BMC Pulmonary Medicine

RESEARCH

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Distance travelled in the six-minute walk test in patients with chronic obstructive pulmonary disease as a predictor of mortality

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Abstract

Background Exercise intolerance in patients with COPD has significant implications for quality of life, hospitalization rates, and survival.

Objective To assess functional capacity using the six-minute walk test (6MWT) by categorizing the distance walked in six minutes (6MWD) into tertiles and to assess the impact of this functional capacity on predictors of survival over a 24-month follow-up in patients with Chronic Obstructive Pulmonary Disease (COPD).

Methods This prospective cohort study followed 118 patients with COPD for 24 months. Participants were stratified based on the 6MWD: Group 1 (mean distance 590–424 m); Group 2 (mean distance 423–337 m); and Group 3 (mean distance < 336 m). Symptoms and disease severity were assessed using CAT scores. Kaplan-Meier was used to determine the association between 6MWD and all-cause mortality.

Results The 6MWD, stratified by functional performance, was a significant predictor of survival in patients with COPD, despite heterogeneity in disease severity between groups. The 6MWD, stratified by functional performance, was a significant predictor of survival in patients with COPD, despite heterogeneity in disease severity between groups. Furthermore, in regression analysis for mortality, it was identified for 6MWD (CI 0.994; $p = 0.043$) and peripheral oxygen saturation (SpO_2) (CI 0.735; $p < 0.001$). Kaplan-Meier survival analysis revealed that patients who walked less than 336 m in the 6MWD had the lowest probability of survival at 24 months (log-rank $p < 0.05$).

Conclusion The 6MWD is a robust predictor of mortality over a 2-year period in patients with COPD, reflecting a broad spectrum of disease severity. Poorer 6MWD performance is associated with increased desaturation, impaired heart rate recovery, and greater symptom burden during exercise, as indicated by CAT scores.

Clinical trial number Not applicable.

Keywords Chronic obstructive pulmonary disease, Six-minute walk test, COPD assessment test

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a chronic respiratory condition characterized by persistent and progressive airway obstruction that is not fully reversible [1]. It is estimated that there are over 384 million cases of COPD globally, with the World Health Organization (WHO) projecting that COPD will become the third leading cause of death by 2030 [2, 3]. In Brazil, 61% of individuals with COPD report frequent emergency room visits and hospitalizations due to exacerbations of respiratory symptoms, increased pulmonary hyperinflation, reduced airflow, and dyspnea—factors that contribute to an elevated risk of mortality [4, 5].

While COPD primarily affects the lungs, it also has significant systemic manifestations. Systemic inflammation and oxidative stress contribute to the progressive loss of muscle mass, which in turn impacts physical capacity and overall health [6–8]. These manifestations result in clinical consequences such as increased fatigue and dyspnea during physical activity, further compounding the functional limitations experienced by patients [9, 10].

In this context, given the impact of COPD on both pulmonary and systemic health, assessing functional capacity early is crucial. Evaluation methods, including specific questionnaires that capture the individual's perception of their disease, symptoms, quality of life, and functional capacity, are essential for effective COPD management [11]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy recommends using the COPD Assessment Test (CAT), a straightforward and practical questionnaire that assesses health status and functional impairment, and serves as a valuable predictor of mortality [12–14].

Exercise intolerance in COPD patients has significant implications for quality of life, hospitalization rates, and survival [15]. Functional physical tests, such as the six-minute walk test (6MWT), are integral to clinical practice for differentiating submaximal exercise intolerance, monitoring disease progression, evaluating responses to various interventions, and predicting mortality [16]. The 6MWT is particularly advantageous due to its simplicity, ease of application, and cost-effectiveness, and it provides valuable prognostic information on both fatal and non-fatal outcomes [16–18].

However, diagnosing mild COPD can be challenging due to often subtle clinical manifestations. Thus, this study hypothesizes that performance in the 6MWT is associated with CAT scores and could serve as a potential predictor of functional capacity across a spectrum of COPD severity. Our objective was to evaluate functional capacity using the 6MWT, stratifying performance into three terciles of distance walked, and to assess the impact of this functional capacity as a predictor of survival over a 24-month follow-up period in COPD patients.

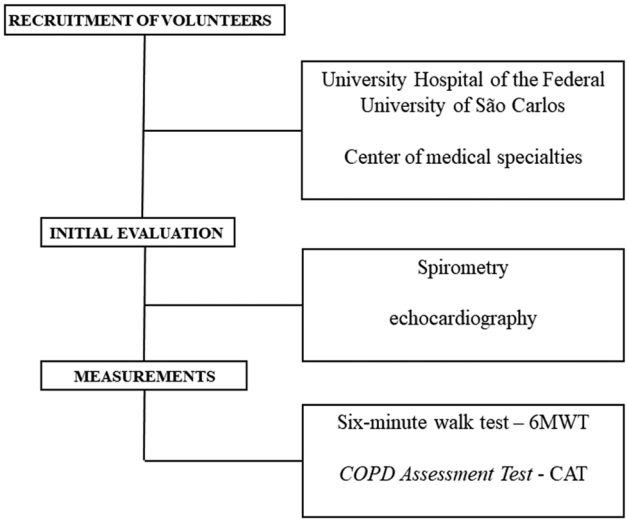

Fig. 1 Experimental protocol

Methodology

Study design and subjects

This study followed the Declaration of Helsinki and all ethics principles. The research was approved by the local ethics committee at the Federal University of São Carlos (protocol number: 91088318.7.1001.5504), and written informed consent was obtained from all participants. Figure 1 describes the experimental protocol used to develop our research. The study design was a 24-month cohort, cross-sectional in nature, guided by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [19]. Recruitment of participants occurred at the pulmonology outpatient clinics of the University Hospital of the Federal University of São Carlos (UFSCar) and the Medical Specialties Center (CEME) in São Carlos, from March 3, 2021, to December 10, 2022. After reviewing medical records of patients seen during this period, telephone contact was made to assess eligibility criteria for inclusion in the study.

Eligibility Criteria were: (1) patients of either sex, aged ≥ 50 years; (2) diagnosed with COPD of any severity (mild, moderate, severe, very severe); (3) clinically stable for at least 3 months (no worsening of symptoms, no exacerbations, 4) no changes in medication dosage, no hospitalizations, and optimized disease treatment); (5) absence of conditions affecting exercise performance; and (6) not participating in a rehabilitation program for at least two months prior to the study. Exclusion Criteria were: (1) use of home oxygen therapy; and (2) presence of neurological or orthopedic conditions that contraindicate exercise testing.

All eligible patients were invited to the laboratory for initial evaluations, including pulmonary function testing and echocardiography. As demonstrated in Figs. 2 and

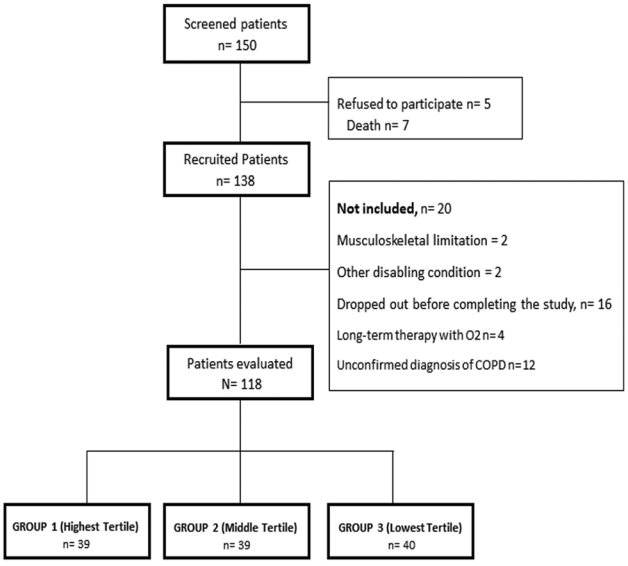

Fig. 2 Study flowchart

150 patients were contacted, but only 118 patients with confirmed COPD by spirometry and who met the study criteria were included. These patients were divided into three groups based on their performance in the 6MWT: Group 1 (distance covered: mean 590–424 m), Group 2 (mean 423–337 m), and Group 3 (mean < 336 m).

Measurements

Six-minute walk test

Recruited individuals who met the inclusion criteria were invited to a second laboratory visit to perform the 6MWT. Participants were instructed to walk as far as possible within 6 min along a 30-meter-long flat corridor, marked with colored tape. Standardized verbal encouragement was provided to motivate participants to achieve their maximum distance. They were informed that they could interrupt the test at any time if necessary. The test was conducted twice with a 30-minute interval between tests, following the American Thoracic Society recommendations [20]. The best performance, defined as the greatest distance covered, was selected for analysis.

Prior to each test, participants rested for two 4-minute periods: one in a seated position and another in an orthostatic position. During the test, the distance covered, occurrence and duration of pauses, and desaturation greater than 4% were recorded at the peak of the exercise. A 6-minute rest period was observed post-exercise.

Physiological variables were measured during the 6MWT, including heart rate (HR) and heart rate delta (peak - rest) using a Polar S810i® monitor (Kempele, Oulu, Finland), and systemic arterial pressure (SBP) using a BIC® sphygmomanometer (Itupeva, São Paulo) with the auscultatory method (Littmann® Classic II Stethoscope, USA). Peripheral oxygen saturation (SpO_2) was measured using a Nonin® 2500 digital oximeter (Minneapolis, MN, USA). The modified BORG CR-10 Perceived Exertion Scale [21] was used to record perceived exertion at rest, at the peak of the exercise, and at 1, 3, and 6 min into recovery. The predicted distance was calculated using the formula [22]: 6MWDpred = 890.46-(6.11×age) + (0.0345×age ^{2}) + (48.87× gender) - (4.87×BMI).

Based on the distribution of the data, we divided the results of the 6MWT into tertiles. This approach facilitated a more detailed analysis of performance across different levels.

Pulmonary function

Pulmonary function was assessed using spirometry (Masterscreen Body, Mijnhardt/Jäger, Würzburg, Germany). Testing was conducted by a trained researcher following the American Thoracic Society and European Respiratory Society (ATS/ERS) guidelines [23]. This involved performing at least three acceptable and reproducible maneuvers, with measurements repeated 20 min after inhalation of Salbutamol Sulfate (400 µg). COPD diagnosis was confirmed using the GOLD criteria, defined by a post-bronchodilator FEV1/forced vital capacity (FVC) ratio < 0.70. Participants were classified into GOLD stages based on the percentage of predicted FEV1: Stage I (mild) > 80%, Stage II (moderate) 50–79%, Stage III (severe) 30–49%, and Stage IV (very severe) < 30% [24].

Echocardiographic

Echocardiographic assessment was performed by a cardiologist specializing in echocardiography using a Phillips HD11 XE ultrasound device with a 3 MHz transducer. Measurements included left ventricular end-diastolic diameter and end-systolic diameter (mm). Color tissue Doppler imaging was used to determine early diastolic mitral filling velocities (E wave) and early diastolic mitral annulus velocity (E' wave). Left ventricular ejection fraction (LVEF) was calculated using the Simpson method [25, 26].

COPD assessment Test - CAT

The CAT score is designed to evaluate the impact of COPD on health status. The questionnaire includes eight items: cough, phlegm, chest tightness, shortness of breath, limitations in daily activities, confidence to leave the house, sleep quality, and energy levels. For each item, patients select one response option, with scores ranging from 0 to 5. The total score is derived by summing the scores for each item. Participants were categorized into groups based on their CAT scores as follows: CAT < 10 (mild impact), CAT 11–20 (moderate impact), and CAT > 20 (severe impact) [12].

Modified medical research council (mMRC)

The mMRC scale was used to assess patients' self-reported perception of dyspnea and physical exertion. This scale classifies the intensity of breathlessness experienced during daily activities into five grades: Grade 0 indicates no breathlessness except during intense physical exertion; Grade 1, breathlessness when walking quickly or climbing a slight incline; Grade 2, breathlessness when walking at the same pace as other people of the same age on level ground; Grade 3, breathlessness when walking at a slower pace than usual speed; and Grade 4, breathlessness so severe that the patient has difficulty even leaving the house or performing light activities. The score is determined based on the patient's selected response and was used to characterize the severity of dyspnea according to their subjective perception of exertion [27].

Follow-up

Patients were monitored over a 24-month period through routine medical consultations and telephone follow-ups conducted every three months. Mortality data were collected during these follow-up calls, where the date and cause of death were recorded. Family members provided information to confirm the date and cause of death when applicable.

Statistical analysis

The sample size was determined probabilistically. Data normality was assessed using the Shapiro-Wilk test. Descriptive statistics are presented as means, standard deviations, and percentages. To test the study hypotheses, the following statistical analyses were conducted: (1) Pearson Correlation Analysis: This two-tailed analysis was used to examine the correlations between measured variables. Correlation strengths were classified as follows: trivial (< 0.1), small (0.30–0.50), moderate (0.50–0.70), large (0.70–0.90), and almost perfect (> 0.90) [28]; (2) One-Way Analysis of Variance (ANOVA): ANOVA was performed to compare means among the three groups (Group 1, Group 2, and Group 3) based on 6MWT performance; (3) Survival Analysis: Kaplan-Meier survival curves were generated, and the log-rank test was used to assess differences in survival across groups, considering exposures such as 6MWD, number of deaths, and follow-up duration; (4) Cox proportional hazards regression models, adjusted for Age (years), Gender (M/F), Smoking, 6MWD, mMRC, FEV1 (L), SpO_2 (%), CAT, HTN, DM, and OSA, were performed. Associations are presented as hazard ratios (HRs) with 95% CIs. All data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM, Armonk, New York). Statistical significance was set at $p < 0.05$.

Results

Table 1 presents the clinical characteristics and anthropometric data of the three groups evaluated. Most participants were male. Regarding comorbidities, stress was more prevalent in groups 2 and 3, which demonstrated a shorter distance walked in the 6MWT compared to Group 1 ($p = 0.014$). Patients in the most severe group (Group 3) presented worse performance in the 6MWT (p = < 0.0001). In addition, Group 3 presented significantly higher scores in the CAT questionnaire ($p = 0.002$), indicating greater severity of symptoms and functional limitations compared to the other groups. Regarding dyspnea, assessed by the modified mMRC scale, patients in Group 1 (distance walked: 590–424 m) demonstrated better scores, reflecting less severe dyspnea.

Figure 3 illustrates that Group 3 (distance covered < 336 m) demonstrated poorer performance, with this group predominantly consisting of individuals classified as having moderate to severe COPD according to the GOLD criteria ($p < 0.007$).

Figure 4 shows that individuals in Group 3, who had the lowest functional performance, also had higher CAT questionnaire scores, reflecting a greater clinical impact of COPD ($p < 0.01$).

Figure 5 displays various physiological parameters at the end of the 6MWT. The dyspnea was significantly higher in Group 3 compared to Group 1 ($p < 0.001$). Group 3 had lower SpO_2 compared to the other groups ($p < 0.05$). Group 3 exhibited a lower HR during the 6MWT compared to the other groups ($p < 0.05$). Additionally, the nadir of SpO_2 was lower in Group 3 compared to Group 1 ($p < 0.05$).

Figure 6 shows the Kaplan-Meier survival analysis, indicating that patients who walked less than 336 m on the 6MWD over a 24-month period had the lowest probability of survival (log-rank $p < 0.05$), with censoring marks indicated along the curves. **Panel A** presents an overview of the survival probabilities, ranging from 0 to 100%, while the **Panel B** magnifies of the range from 70 to 100%, providing a more detailed observation of the curves.

The Cox regression model (Table 2) identified 6MWD (95% CI 0.994; $p < 0.043$) and SpO_2 (%) (95% CI 0.735; $p < 0.001$) as significant predictors of mortality.

Discussion

Our study offers valuable insights into the prognostic value of functional performance assessments in patients with COPD. The key findings of our research are as follows: (1) 6MWT distance is a significant predictor of survival in COPD patients; and (2) lower SpO_2 (%) values are associated with an increased risk of mortality.

Assessing functional capacity through exercise tolerance is pivotal in managing COPD. It aids in differential

Table 1 Anthropometric data, clinical characteristics and complete pulmonary function of the patients evaluated

Variables	G1 6MWT (590–424 m) *n* = 39	G2 6MWT (423 – 337) *n* = 39	G3 6MWT (< 336 m) *n* = 40
Age years	65 ± 7	67 ± 7	68 ± 10
Gender M/F (n)	29/10	26/13	24/16
height, cm	1.66 ± 0.07	1.65 ± 0.10	1.63 ± 0.09
weight, kg	72.6 ± 14.7	71.53 ± 17.6	72.4 ± 22.1
BMI, kg/m2	26.2 ± 5.2	25.6 ± 5.8	27.2 ± 7.7
Smoke (years/pack)	68.0 ± 67.0	76.0 ± 61.0	61.0 ± 60.0
Comorbidities			
Asthma	6(15.4)	5(12.8)	7(17.5)
Osteoporosis	1(2.6)	2(5.1)	5(12.5)
Atherosclerotic Disease	0(0)	1(2.6)	3(7.5)
Congestive Heart Failure	0(0)	1(2.6)	0(0)
Pulmonary Thromboembolism	0(0)	1(2.6)	1(2.5)
Systemic Arterial Hypertension	16(41)	14(35.9)	21(52.5)
Depression	4(10.3)	9(23.1)	8(20)
Obesity	7(17.9)	4(10.3)	11(27.5)
Dyslipidemia	8(20.5)	7(17.9)	7(17.5)
Sedentary behavior	12(30.8)	16(41)	16(40)
Cerebrovascular Accident	1(2.6)	3(7.7)	2(5)
Tuberculosis Sequelae	1(2.6)	2(5.1)	0(0)
Innutrition	0(0)	2(5.1)	2(5)
Anemia	1(2.6)	1(2.6)	2(5)
Deep Vein Thrombosis	0(0)	0(0)	1(2.5)
Stress	0(0)	7(17.9)	8(20)
Diabetes Mellitus	1(2.6)	3(7.7)	3(7.5)
Thyroid Disease	1(2.6)	2(5.1)	4(10)
Obstructive Sleep Apnea Syndrome	9(23.1)	4(10.3)	9(22.5)
Alcoholism	2(5.1)	1(2.6)	2(5)
Bronchiectasis	2(5.1)	0(0)	1(2.5)
Cancer	0(0)	2(5.1)	0(0)
6MWD			
Travelled distance (m)	485.43 ± 45.02	377.48 ± 26.92	255.09 ± 60.70
Deaths, n (%)	2 (14.3%)	0 (0%)	12 (85.7%)
Estimated Distance	506.40 ± 41.23	505.49 ± 43.75	488.99 ± 42.38
Predicted percentage	96.49 ± 12.40	75.23 ± 8.66	52.85 ± 14.95
Pulmonary Function			
FEV1, L/s	1.81 ± 0.76	1.37 ± 0.46	1.17 ± 0.44
FEV1, %	64.6 ± 20.3	53.3 ± 19.6	47.3 ± 16.6
FVC, L/s	3.1 ± 1.1	2.7 ± 0.7	2.4 ± 0.6
FVC, %	83.9 ± 28.1	83.8 ± 22.6	74.9 ± 16.1
FEV1/FVC, L/s	0.56 ± 0.11	0.51 ± 0.12	0.49 ± 0.11
Echocardiogram			
LV end-diastolic diameter (mm)	49.93 ± 6.61	44.86 ± 6.16	47.45 ± 6.56
LV end-systolic diameter (mm)	32.07 ± 8.00	28.55 ± 6.40	29.87 ± 7.04
Mitral E wave (cm/s)	63.38 ± 16.63	60.15 ± 18.43	58.82 ± 20.06
Mitral E' wave(cm/s)	8.71 ± 2.66	8.47 ± 3.05	7.60 ± 2.12
LVEF,%	68.84 ± 7.06	68.96 ± 7.27	70.52 ± 7.42
DPB (mmHg)	89.33 ± 25.12	85.47 ± 26.81	81.82 ± 17.87
SBP (mmHg)	123.57 ± 19.49	116.35 ± 12.56	124.93 ± 13.27
GOLD Internship, I/II/III/IV	9/23/5/2	3/17/16/3	2/13/18/7
CAT score, 0–40	12 ± 8	15 ± 8	19 ± 7
Functional Classification			
mMRC dyspnea score, 0/I/II/III/IV	8/21/7/1/2	4/13/12/6/4	0/14/8/4/14

Table 1 (continued)

Variables	G1 6MWT (590–424 m) *n* = 39	G2 6MWT (423 – 337) *n* = 39	G3 6MWT (< 336 m) *n* = 40
Medications			
LABA, n (%)	9(26.5)	12(42.9)	16(48.5)
SABA, n (%)	16(47.1)	20(71.4)	22(66.7)
LAMA, n (%)	9(23.1)	5(12.8)	9(22.5)
Bronchodilator (mcg)	16(47.1)	10(35.7)	13(39.4)
ECA I e II (mg)	1(2.9)	3(10.7)	5(15.2)
anti-arrhythmic (mg)	1(2.9)	0(0)	0(0)
anti-coagulant (mg)	2(5.9)	1(3.6)	3(9.1)
Antihypertensive (mg)	11(32.4)	3(10.7)	7(21.2)

ANOVA 1 was used for continuous variables and chi-square test for categorical variables; CAT: COPD assessment test; M: male; F: Female; BMI: Body Mass Index; FEV1: Forced Expiratory Volume in 1s; FVC: Forced Vital Capacity; LV: left ventricular, milimeter; centimeter; LVEF: ejection fraction left ventricular; DBP: diastolic blood pressure; SBP: systolic blood pressure; GOLD: *Global Initiative for Chronic Obstructive Lung Disease*; mMrc: modified Medical Research Council scale; LABA: long-acting adrenoceptive β 2 antagonist; SABA: Short-acting beta-agonists; LAMA: Long-acting muscarinic antagonists. ECA: angiotensin converting enzyme. *Significant difference ($p < 0.05$) between G1 6MWD (590–424 m) and G2 (423–337 m). #Significant difference ($p < 0.05$) between G2 6MWD (423–337 m) and G3 (< 336 m). aSignificant difference ($p < 0.05$) between G1 6MWD (590–424 m) and G3 6MWD (< 336 m)

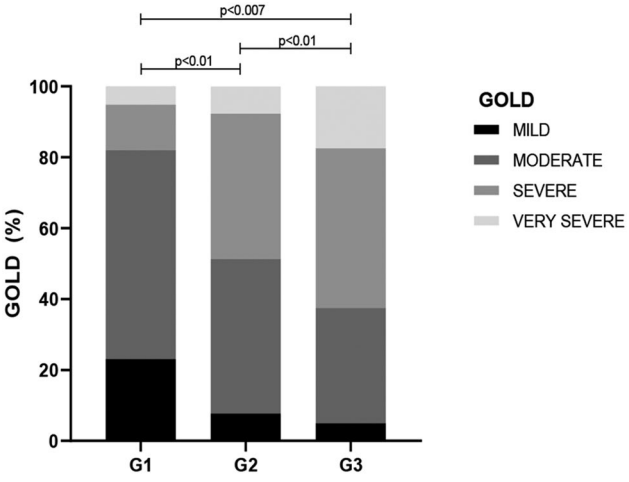

Fig. 3 Classification of patients using the GOLD. GOLD: Global Initiative for Chronic Obstructive Lung Disease; Distance covered in the six-minute walk test (6MWT). GROUPS: G1: 6MWT (590–424 m); G2: 6MWT (423–337 m); G3 6MWT (< 336 m)

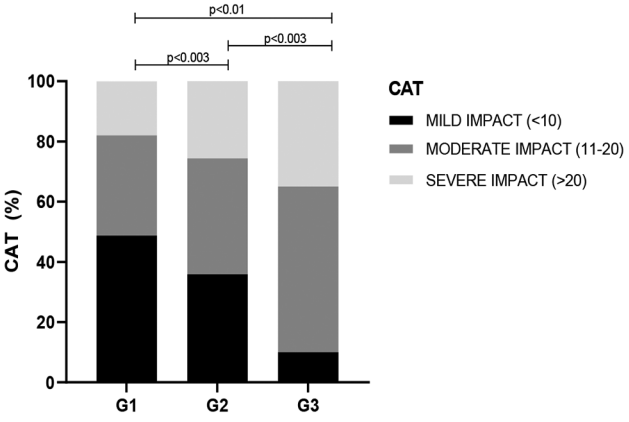

Fig. 4 Classification of patients using the CAT criteria. CAT: COPD assessment test; Distance covered in the six-minute walk test (6MWT). GROUPS: G1: 6MWT (590–424 m); G2: 6MWT (423–337 m); G3 6MWT (< 336 m)

diagnosis. tracking disease progression. evaluating response to interventions. and predicting mortality [29]. The 6MWT and the COPD Assessment Test (CAT) score are essential tools in this regard. Our results underscore that the 6MWT [30] serves as a robust predictor of survival. with patients demonstrating better functional performance (greater 6MWT distance) showing improved survival probabilities. Conversely, those walking less than 336 m exhibited significantly reduced survival rates. as evidenced by Kaplan-Meier survival analysis (Fig. 5).

These findings align with existing literature which highlights the predictive value of exercise capacity for survival in COPD [16, 31]. Celli et al. [31] identified exercise capacity as a crucial predictor of mortality in COPD. and Pinto-Plata et al. [16] found that a 6MWT distance of less than 100 m is associated with a high one-year mortality rate (92%). Dajczman et al. [32] evaluated the relationship between the distance covered in the 6MWD and mortality in patients with severe COPD and a 4-year follow-up. Theuy found that distances shorter than 200 m were associated with a higher risk of mortality. Analyzing different patient profiles, such as those in early and advanced stages of COPD, Provides a more comprehensive understanding of the impact of functional capacity on disease progression. In our investigation, we included individuals classified between GOLD 1 and GOLD 4, allowing for a broader analysis of the applicability of the 6MWD across different stages of the disease. Although longer follow-up periods may offer additional insights into the evolution of COPD, our findings emphasize that even over shorter intervals, the 6MWD remains aa relevant prognostic indicator.

Furthermore. our study reveals that dyspnea. measured by the BORG scale. was notably higher in patients with poorer 6MWT performance (Group 3. <336 m) (Fig. 4A). This increased dyspnea contributes to a progressive decline in physical conditioning. exercise intolerance.

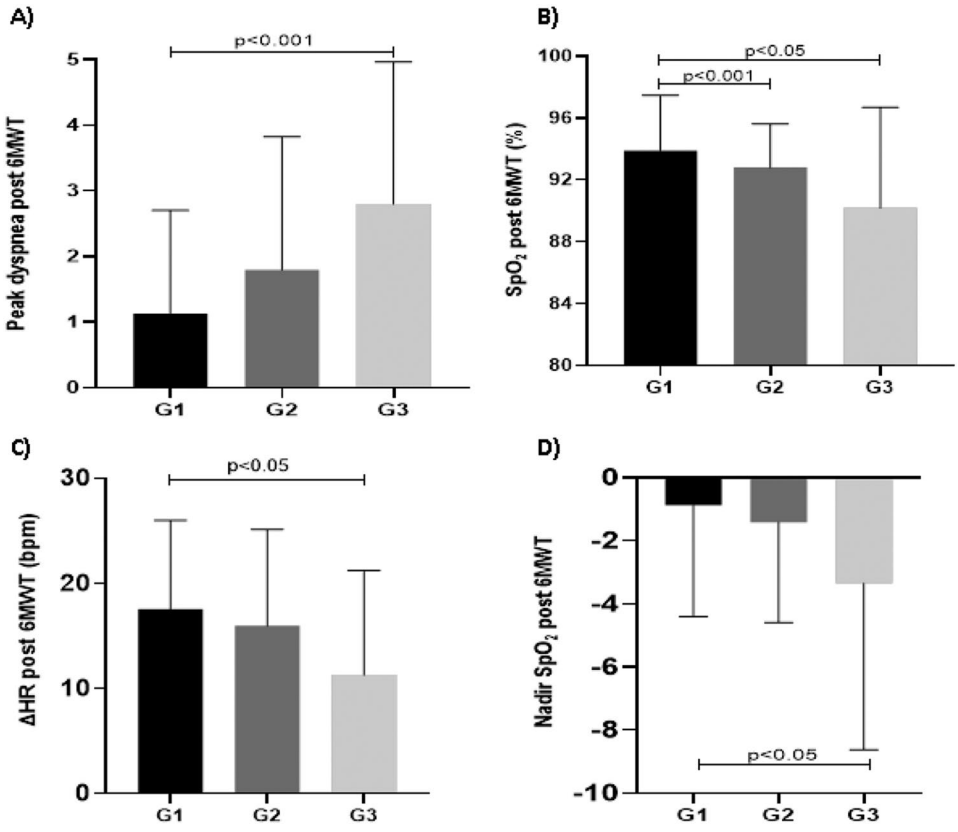

Fig. 5 Physiological variables in 6MWT. **A**: Dyspnea post 6MWT peak; **B**: saturation (SpO2) post 6MWT peak; **C**: Heart rate delta (HR) after the 6MWT; **D**: Nadir (minimum oxygen saturation) SpO2 post 6MWT

and overall functional capacity [33]. Similarly. post-6MWT SpO2 was lower in Group 3 (Fig. 4B). indicating that exercise-induced desaturation is prevalent among patients with more severe disease. The lower heart rate (HR) observed in Group 3 during recovery (Fig. 4C) is particularly noteworthy. Rodríguez et al. [34] found that a slower HR recovery is associated with increased susceptibility to exacerbations. suggesting that impaired autonomic balance in COPD patients may contribute to these findings. Our data corroborate these observations. emphasizing the significance of recovery HR as an indicator of disease severity and prognosis [35, 36].

According to our cox regression analysis model (Table 2), both 6MWT and SpO_2 r were significant predictors of mortality in COPD patients ($p = 0.043$ for 6MWT and $p < 0.001$ for SpO_2). This aligns with findings from Moreira et al. who noted a correlation between desaturation and 6MWT performance while Waatevik et al. [37] did not find a direct association with mortality. Our results reinforce the notion that desaturation during the 6MWT is a critical mortality risk factor. particularly in long-term follow-ups.

The 6MWT remains well-established. standardized assessment tool in clinical settings for evaluating functional capacity across various chronic conditions. including COPD. Its practical application and reliability make it a valuable method for capturing the severity of symptoms and functional status during physical exertion [33]. Although our study indicates a negative correlation between 6MWT performance and the CAT score. the 6MWT provides a more comprehensive evaluation of physical intolerance [20] due to its direct measurement of functional capacity and physiological responses.

Clinical implications

Our study's two-year follow-up duration offers a unique perspective on long-term trends in 6MWT performance. which is critical for understanding the progressive nature of COPD. This extended follow-up period reveals trends not evident in shorter studies. highlighting the impact of additional comorbidities and functional decline on mortality. Integrating objective measures from the 6MWT allied with simple psychophysiological responses during exercise and subjective assessments from the CAT score provides a holistic view of patient health. enhancing clinical practice by enabling more accurate monitoring of disease progression and informing clinical decision-making. This combined approach has the potential to improve patient outcomes and quality of life by facilitating timely interventions and reducing mortality. especially in

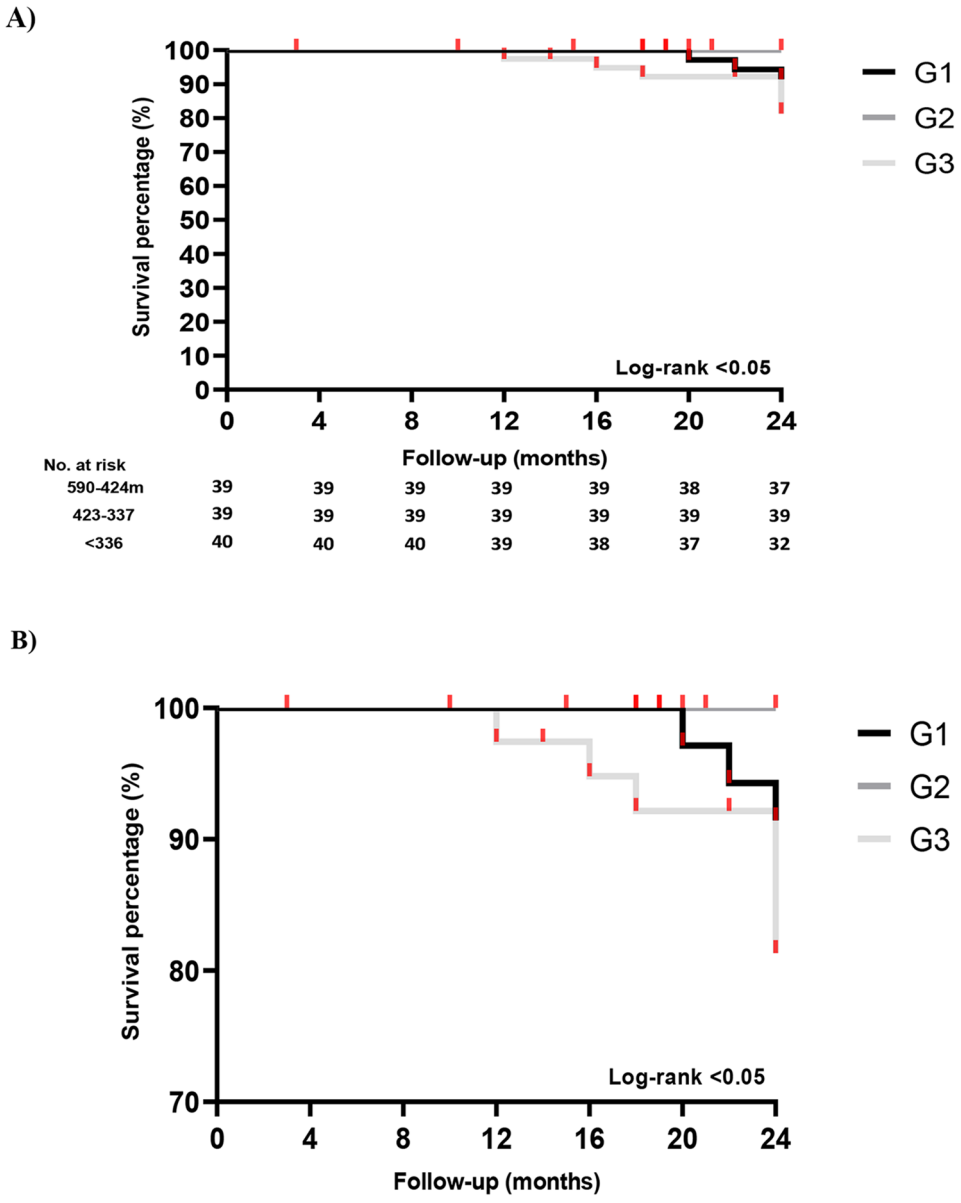

Fig. 6 Kaplan-Meier curve for assessing the mortality risk of COPD patients based on the distance covered in the six-minute walk test. **A**: %: percentage; G1: 6MWT (590–424 m); G2: 6MWT (423–337 m); G3 6MWT (< 336 m); < less than; statistically significant difference for Log-rank; **B**: %: percentage; G1: 6MWT (590–424 m); G2: 6MWT (423–337 m); G3 6MWT (< 336 m); < less than; statistically significant difference for Log-rank

low-income countries. where more robust tests are not used in a broader assessment of exercise tolerance. such as the cardiopulmonary exercise test. In this sense, the walking test can broaden the perspectives of assessment in the context of secondary health care. as a powerful screening indicator.

Additionally. 6MWT is a valuable tool for objectively assessing the efficacy of both pharmacological and non-pharmacological interventions in COPD. It serves as a robust indicator of disease severity and provides critical information that can guide specific evaluations and optimize treatment strategies in clinical practice. Our study underscores the importance of combining the 6MWT with the COPD Assessment Test (CAT) score. Patients with poorer 6MWT performance consistently had higher CAT scores. despite a broaden heterogeneity of severity disease. The CAT is an easily administered tool that can be utilized across all cardiorespiratory rehabilitation settings. offering an accessible method for healthcare professionals to assess symptom severity and functional capacity. This integration of the 6MWT and CAT score not only supports the accurate prescription of exercises by physiotherapists but also enhances the overall

Table 2 Predictive model of death for COPD

Covariates	Coefficient	Standard Error	Hazard ratio (CI 95%)	*p*-value
Age years	0.077	0.055	1.080	0.161
Gender M/F	-1.256	0.917	0.285	0.171
Smoking	-0.552	0.929	0.576	0.553
6MWD	-0.006	0.003	0.994	0.043
mMRC	0.312	0.321	1.367	0.331
FEV_1 (L)	1.090	0.846	2.975	0.197
SpO_2 (%)	-0.307	0.093	0.735	< 0.001
CAT	0.014	0.046	1.014	0.758
HTN	0.817	0.756	2.263	0.280
DM	-13.425	1018.559	< 0.001	0.989
OSA	0.576	0.819	1.779	0.482

M: male; F: Female; 6MWD: Six-Minute Walk Distance; Mmrc: Modified Medical Research Council; FEV1: Forced Expiratory Volume 1 s; L: Liters; Spo2: Peripheral Oxygen Saturation; %: Percent; CAT: COPD Assessment Test; HTN: Hypertension; DM: Diabetes Mellitus; OSA: Obstructive Sleep Apnea; CI: confidence interval

management of COPD by tailoring interventions to individual patient needs and improving clinical outcomes.

Study limitation

This study has limitations that should be acknowledged. First. categorizing patients based on 6MWT may not fully capture disease severity. as this measure may not encompass all aspects of disease impact. The sample size was relatively small, and there was no detailed analysis of demographic variables between groups, which may limit the generalizability of the results. Additionally, the exclusion of patients on home oxygen therapy may further restrict the generalizability of this study. Furthermore, the study was limited by the absence of more comprehensive physiological assessments, such as cardiorespiratory and metabolic variables. Incorporating these measures could have provided deeper insight into the relationship between symptoms and physiological parameters, such as inspiratory capacity. In addition, the study did not account for other factors, such as lower limb muscle condition, cardiovascular health, and socioeconomic factors. Analyzing these variables could offer a more detailed and comprehensive understanding of the 6MWT results, enhancing their interpretation in the context of the disease's impact and its prognostic implications.

Conclusion

Our study highlights that the distance covered in the 6MWT and exercise-induced desaturation are significant predictors of two-year mortality across a wide range of COPD severities. Specifically. diminished performance on the 6MWT is linked with increased desaturation. poorer heart rate recovery. and heightened symptom severity during exercise Our findings show that the distance covered in the 6MWT and desaturation during exercise are predictors of mortality in two years. considering a broad spectrum of COPD severity. Worse performance in the 6MWT is associated with greater desaturation. worse HR recovery. and more symptoms during exercise despite of a broad spectrum of disease severity. Additionally, reduced walking distance correlates strongly with more severe disease and higher COPD Assessment Test (CAT) scores. These findings reinforce the 6MWT's role as a critical prognostic tool for survival in COPD and provide nuanced insights into the physiological factors impacting functional capacity and mortality. By integrating both objective measures like the 6MWT and subjective assessments such as the CAT score, our study offers a comprehensive approach to understanding and managing COPD. suggesting potential advancements in clinical practice and patient care.

Acknowledgements
To the Coordination for the Improvement of Higher Education Personnel (CAPES), National Council for Scientific and Technological Development (CNPq), and São Paulo Research Foundation (FAPESP- 2015/26501-1) for funding this research. To the University Hospital of Federal University of São Carlos - SP-Brazil (HU-UFSCar) Brazilian Company of Hospital Services (EBSERH). Professor Ph.D. Audrey Borghi-Silva is CNPq Research Productivity Scholarship - Level 1B.

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Funding
The São Paulo Research Foundation (Process: 15/26501-1).

Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate
Approval by the Research Ethics Committee of the Universidade Federal de São Carlos (protocol number: 5.188.654). All individuals who voluntarily agreed to participate signed a consent form.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 27 September 2024 / Accepted: 12 May 2025
Published online: 23 May 2025

References

1. Klanidhi K, Chakrawarty A, Bhadouria S, George S, Sharma G, Chatterjee P, et al. Six-minute walk test and its predictability in outcome of COVID-19 patients. J Educ Health Promot. 2022;11.
2. Boers E, Barrett M, Su JG, Benjafield AV, Sinha S, Kaye L, et al. Global burden of chronic obstructive pulmonary disease through 2050. JAMA Netw Open. 2023;6:E2346598.
3. Sharma M, Joshi S, Banjade P, Ghamande SA, Surani S. Global initiative for chronic obstructive lung disease (GOLD) 2023 guidelines reviewed. Open Respir Med J. 2024;18:4.
4. Landis SH, Muellerova H, Mannino DM, Menezes AM, Han MLK, van der Molen T, et al. Continuing to confront COPD international patient survey: methods, COPD prevalence, and disease burden in 2012–2013. Int J Chron Obstruct Pulmon Dis. 2014;9:597–607.
5. Santo AH, Fernandes FLA. Chronic obstructive pulmonary Disease-Related mortality in Brazil, 2000–2019: A Multiple-Cause-of-Death study. COPD. 2022;19:216–25.
6. Hajiro T, Nishimura K, Tsukino M, Ikeda A, Toru O, Izumi T. A comparison of the level of dyspnea vs disease severity in indicating the health-related quality of life of patients with COPD. Chest. 1999;116:1632–7.
7. Casaburi R, Gosselink R, Decramer M, Dekhuijzen RPN, Fournier M, Lewis MI, et al. Skeletal muscle dysfunction in chronic obstructive pulmonary disease. A statement of the American thoracic society and European respiratory society. Am J Respir Crit Care Med. 1999;159(4 Pt 2).
8. Schols AMWJ, Buurman WA, Staal-van Den Brekel AJ, Dentener MA, Wouters EFM. Evidence for a relation between metabolic derangements and increased levels of inflammatory mediators in a subgroup of patients with chronic obstructive pulmonary disease. Thorax. 1996;51:819–24.
9. Velloso M, Garcia Stella S, Cendon S, Silva AC, Jardim JR. Metabolic and ventilatory parameters of four activities of daily living accomplished with arms in COPD patients. Chest. 2003;123:1047–53.
10. Gulart AA, Munari AB, Queiroz APA, De, Cani KC, Matte DL, Mayer AF. Does the COPD assessment test reflect functional status in patients with COPD? Chron Respir Dis. 2017;14:37–44.
11. Karloh M, Mayer AF, Maurici R, Pizzichini MMM, Jones PW, Pizzichini E. The COPD assessment test: what do we know so far?? A systematic review and Meta-Analysis about clinical outcomes prediction and classification of patients into GOLD stages. Chest. 2016;149:413–25.
12. 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;34:648–54.
13. Sakhamuri S, Seemungal T. COPD: gaps in the GOLD recommendations and related imperative research needs. COPD. 2020;17:1–3.
14. Zanoria SJT, Zuwallack R. Directly measured physical activity as a predictor of hospitalizations in patients with chronic obstructive pulmonary disease. Chron Respir Dis. 2013;10:207–13.
15. da Luz Goulart C, Oliveira MR, Sendín FA, Mendes RG, Arena R, Borghi-Silva A. Prognostic value of key variables from cardiopulmonary exercise testing in patients with COPD: 42-month follow-up. Respir Med. 2022;197.
16. Pinto-Plata VM, Cote C, Cabral H, Taylor J, Celli BR. The 6-min walk distance: change over time and value as a predictor of survival in severe COPD. Eur Respir J. 2004;23:28–33.
17. Dal Corso S, Duarte SR, Neder JA, Malaguti C, de Fuccio MB, de Castro Pereira CA, et al. A step test to assess exercise-related oxygen desaturation in interstitial lung disease. Eur Respir J. 2007;29:330–6.
18. Perez T, Deslée G, Burgel PR, Caillaud D, Le Rouzic O, Zysman M, et al. Predictors in routine practice of 6-min walking distance and oxygen desaturation in patients with COPD: impact of comorbidities. Int J Chron Obstruct Pulmon Dis. 2019;14:1399.
19. Malta M, Cardoso LO, Bastos FI, Magnanini MMF, da Silva CMFP. STROBE initiative: guidelines on reporting observational studies. Rev Saude Publica. 2010;44:559–65.
20. Crapo RO, Casaburi R, Coates AL, Enright PL, MacIntyre NR, McKay RT, et al. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166:111–7.
21. Borg GAV. Psychophysical bases of perceived exertion. 1982;377–81.
22. Britto RR, Probst VS, De Dornelas AF, Samora GAR, Hernandes NA, Marinho PEM, et al. Reference equations for the six-minute walk distance based on a Brazilian multicenter study. Brazilian J Phys Ther. 2013;17:556–63.
23. Graham BL, Steenbruggen I, Barjaktarevic IZ, Cooper BG, Hall GL, Hallstrand TS, et al. Standardization of spirometry 2019 update. An official American thoracic society and European respiratory society technical statement. Am J Respir Crit Care Med. 2019;200:e70.
24. Agustí A, Celli BR, Criner GJ, Halpin D, Anzueto A, Barnes P, et al. Global initiative for chronic obstructive lung disease 2023 report: GOLD executive summary. Am J Respir Crit Care Med. 2023;207:819–37.
25. Lang RM, Badano LP, Victor MA, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American society of echocardiography and the European association of cardiovascular imaging. J Am Soc Echocardiogr. 2015;28:1–e3914.
26. McDonagh TA, Metra M, Adamo M, Baumbach A, Böhm M, Burri H, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42:3599–726.
27. Kovelis D, Segretti NO, Probst VS, Lareau SC, Brunetto AF, Pitta F. Validação do modified pulmonary functional status and dyspnea questionnaire e Da Escala do medical research Council Para O Uso Em Pacientes com Doença pulmonar obstrutiva crônica no Brasil. J Bras Pneumol. 2008;34:1008–18.
28. Mukaka MM. A guide to appropriate use of correlation coefficient in medical research. Malawi Med J. 2012;24:69.
29. Spruit MA, Polkey MI, Celli B, Edwards LD, Watkins ML, Pinto-Plata V, et al. Predicting outcomes from 6-minute walk distance in chronic obstructive pulmonary disease. J Am Med Dir Assoc. 2012;13:291–7.
30. Cote CG, Pinto-Plata V, Kasprzyk K, Dordelly LJ, Celli BR. The 6-min walk distance, peak oxygen uptake, and mortality in COPD. Chest. 2007;132:1778–85.
31. Celli BR. Predictors of mortality in COPD. Respir Med. 2010;104:773–9.
32. Dajczman E, Wardini R, Kasymjanova G, Préfontaine D, Baltzan MA, Wolkove N. Six minute walk distance is a predictor of survival in patients with chronic obstructive pulmonary disease undergoing pulmonary rehabilitation. Can Respir J. 2015;22:225–9.
33. Moreira MÂF, de Medeiros GA, Boeno FP, Sanches PRS, da Silva Júnior DP, Müller AF. Análise Da dessaturação de oxigênio Durante O teste de Caminhada de seis minutos Em Pacientes com DPOC. J Bras Pneumol. 2014;40:222–8.
34. Rodríguez DA, Kortianou EA, Alison JA, Casas A, Giavedoni S, Barberan-Garcia A, et al. Heart rate recovery after 6-min walking test predicts acute exacerbation in COPD. Lung. 2017;195:463–7.
35. Polkey MI, Spruit MA, Edwards LD, Watkins ML, Pinto-Plata V, Vestbo J, et al. Six-minute-walk test in chronic obstructive pulmonary disease: minimal clinically important difference for death or hospitalization. Am J Respir Crit Care Med. 2013;187:382–6.
36. Lisboa BC, Barría PP, Yáñez VJ, Aguirre ZM, Díaz PO. Six minutes walk for the assessment of patients with chronic obstructive pulmonary disease. Rev Med Chil. 2008;136:1056–64.
37. Waatevik M, Frisk B, Real FG, Hardie JA, Bakke P, Nilsen RM, et al. One year change in 6-Minute walk test outcomes is associated with COPD prognosis. COPD. 2020;17:662–71.

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