass and strength in patients with non-dialysis chronic kidney disease. Clin Nutr. 2020;39(8):2435–2441. doi:10.1016/j.clnu.2019.10.027

https://doi.org/10.2147/COPD.S356314
22. Yanishi M, Kinoshita H, Tsukaguchi H, et al. The creatinine/cystatin C ratio provides effective evaluation of muscle mass in kidney transplant recipients. *Int Urol Nephrol*. 2019;51(1):79–83. doi:10.1007/s11255-018-0156-6

23. Kashani K, Sarvottam K, Pereira NL, Barreto EF, Kennedy CC. The sarcopenia index: a novel measure of muscle mass in lung transplant candidates. *Clin Transplant*. 2018;32(3):e13182. doi:10.1111/ctr.13182

24. Tang T, Zhuo Y, Xie L, Wang H, Yang M. Sarcopenia index based on serum creatinine and cystatin C is associated with 3-year mortality in hospitalized older patients. *Sci Rep*. 2020;10(1):1260. doi:10.1038/s41598-020-58304-z

25. Hirai K, Tanaka A, Homma T, et al. Serum creatinine/cystatin C ratio as a surrogate marker for sarcopenia in patients with chronic obstructive pulmonary disease. *Clin Nutr*. 2021;40(3):1274–1280. doi:10.1016/j.clnu.2020.08.010

26. Puh U. Age-related and sex-related differences in hand and pinch grip strength in adults. *Int J Rehabil Res*. 2010;33(1):4–11. doi:10.1097/MRR.0b013e328325a8ba

27. Tan L, Li B, Hu X, et al. Serum creatinine/cystatin C ratio as a case-finding tool for low handgrip strength in Chinese middle-aged and older adults. *Sci Rep*. 2020;10(1):14028. doi:10.1038/s41598-020-71028-4

28. Warnken-Miralles MD, Lopez-Garcia F, Zamora-Molina L, Soler-Sempere MJ, Padilla-Navas I, Garcia-Pachon E. [Sarcopenia index in hospitalized patients with chronic obstructive pulmonary disease exacerbation]. *Medicina*. 2021;81(3):323–328. Spanish.

29. Amado CA, Garcia-Unzueta MT, Lavin BA, et al. The ratio serum creatinine/serum cystatin C (a surrogate marker of muscle mass) as a predictor of hospitalization in chronic obstructive pulmonary disease outpatients. *Respiration*. 2019;97(4):302–309. doi:10.1159/000494296

30. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD assessment test. *Eur Respir J*. 2009;34(3):648–654. doi:10.1183/09031936.0010509

31. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax*. 1999;54(7):581–586. doi:10.1136/thx.54.7.581

32. Pulmonary Function Professional Group. Pulmonary function test guide-lung volume test. *Chin J Tuberc Respir*. 2017;42(2):235–260. Chinese.

33. Hunter GR, Singh H, Carter SJ, Bryan DR, Fisher G. Sarcopenia and its implications for metabolic health. *Respirology*. 2019;24(4):946–955. doi:10.1111/resp.13315

34. Ichikawa T, Miyaaki H, Miuma S, et al. Indices calculated by serum creatinine and cystatin C as predictors of liver damage, muscle strength and fractures: the Longitudinal Aging Study Amsterdam. *J Gerontol A Biol Sci Med Sci*. 2018;73(9):1199–1204. doi:10.1093/gerona/glx245

35. Newman AB, Kupelian V, Visser M, et al. Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. *J Gerontol B Psychol Sci Soc Sci*. 2006;61(1):72–77. doi:10.1093/gerona/gli72

36. Lee CT, Wang PH. Handgrip strength during admission for COPD exacerbation: impact on further exacerbation risk. *BMC Pulm Med*. 2021;21(1):245. doi:10.1186/s12890-021-01610-7

37. Ichikawa T, Miyaaki H, Miuma S, et al. Indices calculated by serum creatinine and cystatin C as predictors of liver damage, muscle strength and sarcopenia in liver disease. *Biomed Rep*. 2020;12(3):89–98. doi:10.3892/br.2020.1273

38. Chen L, Liu X, Wang Q, et al. Better pulmonary function is associated with greater handgrip strength in a healthy Chinese Han population. *BMC Pulm Med*. 2020;20(1):114. doi:10.1186/s12890-020-1155-5

39. Shin HI, Kim DK, Seo KM, Kang SH, Lee SY, Son S. Relation between respiratory muscle strength and skeletal muscle mass and hand grip strength in the healthy elderly. *Ann Rehabil Med*. 2017;41(4):686–692. doi:10.5535/arm.2017.41.4.686

40. Vilaro J, Ramirez-Sarmiento A, Martinez-Llorens JM, et al. Global muscle dysfunction as a risk factor of readmission to hospital due to COPD exacerbations. *Respir Med*. 2010;104(12):1896–1902. doi:10.1016/j.rmed.2010.05.001

41. Piquet J, Chavaillon JM, David P, et al. High-risk patients following hospitalisation for an acute exacerbation of COPD. *Eur Respir J*. 2013;42(4):946–955. doi:10.1183/09031936.00180312

42. Kashani KB, Frazee EN, Kukralova L, et al. Evaluating muscle mass by using markers of kidney function: evaluation of the sarcopenia index. *Crit Care Med*. 2017;45(1):e23–e29. doi:10.1097/CCM.0000000000002013