Raw Bioelectrical Impedance Analysis Variables are Independent predictors of Early All-Cause Mortality in Patients With COPD

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Raw Bioelectrical Impedance Analysis Variables are Independent predictors of Early All-Cause Mortality in Patients With COPD

Authors

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Conflict of interest:

The authors have no conflict of interest to declare
Abstract

Background: Bioelectrical impedance analysis is a valuable method for estimating fat-free mass (FFM) and fat mass (FM) in COPD patients by means of specific predictive equations. In addition, raw BIA variables such as high to low frequency impedance ratios (IRs) and phase angle, most likely as a result of providing information on muscle quality, have been related to disease severity and mortality in patients suffering from several diseases, but never in COPD. The aim of this study was to investigate the predictive role of raw BIA variables on two-year survival in COPD.

Methods: Impedance (Z) at 5-10-50-100-250 kHz and phase angle at 50 kHz were determined in 210 COPD patients. Three IRs were calculated: Z at 50 kHz/Z at 5 kHz (50/5 IR), Z at 100 kHz/Z at 5 kHz (100/5 IR) and Z at 250 kHz/Z at 5 kHz (250/5 IR). Demographical, respiratory and body composition data at the baseline were recorded. All-cause mortality was assessed during 2 years of follow-up.

Results: After the follow up period, all-cause mortality was 13.8%. Statistically significant differences between non-survivors and survivors emerged in terms of age, weight, BMI, FEV₁, inspiratory capacity (IC), mMRC dyspnea score. With respect to nutritional variables, non-survivors had lower FFM (P=0.031), lower FM (P=0.015), higher IRs (P<0.001 for all the ratios) and lower phase angle (P<0.001) compared to survivors. After adjustment for confounding factors, each unit increase of IRs and each unit decrease of phase angle was associated with a higher risk of death.

Conclusions: Impedance ratios and phase angle, as raw BIA variables, are independent and powerful predictors of all-cause mortality in COPD and should be considered, together with inspiratory capacity and 6MWD, as significant prognostic factors in the short-middle term.
Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous and multicomponent condition. Although defined by chronic airflow obstruction, the presence of other conditions significantly contributes to the severity of the disease, affecting not only symptoms, functional performance and health status, but also risk of hospitalization and mortality. Among these conditions, skeletal muscle dysfunction and changes in body composition are important extra-pulmonary manifestations in COPD associated with poor outcome. Indeed, survival studies in COPD have identified several prognostic factors beyond airflow obstruction, such as hyperinflation, reduced exercise capacity, dyspnea, impaired health status, depressive symptoms, low-grade systemic inflammation and low physical activity that were shown to predict all-cause mortality in COPD.

With respect to nutritional variables, low body weight, low fat-free mass (FFM) and skeletal muscle mass are closely related to survival suggesting that assessment of body composition may be useful in the clinical evaluation of patients with COPD. Indeed, the mechanisms by which cross-talking between respiratory system and other organs, such as muscle and adipose tissue, occurs is not fully understood; adipokine pathways appears to play a relevant role.

Bioelectrical impedance analysis (BIA) is a bedside, non-invasive method for evaluating body composition, widely used in patients with COPD. It provides estimates of body compartments throughout the measurement of body impedance (Z), i.e. resistance of body tissues to an electric current passing through the body. Furthermore, the use of raw BIA variables that are not susceptible to equation inherent errors has increased in recent years. Among these, high to low frequency impedance ratio (IR, i.e. Z at 250 kHz / Z at 5 kHz) and phase angle (PhA) are raw BIA variables which provide information on water distribution between intra and extra-cellular compartments and therefore on body cell mass and cellular integrity. COPD patients with disease-related malnutrition or sarcopenia (or both) are characterized by an increased extracellular water/intracellular water ratio, with a concomitant decrease in body cell mass and cellular integrity. These nutritional alterations are reflected in increased IR and decreased PhA values.

From a clinical point of view, PhA is an indicator of survival and other clinical outcomes among the elderly as well as in many chronic conditions, such as cancer, cirrhosis and surgery, but its potential as predictor of survival has never been demonstrated in COPD.

The main aim of this study was to assess whether IR and PhA had independent prognostic value for 2-year survival in a population of patients with COPD. Secondly, we aimed to identify other possible predictors of survival among nutritional and respiratory parameters.

Methods
Subjects

Between March 2013 and February 2015, COPD patients consecutively admitted to undergo a 4-6 week comprehensive pulmonary rehabilitation protocol at the Respiratory Medicine and Pulmonary Rehabilitation Section of the Clinic Center Private Hospital (Naples, Italy) were investigated. The patients were enrolled in a prospective observational study to investigate the role of body composition parameters on disease severity and disease progression. All patients met the following inclusion criteria: age >50 years with a baseline post-bronchodilator forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) <0.7. Exclusion criteria were related to diagnosis of known respiratory disorders other than COPD, known history of significant inflammatory disease other than COPD and a COPD exacerbation within 4 weeks of enrolment. Because of the observational nature of the study and given that all of the tests were done as part of the routine initial assessment, the Ethics Committee of the “Federico II” University of Naples approved the research protocol, without releasing any reference number. The study was also approved by the Institutional Review Board of Directors at Clinic Center Private Hospital (reference number #008/2014) and all patients gave their informed consent to participate in the study.

Lung function

All COPD patients performed a baseline post-bronchodilator spirometry and body plethysmography for measurement of lung volumes (QBOX® COSMED), according to American Thoracic Society (ATS)/European Respiratory Society (ERS) standardization. FEV1 and FVC were assessed in accordance with the latest GOLD guidelines. Inspiratory capacity (IC) and total lung capacity were assessed and IC/TLC ratio was calculated.

Patients were classified into four spirometric stages according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. If FEV1≥80% of the predicted, patients were classified as GOLD stage I (mild), if 50%≥FEV1>80% as GOLD stage II (moderate), 30%≥FEV1>50% as GOLD stage III (severe), and if <30% as GOLD stage IV (very severe).

Body composition

Body composition was assessed by performing multifrequency bioelectrical impedance analysis (BIA), using a Human Im-Touch analyzer (© DS Medica S.r.l., Milan, Italy). Measurements were performed in standardized conditions (i.e. ambient temperature between 23 and 25°C, fast >3 h, empty bladder, supine position for at least 10 minutes before starting the measurement). In addition, after cleaning the skin surface, patients were asked to lie down with their legs and arms slightly abducted at 30° to ensure no contact between the extremities and trunk.

Z and PhA were obtained at five frequencies for both dominant and non-dominant sides of the body with an imperceptible electrical current of 800 mA. The ratio between impedances at high (i.e. 250, 100 and 50 kHz) and low (5 kHz) frequencies and PhA at 50 kHz, expressed as a degree, provides information on hydration status, cellular mass and quality. FFM and FFM index (FFM/height²) were estimated from Z at 50 kHz.
using a disease-specific BIA equation proposed by Rutten et al.\textsuperscript{23} Fat mass (FM) was calculated as total body weight minus FFM.

Other measurements

6MWT was performed according to ATS standards.\textsuperscript{24} Dyspnea was assessed using the modified Medical Research Council (mMRC) dyspnea scale.\textsuperscript{25}

All-cause mortality

After 24 months, vital status was confirmed by follow-up visits and telephone contacts. Date of death was verified by contacting relatives and primary care physicians. Survival time was defined as the time (in months) from the baseline visit to the date of death.

Statistical analysis

Characteristics of survivors and non-survivors are presented as mean and SD or number and percent (dichotomous variables). Comparisons between patients who survived and died were done using unpaired student t test for normally distributed variables, and Chi square for dichotomous variables. To analyse the relative risk of mortality for body composition variables as a continuous variable, we used Cox proportional hazard analyses. The relation of all-cause mortality with IRs and PhA and was confirmed by Kaplan-Meier survival plots and log-rank tests using median values (0.810 for IR and 5.03 for PhA) for categorization. Data analysis was performed with the statistical software SPSS, version 20.0 (SPSS Inc; Chicago, Illinois).

Results

Patients’ characteristics

Characteristics of all patients are presented in Table 1. Of the 210 participants, 29 (13.8\%) had died by the end of the follow up period. The mortality rate was not significantly different between males and females (13.1\% vs 14.9\%, respectively), being slightly higher in patients with severe or very severe disease (GOLD III and IV) compared to those with mild or moderate disease (GOLD I and II) (15.9\% vs 8.2\%, P=0.102). The mortality rate was significantly higher among underweight patients compared to the other BMI classes when grouped (32.4\% when BMI<21 kg/m\textsuperscript{2} vs 9.7\% when BMI ≥21 kg/m\textsuperscript{2}, p=0.001). All non survivor patients had an MRC dyspnea score of 4 (very severe dyspnea).

With respect to respiratory variables, statistically significant differences between non-survivors and survivors emerged in terms of FEV\textsubscript{1} measured (0.72±0.56 L vs 93±0.38 L, P=0.013) and IC (1.13±0.52 L vs 1.48±0.54, P=0.001).

With respect to nutritional variables, non-survivors had lower FFM (43.2±9.2 kg vs 46.8±8.5, P=0.031) and FM (16.7±10.9 kg vs 21.8±10.1 kg, P=0.015) than survivors, but similar estimates of FFM index. With respect to raw BIA variables, higher IRs (P<0.001 for all the ratios) and lower PhA (P<0.001) were registered in non-survivors patients, compared to survivors. BIA variables were still significantly different
between survivors and non survivors, even after including in the analysis only patients with an MRC dyspnea score of 4.

Significant differences also emerged in terms of functional measurements: the distance walked with 6MWD ranged between 0 and 360 m (median value = 28) in non-survivors and between 0 and 552 m (median value = 172 m) in survivors, resulting in a statistically significant difference between groups (P<0.001).

Patients of our cohort had similar prevalence of comorbidities. The most common comorbidity (across all groups of COPD) was arterial hypertension (47.1% of the sample) followed by dyslipidemia (33.3%), coronary artery disease (31.1%) and diabetes (13.8%). When grouped according to the Charlson Index Score we did not find statistically significant differences among 2-yrs survivors vs non survivors patients (CCI 2.5 + 0.7 vs 2.7 + 0.8, respectively; P=0.16).

Predictors of mortality
The probability of survival after 24 months of follow up was significantly lower in underweight patients and in more severe GOLD stages. As a matter of fact, that probability was 67%/92%/90%/90% for underweight/normal weight/overweight/obese patients (log rank test=16.24, P<0.001) and 91%/87%/76% for GOLD I-II/III/IV patients (log rank test= 6.73, P<0.05). Furthermore, we evaluated the prognostic value of general, respiratory and nutritional variables, with particular interest to IRs and PhA, as continuous variables. Table 2 presents the results of the Cox regression analyses (crude and adjusted HRs). In the crude model 1, highly significant (P<0.001) HRs were observed for IC, 50/5 IR, 100/5 IR, 250/5 IR and PhA. Significant (P<0.05) HRs were also observed for age, weight, BMI, FEV₁, IC/TLC, BMI, FFM, FM, 6MWD and mMRC.

After adjustment for sex, age, weight and BMI, Cox regression model 2 revealed lower IC, higher IRs and lower PhA to be still significantly associated with a higher risk of all-cause mortality (Table 2). After adjustment for sex, age, weight and BMI, no evidence of association with mortality was found with respect to FEV₁, IC/TLC and body composition parameters.

In the Cox regression model 3 (adjusted for sex, age, FEV₁, IC and 6MWD), each unit increase of IRs (50/5 IR, 100/5 IR and 250/5 IR as raw ratios multiplied by 100) and each unit decrease of PhA was confirmed to be associated with a higher risk of death, independently of IC and 6MWD (Table 2). In addition to BIA variables, other variables entered into the model and were: IC (HRs: 0.34, 95% CI 0.13-0.95 and 0.35, 95% CI 0.13-0.95, with 250/5 IR and PhA as covariates, respectively) and 6MWD (HRs: 0.95, 95% CI 0.91-0.98 and 0.95, 95% CI 0.13-0.95, with 250/5 IR and PhA as covariates, respectively).

When considering only patients with very severe dyspnea (MRC = 4), after adjustment for sex and age, BIA variables were still predictive of survival with the following HRs: 1.33 for 50/5 IR (95% CI 1.07-1.65,
P<0.05); 1.27 for 100/5 IR (95% CI 1.08-1.51, P<0.001); 1.17 for 250/5 IR (95% CI 1.02-1.34, P<0.05); 0.46 for phase angle (95% CI 0.32-0.66, P<0.001).

Kaplan-Meier survival plots and log-rank tests further confirmed the relationship between IRs and PhA with all-cause mortality. Median values for 250/5 IR and phase angle were used as cut off points for categorization and results are shown in Figures 1. As shown in Figure 2, the risk of dying progressed according to the increase of raw BIA variables (IR and phase angle), with a significant interaction of the risk of death with quintiles of 250/5 IR and phase angle: patients in the highest quintile of 250/5 IR (mean value: 0.860±0.016; cut off: 0.843) had a higher risk of death compared with patients in the lowest quintile (mean value: 0.769±0.013). Similarly, the patients in the lowest quintile of phase angle (mean value: 3.5±0.5 grades; cut off: 4.1 grades) had a higher risk of death compared with patients in the highest quintile (mean value: 6.3±0.4 grades). The HR for highest versus lowest quintile of 250/5 IR was 5.58 (95% CI 1.60-19.41; P=0.007) and the HR for lowest versus highest quintile of phase angle was 9.00 (95% CI 2.06-39.03; P=0.004).
**Discussion**

The main finding of our study was that directly measured raw BIA variables (IRs and PhA) are strong and independent predictor of 2-year mortality in patients with COPD. In addition, higher values of IC among respiratory parameters and higher 6MWD provided prognostic information in our cohort, independently of airflow obstruction.

**Overall predictors of mortality in COPD**

COPD is increasingly recognized as a disease characterized by significant systemic consequences and nutritional alterations. In this context, it becomes important to recognize respiratory and systemic manifestations of COPD that can effectively increase the mortality risk, and to identify those variables that may serve as proxy (or surrogates) for survival. The recognition and improvement of such risk factors may provide an additional opportunity to prevent morbidity and improve survival.27

Beyond airflow obstruction, survival studies have identified other determinants of all-cause mortality in COPD, such as hyperinflation,3,4 exercise capacity,5,6 dyspnea,7 health status,6 depressive symptoms,8 low-grade systemic inflammation28,29 and physical activity10. Our study is specifically concerned with the prognostic utility of distinct nutritional variables and body composition estimates. It was not intended to systematically analyse all potential determinants of survival, i.e. comorbidities or pulmonary rehabilitation. Our data are consistent with previous results, indicating that patients who do not survive after 2-year follow up not only have lower FEV1, but also lower IC and higher mMRC. Remarkably, in the present study all non survivor patients have an MRC dyspnea score of 4.

**Nutritional variables as predictors of mortality in COPD**

With respect to nutritional status, malnutrition and sarcopenia are particularly prevalent among very severe COPD patients,30 and are expected to have important clinical consequences.31 In fact, low values of BMI,11,32,33 FFM (or FFMI)9,12,13 and limb muscle mass14 have been previously shown to be associated with a higher risk of death among COPD patients. A few studies have also demonstrated that in patients with moderate to severe airflow obstruction, a BMI <25 kg/m² is consistently associated with increased mortality risk relative to overweight and even obese patients.31 The present study shows that patients with a BMI<21 kg/m² had a lower probability to survive after 2-year follow up (67%) than normal weight (92%), overweight (90%) and even obese patients (90%). Nevertheless, our results do not confirm a strong association between body composition estimates and survival with respect to both FFM and FM.9,12,13 In fact, although significantly associated with a higher risk for mortality in the crude Cox regression model, the prognostic value of FFM, FFMI and FM has not been confirmed after adjusting for sex, age, weight and BMI. This apparent lack of association is in contrast to some previous studies in the literature,9,34 but is consistent with others which reported no association between low FFMI and mortality among COPD patients.35,36 Possibly, the predictive value of FFM depletion depends on the choice of cut-off points, which should be developed specifically for the studied population.
Raw BIA variables

In recent years, there has been growing interest in raw BIA variables, such as the ratio between high-to-low frequency impedances and PhA. Although it remains uncertain what pathological mechanisms cause abnormalities of raw BIA measures, they are considered to be indices of water distribution (extracellular/intracellular water ratio), body cell mass as well as cellular integrity.\(^{37-43}\). Regarding the choice of what high-to-low frequency IR to use, no specific recommendations exist in the literature, since no pathological or clinical differences exist between various IRs. Nevertheless, although it is possible to create ratios from impedance measured at other frequencies, 250/5 IR and 200/5 IR have been the most commonly investigated as potential markers for nutrition status. In this paper, three IRs has been considered for the analysis (50/5 IR, 100/5 IR and 250/5 IR), with a similar increase in HR in the three cases, after standardization for one standard deviation (data not shown).

The practical advantage of raw BIA variables is the lack of need to measure weight and height to assess nutritional risk.\(^{22,37}\). Lower values of IRs and higher values of PhA are considered to indicate greater cellularity, cell membrane integrity and function, and, thus cellular health. Actually, higher IRs and lower PhA are independent and valuable predictors of lower peripheral and respiratory muscle strength in COPD patients,\(^{38,44}\) being associated with a more severe airflow obstruction\(^{41}\) and with concomitant malnutrition and/or sarcopenia.\(^{17}\)

Few studies have consistently shown a great prognostic relevance of IRs\(^{45}\) and PhA\(^{39}\) with regard to mortality in several diseases such as kidney disease and cancer. However, this association has never been studied in COPD yet. Maddocks et al.\(^{38}\) demonstrated that phase angle is associated with physical function, disease severity and prognosis, this latter in terms of exacerbations and hospital admissions, only suggesting a possible role in predicting mortality. Our results show that IRs and PhA are strong predictors of mortality in patients with COPD, independently of age and BMI. Furthermore, IRs and PhA are still significantly associated with survival even after adjusting for respiratory parameters: for every percentage point increase of 50/5, 100/5 and 250/5 IRs (mathematical ratios multiplied by 100), the relative risk of death is 38%, 29% and 16% higher, respectively while for every degree increase of PhA the risk of death is 47% lower. Interestingly, even after adjusting for functional measurements (i.e. 6MWD), IRs and PhA remain significantly associated with survival in our cohort of patients, thus reinforcing the message of our observational study (i.e., the significant prognostic utility of raw BIA variables and body composition estimates, not affected by other factors related to PR).

Authors are aware that these results could not be extended to a population with different characteristics and/or a wider range of functional impairment. Nevertheless, in line with the great majority of previous survival studies, we studied patients in GOLD stages II, III and IV (i.e. commonly considered in clinical studies) and eligible for pulmonary rehabilitation.

Strengths and limitations
To our knowledge, this is the first study to investigate the role of IRs and PhA as indicators of prognosis in COPD. However, some technical and methodological concerns must be pointed out, specifically regarding the fact that no data on body composition has been obtained with dual-energy X-ray absorptiometry (DXA) or other criterion techniques. Furthermore, the total number of deaths in our study is relatively low, but indeed consistent with the results of other COPD cohort studies.\textsuperscript{3,46,47}

Conclusions

Overall, IRs and PhA, as raw BIA variables, may play a role in assessing mortality risk in COPD, independently of age, BMI and respiratory parameters, and should be considered, together with inspiratory capacity, as significant prognostic factors in the short-middle term. Given its prognostic utility, these findings suggest that the evaluation of body composition through raw BIA variables should be included in the clinical routine of COPD patients, especially in those in GOLD III and IV, in order to identify those potentially at risk. Further studies should be conducted to confirm these findings. Indeed, very high values of IR (> 0.843, see results) and very low values of phase angle (< 4.2 grades) are likely to indicate a very higher risk of poor nutritional status and mortality.

Author contributions

Conception and design of the work: Francesco dB and LS. Data collection: Francesca dB, ADG, PA, BB. Data analysis and interpretation: Francesca dB, LS, Francesco dB. Drafting the article: Francesca dB. Critical revision of the article: LS, Francesco dB, CT, AB. Final approval of the version to be published: all the listed authors.

Acknowledgments

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References


Table 1: Respiratory and nutritional characteristics of all 210 patients, divided in Survivors vs Non Survivors after 2-year follow-up.

<table>
<thead>
<tr>
<th></th>
<th>Survivors (181)</th>
<th>Non-survivors (29)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.9±8.0</td>
<td>72.4±8.3</td>
<td>0.028</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>126/57</td>
<td>19/10</td>
<td>0.720</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.5±15.4</td>
<td>59.3±16.3</td>
<td>0.003</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.2±5.4</td>
<td>23.8±6.4</td>
<td>0.041</td>
</tr>
<tr>
<td>GOLD Stage (%)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>I</td>
<td>0</td>
<td>6.9</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>30.9</td>
<td>10.3</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>39.8</td>
<td>31.0</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>29.3</td>
<td>51.7</td>
<td></td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>0.93±0.38</td>
<td>0.72±0.56</td>
<td>0.013</td>
</tr>
<tr>
<td>FEV1 (% pred)</td>
<td>41.0±16.0</td>
<td>36.0±23.9</td>
<td>0.156</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>55.0±8.1</td>
<td>55.4±7.0</td>
<td>0.783</td>
</tr>
<tr>
<td>RV (L)</td>
<td>6.08±1.52</td>
<td>5.64±1.55</td>
<td>0.156</td>
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<tr>
<td>RV (% pred)</td>
<td>269±67</td>
<td>249±67</td>
<td>0.148</td>
</tr>
<tr>
<td>IC (L)</td>
<td>1.48±0.54</td>
<td>1.13±0.52</td>
<td>0.001</td>
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<tr>
<td>TLC (L)</td>
<td>7.10±1.63</td>
<td>6.49±1.68</td>
<td>0.063</td>
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<tr>
<td>TLC (% pred)</td>
<td>129±31</td>
<td>128±33</td>
<td>0.883</td>
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<tr>
<td>IC/TLC</td>
<td>0.22±0.09</td>
<td>0.18±0.07</td>
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<td>Fat-free mass (kg)</td>
<td>46.8±8.5</td>
<td>43.2±9.2</td>
<td>0.031</td>
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<tr>
<td>Fat-free mass index (kg/m²)</td>
<td>17.8±2.2</td>
<td>17.0±2.7</td>
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<tr>
<td>Fat mass (kg)</td>
<td>21.8±10.1</td>
<td>16.7±10.9</td>
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<td>50/5 Impedance ratio</td>
<td>0.90±0.026</td>
<td>0.92±0.024</td>
<td>&lt;0.001</td>
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<tr>
<td>100/5 Impedance ratio</td>
<td>0.86±0.033</td>
<td>0.89±0.029</td>
<td>&lt;0.001</td>
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<td>250/5 Impedance ratio</td>
<td>0.807±0.038</td>
<td>0.834±0.038</td>
<td>&lt;0.001</td>
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<td>Phase angle (degrees)</td>
<td>5.2±1.2</td>
<td>4.3±1.2</td>
<td>&lt;0.001</td>
</tr>
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<td>6-minute walk distance (m)</td>
<td>0; 360 (28)</td>
<td>0; 552 (172)</td>
<td>&lt;0.001</td>
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<tr>
<td>mMRC dyspnea score</td>
<td>3.72±0.48</td>
<td>4.00±0.00</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Note: Data are presented as mean±standard deviation except gender, presented as count number, and 6-minute walk distance, presented as minimum-maximum (median value).

Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IC, inspiratory capacity; TLC, total lung capacity; mMRC, modified medical research council.
### Table 2. Predictors of mortality in COPD patients: Cox regression

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Crude Cox Regression model 1</th>
<th>Adjusted Cox Regression model 2</th>
<th>Adjusted Cox Regression model 3</th>
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<tbody>
<tr>
<td></td>
<td>B</td>
<td>Hazard Ratio</td>
<td>95% CI</td>
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<tr>
<td>Age (yrs)</td>
<td>0.53</td>
<td>1.05</td>
<td>1.00-1.11*</td>
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<tr>
<td>Weight (kg)</td>
<td>-0.05</td>
<td>0.96</td>
<td>0.94-0.99**</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>-0.08</td>
<td>0.92</td>
<td>0.86-0.99*</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>-1.73</td>
<td>0.18</td>
<td>0.05-0.64***</td>
</tr>
<tr>
<td>Inspiratory capacity (L)</td>
<td>-1.56</td>
<td>0.21</td>
<td>0.08-0.55***</td>
</tr>
<tr>
<td>Total lung capacity (L)</td>
<td>-0.21</td>
<td>0.81</td>
<td>0.64-1.02</td>
</tr>
<tr>
<td>Inspiratory capacity/total lung capacity</td>
<td>-5.25</td>
<td>0.05</td>
<td>0.00-0.09**</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>-0.05</td>
<td>0.96</td>
<td>0.91-0.99*</td>
</tr>
<tr>
<td>Fat-free mass index (kg/m²)</td>
<td>-0.16</td>
<td>0.86</td>
<td>0.72-1.02</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>-0.05</td>
<td>0.95</td>
<td>0.91-0.99*</td>
</tr>
<tr>
<td>50/5 impedance ratio</td>
<td>0.38</td>
<td>1.47</td>
<td>1.23-1.76***</td>
</tr>
<tr>
<td>100/5 impedance ratio</td>
<td>0.31</td>
<td>1.36</td>
<td>1.19-1.55***</td>
</tr>
<tr>
<td>250/5 impedance ratio</td>
<td>0.22</td>
<td>1.24</td>
<td>1.12-1.38***</td>
</tr>
<tr>
<td>Phase angle (grades)</td>
<td>-0.79</td>
<td>0.46</td>
<td>0.32-0.66***</td>
</tr>
<tr>
<td>6MWD (for 10 m change)</td>
<td>-0.06</td>
<td>0.94</td>
<td>0.90-0.98**</td>
</tr>
<tr>
<td>mMRC dyspnea score</td>
<td>1.89</td>
<td>6.56</td>
<td>1.72-25.7**</td>
</tr>
<tr>
<td>Charlson Index Score</td>
<td>-0.17</td>
<td>0.85</td>
<td>0.67-1.10</td>
</tr>
</tbody>
</table>

Mathematical rates for the three IRs were multiplied x 100
Model 2: data adjusted for sex, age, weight and BMI.
Model 3: data adjusted for sex, age, FEV₁, inspiratory capacity and 6MWD
* P value<0.05; ** P value < 0.01; *** P value <0.001
Figure 1. Kaplan Meier curve of survival in COPD patients showing 250/5 impedance ratio (250/5 IR) and phase angle being above (High) or below (Low) median value.
Figure 2. Hazard Ratios for mortality in 210 COPD patients according to quintiles of 250/5 impedance ratio (Quintile 1 was taken as reference category) and phase angle (Quintile 5 was taken as reference category).

Cut-offs for quintiles from 1 to 5 of 250/5 impedance ratio are the following: <0.785, 0.785 - 0.803, 0.803 - 0.820, 0.820 - 0.843, >0.843.

Cut-offs for quintiles from 1 to 5 of phase angle are the following: <4.1 grades, 4.1-4.8 grades, 4.8-5.3 grades, 5.3-5.8 grades, >5.8 grades.
Abbreviation List

ATS: American Thoracic Society
BIA: Bioelectrical Impedance Analysis
BMI: Body Mass Index
COPD: Chronic Obstructive Pulmonary Disease
ERS: European Respiratory Society
FEV\textsubscript{1}: Forced Expiratory Volume in 1 Second
FVC: Forced Vital Capacity
FM: Fat Mass
FFM: Fat-Free Mass
GOLD: Global Initiative for Chronic Obstructive Lung Disease
IC: Inspiratory Capacity
IR: Impedance Ratio
mMRC: modified Medical Research Council
TLC: Total Lung Capacity
RV: Residual Volume
Z: Impedance