

# SARCOPENIA, LUNG DISEASE AND MORTALITY: A SECONDARY ANALYSIS OF THE CRELES STUDY

## Sarcopenia, doença pulmonar e mortalidade: uma análise secundária do estudo CRELES

Miguel Germán Borda<sup>a,b,c,d</sup> , Daniela Patino-Hernandez<sup>b,d</sup> , Carlos Alberto Cano-Gutiérrez<sup>b,c,d</sup> , Carlos Andrés Celis-Preciado<sup>e</sup> , Mario Ulises Pérez-Zepeda<sup>b,d,f</sup> 

### ABSTRACT

**AIM:** Chronic obstructive pulmonary disease (COPD) is a pro-inflammatory condition leading to wasting states such as sarcopenia. We aimed to describe the effect of COPD and sarcopenia on mortality in Costa Rican older adults in the Costa Rican Longevity and Healthy Aging Study (CRELES). **METHOD:** This is a secondary analysis of the CRELES, a cohort study consisting of three waves of interviews. For the current study, data from the first and third waves were used. The dependent variable was survival status. COPD and sarcopenia were independent variables. Bivariate analyses were used to compare mortality curves for each group. Association with 3-year mortality was tested with Cox regression models, and hazard ratios (HR) with 95% confidence intervals (CI) were estimated as a measure of the strength of association. **RESULTS:** Of a total of 2704 participants, 54.29% (n = 1468) were women. Overall mortality was 9.05%. Sarcopenic older adults had the strongest association with mortality (HR = 2.65; 95%CI, 1.81–3.90; p < 0.001), followed by those with both COPD and sarcopenia (HR = 2.59; 95%CI, 1.37–4.92; p = 0.003). The weakest association with mortality was found in patients with neither COPD nor sarcopenia. **CONCLUSIONS:** The synergistic effect of sarcopenia and COPD has been shown to independently increase mortality in older patients. Our results may be applicable to both Latin American residents and subjects of Hispanic descent living in developed countries. Sarcopenia should be assessed in all patients with COPD since the latter is not a disease limited to the lungs, but rather a systemic disease.

**KEYWORDS:** sarcopenia; chronic obstructive pulmonary disease; mortality; aged.

### RESUMO

**OBJETIVO:** A doença pulmonar obstrutiva crônica (DPOC) é uma condição pró-inflamatória que conduz a estados de perda como a sarcopenia. Nosso objetivo foi descrever o efeito da DPOC e da sarcopenia sobre a mortalidade em idosos costa-riquenhos do estudo *Costa Rican Longevity and Healthy Aging Study* (CRELES). **MÉTODO:** Esta é uma análise secundária do CRELES, um estudo de coorte composto por três ondas de entrevistas. Para o presente estudo, foram utilizados dados da primeira e terceira ondas. A variável dependente foi o status de sobrevivência. DPOC e sarcopenia foram variáveis independentes. Foram realizadas análises bivariadas para comparar as curvas de mortalidade para cada grupo. Testou-se a associação à mortalidade em 3 anos com modelos de regressão de Cox, e razões de risco (HR) com intervalos de confiança (IC) de 95% foram estimadas como medida da força da associação. **RESULTADOS:** De um total de 2704 participantes, 54,29% (n = 1468) eram mulheres. A mortalidade geral foi 9,05%. Idosos sarcopênicos apresentaram a associação mais forte à mortalidade (HR = 2,65; IC95%, 1,81–3,90; p < 0,001), seguidos por aqueles com DPOC e sarcopenia (HR = 2,59; IC95%, 1,37–4,92; p = 0,003). A associação mais fraca à mortalidade foi encontrada em pacientes sem DPOC e sarcopenia. **CONCLUSÕES:** Demonstrou-se que o efeito sinérgico da sarcopenia e da DPOC aumenta de forma independente a mortalidade em pacientes idosos. Nossos resultados podem ser aplicáveis a residentes latino-americanos e a descendentes de hispânicos que vivem em países desenvolvidos. A sarcopenia deve ser avaliada em todos os pacientes com DPOC, visto que esta não é uma doença limitada aos pulmões, mas sim uma doença sistêmica.

**PALAVRAS-CHAVE:** sarcopenia; doença pulmonar obstrutiva crônica; mortalidade; idoso.

<sup>a</sup>Centre for Age-Related Medicine (SESAM), Stavanger University Hospital – Stavanger, Norway.

<sup>b</sup>Semillero de Neurociencias y Envejecimiento, School of Medicine, Pontificia Universidad Javeriana – Bogotá D.C., Colombia.

<sup>c</sup>Geriatrics Unit, Hospital Universitario San Ignacio – Bogotá D.C., Colombia.

<sup>d</sup>Ageing Institute, Pontificia Universidad Javeriana – Bogotá D.C., Colombia.

<sup>e</sup>Pulmonology Unit, Hospital Universitario San Ignacio – Bogotá D.C., Colombia.

<sup>f</sup>Geriatric Epidemiology Research Department, Instituto Nacional de Geriatria – Mexico D.F, Mexico.

### Correspondence data

Daniela Patino-Hernandez – Carrera 7 N. 40-62 – Hospital San Ignacio, Piso 8, Facultad de Medicina – E-mail: patinohernandezd@gmail.com

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## INTRODUCTION

Demographic transition should be understood as a success for humankind. However, it does imply a challenge for modern societies. As the population ages, chronic diseases become more prevalent. Respiratory diseases are among the most common conditions in older adults.<sup>1,2</sup> Chronic obstructive pulmonary disease (COPD) is a multifactorial entity with a wide range of clinical manifestations,<sup>3</sup> which is also frequently found alongside multiple comorbidities. In addition, COPD is a pro-inflammatory condition that leads to increased vulnerability toward wasting states such as sarcopenia.<sup>4</sup>

Sarcopenia is defined as an age-related loss of muscle mass, paired with a decrease in strength and/or function.<sup>5</sup> It is a highly prevalent syndrome, which is often related to adverse outcomes in the studied populations.<sup>6</sup> Also, sarcopenia has been extensively associated with pulmonary disease.<sup>4,5</sup> Sarcopenia and COPD seem to converge during the aging process. Some of the described associations include lower energy intake leading to lower amino acid availability for muscle synthesis, hypoxemia leading to proteolysis, and increased pro-inflammatory cytokines with concomitant catabolism.<sup>3</sup> Nevertheless, the synergistic effect of these conditions on mortality has not been previously described.

Therefore, we aimed to describe the effect of COPD and sarcopenia on mortality in Costa Rican older adults in order to better understand this phenomenon.

## METHOD

This is a secondary analysis of the Costa Rican Longevity and Healthy Aging Study (CRELES), a cohort study of Costa Rican older adults aged  $\geq 60$  years at the time the study was conducted. It consists of three waves of in-home standardized interviews conducted by trained staff, including in-depth data on demographics, health-related issues, social support, and blood sampling. The CRELES is a publicly available dataset that includes a representative sample of older adults obtained through a stratified two-stage probabilistic sampling design. A full description of sampling methods and objectives can be found elsewhere.<sup>7</sup> For the purposes of the present study, data from the first (2005) and third (2009) waves were used. The follow-up period was 60 months.

### Adverse outcome: dependent variable

The dependent variable was survival status, obtained from the next of kin. The date of death was recorded in order to estimate the time (months) to death in the survival analysis.

To define the effect of sarcopenia on patients with self-reported COPD, participants were divided into four groups for analysis:

- 0: No COPD + No sarcopenia;
- 1: COPD + No sarcopenia;

- 2: No COPD + Sarcopenia;
- 3: COPD + Sarcopenia.

### Independent variables

COPD was assessed by asking the following question: "Has a doctor or nurse ever told you that you have COPD, asthma, or chronic bronchitis?". The algorithm proposed by the European Working Group on Sarcopenia in Older People was used to define sarcopenia,<sup>5</sup> since walking speed, handgrip strength and calf circumference had been measured as part of the anthropometric assessment during the CRELES. Cutoff values were tailored specifically to the studied population (available upon request).

### Statistical analysis

Descriptive statistics were used to characterize the sample. Bivariate analyses included both the graphical assessment of mortality with Kaplan-Meier curves and log-rank tests for comparison of mortality curves for each group. Association with 3-year mortality was tested with Cox regression models, and hazard ratios (HR) with 95% confidence intervals (CI) were estimated as a measure of the strength of association. Independent associations were confirmed by adjusting for confounding variables. The level of significance was set at  $p < 0.05$ . Data were analyzed with STATA 14® (further information regarding statistical analysis can be obtained upon request).

### Ethical considerations

All participants provided written informed consent prior to inclusion in the study. All procedures were performed in accordance with the ethical standards outlined in the Helsinki Declaration. The study was approved by the research ethics committee at our institution through the protocol number 03/2017 as disclosed by the document FM-CIE-0049-17.

## RESULTS

Of a total of 2,704 participants with a mean age of 76.4 (SD, 10.24) years, 54.29% ( $n = 1468$ ) were women. Overall mortality was 9.05%. Group distribution was as follows: 76.05% in group 0 (reference group); 16.00% in group 1 (only COPD); 6.00% in group 2 (only sarcopenia); and 1.96% in group 3 (both COPD and sarcopenia). No significant differences were found between groups in number of medications or smoking habits. The lowest mortality rate was found in the reference group (7.73%), while the highest mortality rate was found in patients with sarcopenia (19.14%), with a significant difference between groups ( $p < 0.001$ ).

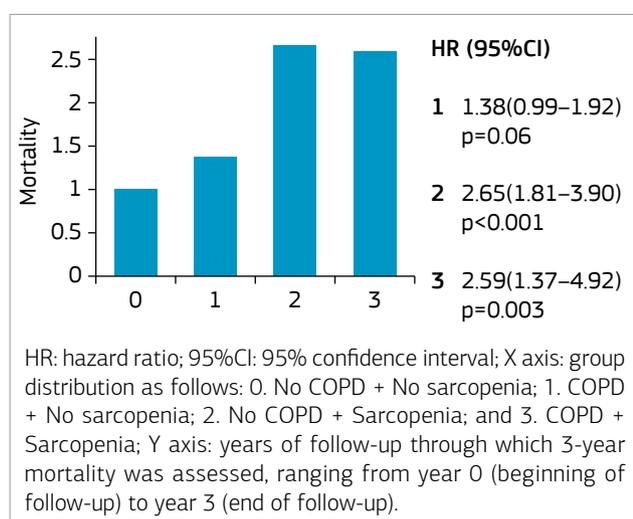
After adjustment, Cox regression models showed that older adults with sarcopenia had the strongest association with mortality (HR = 2.65; 95%CI, 1.81–3.90;  $p < 0.001$ ), followed by

those with both COPD and sarcopenia (HR = 2.59; 95%CI, 1.37–4.92;  $p = 0.003$ ). The weakest association with mortality was found in patients with neither COPD nor sarcopenia (Figure 1).

## DISCUSSION

This study suggests an important role of sarcopenia in people with COPD. The strongest association with mortality was found in older adults with sarcopenia alone and with sarcopenia and COPD, regardless of age, sex, smoking status, and number of medications.

These findings are consistent with previous studies, which have reported associations between COPD and sarcopenia as well as between sarcopenia and mortality, suggesting that sarcopenia should be thoroughly assessed in patients with pulmonary disease because of the potential worsening of prognosis.<sup>8</sup> Our results demonstrate that, although COPD does not appear to significantly increase mortality in patients with sarcopenia, sarcopenia does greatly increase mortality in patients with COPD.



**Figure 1** Three-year mortality by group.

This study has several strengths. It is a secondary analysis of a representative sample of older adults in Costa Rica. The cut-off values were tailored specifically to the studied population. Also, to the best of our knowledge, this association had never been statistically proven before in a Latin American population. Therefore, our results may be applicable to both Latin American residents and subjects of Hispanic descent living in developed countries. However, there are some limitations to consider when interpreting the results. COPD was assessed by self-report, since spirometry data were not available. Also, age-related changes in fat deposits and loss of skin elasticity may contribute to errors in the estimation of muscle mass. Because of the study design, it was not established whether patients were receiving any type of treatment at the time the study was conducted.

## CONCLUSION

The synergistic effect of sarcopenia and COPD has been shown to increase mortality in older patients. Therefore, evaluation of sarcopenia should be included in pulmonary assessments whenever possible. Also, sarcopenia should be assessed in all patients with COPD since the latter is not a disease limited to the lungs, but rather a systemic disease.

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## CONFLICT OF INTERESTS

On behalf of all authors, the corresponding author declares that there is no conflict of interest.

## REFERENCES

- de Oca MM, Tálamo C, Halbert RJ, Perez-Padilla R, Lopez MV, Muiño A, et al. Frequency of self-reported COPD exacerbation and airflow obstruction in five Latin American cities: the Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar (PLATINO) study. *Chest*. 2009;136(1):71–8. <https://doi.org/10.1378/chest.08-2081>
- Caballero A, Torres-Duque CA, Jaramillo C, Bolívar F, Sanabria F, Osorio P, et al. Prevalence of COPD in five Colombian cities situated at low, medium, and high altitude (PREPOCOL study). *Chest*. 2008;133(2):343–9. <https://doi.org/10.1378/chest.07-1361>
- Patino Hernandez D. Chronic Obstructive Pulmonary Disease (COPD) and Sarcopenia: A Bidirectional Pathway. *Gerontol & Geriatric Stud*. 2017;1(1). <http://dx.doi.org/10.31031/ggs.2017.01.000505>
- Celis Preciado CA, Borda M, Patino-Hernandez D, Cano C, Perez Cepeda M. Sarcopenia as a Predictor of Mortality in Obstructive Lung Disease: A Secondary Analysis of the CRELES Study. *Am J Respir Crit Care Med*. 2017;195(A1013).
- Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing*. 2010;39(4):412–23. <https://doi.org/10.1093/ageing/afq034>
- Chang S-F, Lin P-L. Systematic Literature Review and Meta-Analysis of the Association of Sarcopenia With Mortality. *Worldviews Evid Based Nurs*. 2016;13(2):153–62. <https://doi.org/10.1111/wvn.12147>
- Rosero-Bixby L, Fernandez X, Dow WH. CRELES: Costa Rican Longevity and Healthy Aging Study, 2005 (Costa Rica Estudio de Longevidad y Envejecimiento Saludable): Archival Version [Internet]. 2010 [cited 2017 Feb 13]. Available from: <http://www.icpsr.umich.edu/NACDA/studies/26681>
- Tang T, Wu L, Yang L, Jiang J, Hao Q, Dong B, et al. A sarcopenia screening test predicts mortality in hospitalized older adults. *Sci Rep*. 2018;8:2923. <https://doi.org/10.1038/s41598-018-21237-9>