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Letter to the editor

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Dear editor

Peripheral muscle weakness and atrophy have been associated with increased fatigue and use of healthcare services in people with chronic obstructive pulmonary disease (COPD) [1]. Muscle strength of the lower limbs is relatively less preserved as compared with upper limbs and more vulnerable to atrophy [1]. People with COPD who have better quadriceps muscle strength, as measured by the maximum voluntary contraction test > 120% body mass index (BMI), presented lower mortality risk (hazard ratio [HR] 0.91) than those with worse quadriceps muscle strength [2].

Pulmonary rehabilitation, a non-pharmacological essential intervention for managing COPD, frequently includes quadriceps muscle strength training. Prescription of this training is often based on the 1-repetition maximum (1RM) test given the test's simplicity and low-cost application. In addition, performing the assessment test using the same equipment as in the training protocol increases the responsiveness of the measurement [3]. However, simple predictors with good discriminative ability to detect increased mortality risk are unknown but are essential to prioritize interventions in this population. Thus, we aimed to determine cut-off points for knee extensor muscle weakness (based on 1RM) associated with 4-year mortality in people with COPD.

This was a longitudinal retrospective study developed in the Laboratory of Research in Respiratory Physiotherapy (LFIP) at the State University of Londrina, Brazil. The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [4].

Participants with a diagnosis of COPD were assessed to participate in a research project that offered a 12-week (3 times a week) exercise training program [5]. Inclusion criteria were diagnosis of COPD according to international criteria of the Global Initiative for Chronic Obstructive Lung Disease [6], no disease exacerbations in the least 3 months, and absence of bone-neuromuscular dysfunctions that could interfere with or limit the performance of the proposed tests. The study was approved by the University Ethics Committee (no. 3.058.086) and all participants signed an informed consent to be in the study.

All participants were naive to rehabilitation and were assessed for anthropometric characteristics and body composition (Biodynamics model 310) before initiating an exercise training program. The values of fat-free mass index were estimated by Kyle's equation, and participants were classified as sarcopenic or not according to the 10th percentile proposed [7,8]. Lung function (Spirobank G, MIR, Italy) [9], exercise capacity (6-min walk test [6MWT]) [10], degree of limitation due to dyspnea in daily life (Medical Research Council scale) [11], and peripheral muscle strength (1RM of the quadriceps femoris) were also assessed. In addition, maximal voluntary isometric contraction (MVIC) of the quadriceps was obtained but only in a subgroup of participants for logistic reasons.

To perform the 1RM test, participants were initially seated in a multi-station weight-training device (CRW 1000, Brazil) with support for the trunk, knees flexed at 90°, and both hands resting on the thighs and were instructed to perform the maximum knee extension bilaterally without compensation. The load was initially estimated individually (in kg) and was increased until the participant could not complete the movement or presented compensations. To avoid fatigue, a 1-min rest was given between attempts [12].

Quadriceps MVIC was performed with a hand-held dynamometer (MicroFET 2; Hoggan Health Industries, West Jordan, UT, USA) [13]. The dynamometer was attached to the arm of the knee extension chair of a multi-station unit and positioned above the ankle joint of the self-reported dominant limb. Assessment consisted of the MVIC of the quadriceps femoris for 6 s at a knee joint angle of 60° [14]. A minimum of 4 and maximum of 10 measurements were conducted by a properly trained evaluator with standardized verbal encouragement.

Finally, the vital status of each participant was identified retrospectively. All-cause mortality after a 4-year follow-up was considered the primary outcome. The vital status of participants without a death record in the Mortality Information Center was confirmed by telephone contact and/or in person during routine evaluation.

For statistical analysis, the Shapiro-Wilk test was used to analyze data distribution. Receiver operating characteristic (ROC) curves were used to identify cut-off points for quadriceps muscle strength. Muscle strength values used in the analysis were those obtained in the 1RM test (kg) and the values adjusted for BMI (kg/m^2; 1RM/BMI [%]) and weight (kg; 1RM/weight [%]). Two different criteria were used in the ROC curve analysis: the classification of all participants according to the 6MWT (cut-off < 479 m, as suggested [5]), as well as the classification of a subsample according to quadriceps muscle weakness assessed with the MVIC (cut-off < 80% predicted [pred], as suggested [15]). The area under the ROC curve (AUC) with the best sensitivity and specificity was determined to identify quadriceps muscle weakness as assessed with 1RM test.

Both the Kaplan-Meier and log-rank tests were used to verify associations with mortality at 4-year follow-up between participants classified as having normal or reduced muscle strength according to the identified cut-off point. Cox step-wise regression was used to analyze whether the identified cut-off points had significant prognostic value for mortality at 4-year follow-up on univariate analysis. HRs and 95% confidence intervals were estimated. Cox regression was

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Table 1
Characteristics of the patients included in the study ($n = 204$).

Male, n (%)	106 (52)
Age, years, mean (SD)	66 (8)
Weight, kg	68 [56–78]
BMI, kg/m^2	26 [22–30]
FFMI, kg/m^2	16 [15–18]
FVC,%pred	67 [57–84]
FEV$_1$,%pred	46 [33–57]
FEV$_1$/FCV	59 [49–74]
GOLD 1, n (%)	3 (1)
GOLD 2, n (%)	82 (40)
GOLD 3, n (%)	80 (39)
GOLD 4, n (%)	39 (20)
6MWT, m	483 [421–530]
6MWT,%pred	89 [79–98]
MRC, 1–5 points	3 [2–4]
1RM QF, kg	18 [14–24]
1RM/BMI,%	70 [50–95]
1RM/weight,%	28 [21–37]

Data are median [interquartile range] unless indicated.
BMI, body mass index; FEV$_1$, forced expiratory volume in 1 s; FFMI, fat free mass index; FVC, forced vital capacity; GOLD, Classification of severity of airflow limitation by Global Initiative for Chronic Obstructive Lung Disease; MRC, Medical Research Council (2 patients had incomplete MRC data); QF, quadriceps femoris; 1RM, 1-repetition maximum; 6MWT, 6-min walk test.

also used to confirm whether the cut-off points remained associated with mortality on multivariable analysis after adjustment for confounding factors such as sex, age and force expiratory volume in 1 s (FEV$_1$) and to confirm whether the patient completed the exercise training program or not. SPSS 22.0 was used for analysis. The level of significance was set at $P < 0.05$.

In total, 204 individuals with COPD were included in the study; 63% had sarcopenia [8]. Characteristics of participants are in Table 1. All participants performed the 6MWT and 48% ($n = 98$) were classified as having impaired exercise capacity (<479 m). Only 67 participants had quadriceps muscle strength assessment with the MVIC, and 69% ($n = 46$) showed quadriceps muscle weakness (<80% pred).

Cut-off values for 1RM (kg), 1RM/BMI (%) and 1RM/weight (%) according to both criteria (6MWT and quadriceps maximal voluntary isometric contraction) are presented in Table 2. For all cut-offs, the AUC was > 0.60, except for 1RM derived from the quadriceps MVIC. The best cut-off values for quadriceps muscle strength in terms of 1RM/weight (%) were equal according to both criteria; therefore, 0.31 was suggested as a cut-off.

In total, 153 participants underwent initial assessments until 2014 and their vital status was assessed after at least 4 years: 55% were male; mean (SD) age was 67 (8) years, BMI 26 (6) kg/m^2, and FEV$_1$%pred 44 (16). At the 4-year follow-up from the evaluation to the last contact revealed 44 deaths (29%). Unfortunately, 25 (16%) of the sample was censored due to loss of contact. Nevertheless, analysis of mortality included all 153 participants, and the last contact during the 4-year follow-up was considered.

From all cut-off values described in Table 2, only 1RM/weight <31% was significantly associated with mortality on univariate Cox regression. 1RM/weight <31% remained significant (HR 2.73, 95% CI 1.14–5.46; $p = 0.005$) on multivariate Cox regression analysis adjusted for sex, age, FEV$_1$ and whether the exercise training program was completed or not. With participants classified as having impaired or not impaired muscle strength using the cut-off of 1RM/weight < 31%, the Kaplan-Meier method showed significant differences in survival time (log-rank test, $p = 0.040$) (Fig. 1.).

The use of the ratios 1RM/BMI and 1RM/weight to find new cut-off points was proposed because the quadriceps muscle strength is closely related to body weight; therefore, normalizing muscle strength by this characteristic is recommended. However, the 1RM/BMI ratio was not significantly associated with mortality, perhaps because height (part of the BMI measurement) does not vary considerably. Therefore, the cut-off value proposed by the present study was adjusted by weight and reinforces that quadriceps strength is proportional to body weight. Methods to assess the 1RM test and weight are simple and low-cost, which favours its widespread use not only by researchers but also in clinical practice.

The 1RM test is usually performed at the baseline assessment of an exercise training program, and it could be used to identify individuals with the highest risk of mortality from their physical characteristics. Camillo and colleagues studied the effects of pulmonary rehabilitation on mortality of individuals with COPD: in addition to improvement in 6MWT, other responses to exercise were also related to mortality, such as improvement in muscle strength of knee extensors, which is directly related to longer survival [16]. These findings agree with the present results and reinforce that the values determined as cut-off points for peripheral muscle strength in this study might help to detect people with COPD at increased risk of mortality.

A strong point of the study is the focus on a widely available assessment of muscle strength. Another strength was the inclusion of participants regardless of their COPD stage because quadriceps muscle weakness is present across all COPD stages, which increases the external validity of our findings. This study adds new information

Table 2
Cut-off points to identify patients with reduced muscle strength in knee extensors found by receiver operating characteristic curve analysis and risk of 4-year mortality due to any cause using the cut-off points of muscle strength.

	Cut-off	Sensitivity	Specificity	AUC	Univariate analysis HR (95% CI)	p value	Multivariate analysis (HR (95% CI)	p value
1RM (kg)[a]	17.5	0.632	0.649	0.676	1.68 (0.91–3.10)	0.099	–	–
1RM (kg)[b]	12.5	0.952	0.130	0.456	1.87 (0.99–3.48)	0.050	–	–
1RM/BMI (%)[a]	56	0.830	0.469	0.677	1.49 (0.81–2.75)	0.192	–	–
1RM/BMI (%)[b]	81	0.650	0.543	0.604	1.50 (0.77–2.93)	0.231	–	–
1RM/weight (%)[a]	31	0.575	0.701	0.669	2.20 (1.02–3.99)	0.044[c]	2.73 (1.14–5.46)	0.005[c]
1RM/weight (%)[b]	31	0.714	0.587	0.655	2.20 (1.02–3.99)	0.044[c]	2.73 (1.14–5.46)	0.005[c]

AUC, area under the receiver operating characteristic curve; BMI, body mass index; 1RM, 1-repetition maximum; 1RM/BMI, ratio of 1-repetition maximum by BMI; 1RM/Weight, ratio of 1-repetition maximum by weight; HR, hazard ratio; CI, confidence interval.
Each cut-off point was tested with a Cox regression model.
Muscle strength was adjusted in multivariate analysis for the variables sex, age, forced expiratory volume in 1 s, and whether exercise training was performed. Each cut-off point was tested with a Cox regression model.
[a] Based on 6MWT criteria.
[b] Based on quadriceps maximal voluntary isometric contraction.
[c] 1RM/weight (%) HR involved just one cut-off point (31%) because the values for both criteria were equal.

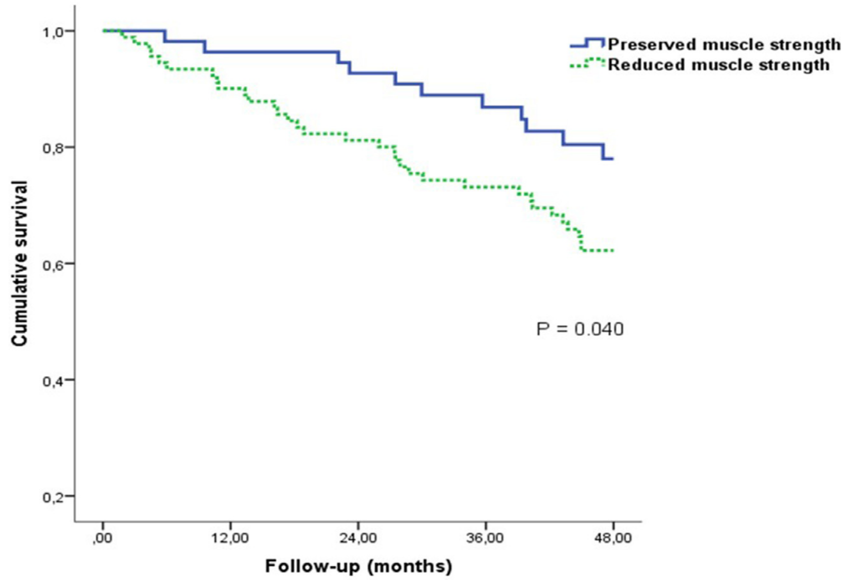

Fig. 1. Kaplan-Meier survival curve with log-rank test during the 4-year follow-up. Short dashed line indicates reduced muscle strength as defined by the ratio of 1-repetition maximum test to weight < 31%; long dashed line indicates preserved muscle strength.

with clinical applicability, in addition to reflecting a typical group referred to pulmonary rehabilitation programs.

Some limitations include the retrospective design, with a relatively small sample, 16% of censored patients within the 4-year follow-up, cut-off points studied in only one cohort and the absence of information on acute exacerbations. Although the values of muscle strength assessed by the 1RM test are similar to those in some studies [17,18], which indicates the representativeness of the sample, Daabis and colleagues showed a 5% variation in quadriceps muscle strength in people with COPD in comparison to the present study. Therefore, future studies could validate the proposed cut-off points in independent samples and focus on the effect of different methodological aspects [3] and equipment [19].

In conclusion, quadriceps muscle weakness assessed by the 1RM test and adjusted for weight was able to predict mortality at 4-year follow-up in individuals with COPD independent of sex, age, airway obstruction and previous participation in an exercise training program. We identified a cut-off value of 31% for the ratio 1RM/weight that might be useful in clinical practice to identify individuals with COPD with reduced quadriceps strength associated with increased 4-year mortality risk.

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Data availability

Data will be made available on request.

Conflict of interest

None declared.

SUPPLEMENTAL MATERIAL

Supplemental materials associated with this article can be found in the online version at https://doi.org/10.1016/j.amepre.2021.08.020.

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Thamyres Spositon[a,b,$]
Joice M. Oliveira[a,b,$]
Antenor Rodrigues[a,c]
Jéssica Fonseca[a]
Lais Santin[a]
Felipe V.C. Machado[a,d,e]
Nidia A. Hernandes[a]
Alda Marques[f]
Fabio Pitta[a]
Karina C. Furlanetto[a,b,*]

[a] *Laboratory of Research in Respiratory Physiotherapy (LFIP), Department of Physiotherapy, State University of Londrina (UEL), Londrina, Brazil*
[b] *Stricto Sensu Graduate Program in Rehabilitation Sciences, University Pitágoras Unopar (UNOPAR), Londrina, Brazil*
[c] *Rehabilitation Aimed at Muscle Performance Laboratory (RAMP), University of Toronto, Toronto, Canada*
[d] *Department of Research and Development, Center of Expertise for Chronic Organ Failure (CIRO), Horn, Netherlands*
[e] *Department of Respiratory Medicine, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre+, Maastricht, The Netherlands*
[f] *Respiratory Research and Rehabilitation Laboratory (Lab 3R), School of Health Sciences, University of Aveiro, Aveiro, Portugal*

*Corresponding author.
E-mail address: karina.couto@kroton.com.br (K.C. Furlanetto).

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$ Both authors contributed equally to the study and share first authorship.