

# Applicability of Brazilian reference equations for the 6-minute walk test in patients with lung cancer

*Aplicabilidade das equações de referência brasileiras para o teste de caminhada de 6 minutos em pacientes com câncer de pulmão*

*Aplicabilidad de las ecuaciones de referencia brasileñas para la prueba de caminata de 6 minutos en pacientes con cáncer de pulmón*

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**ABSTRACT** | The aim of this study was to verify the impact of using different Brazilian reference equations for the distance covered in the 6-minute walk test (6MWT) in the evaluation of functional exercise capacity in patients with lung cancer (LC). This cross-sectional study included 48 patients with LC (average age of 60±12 years-old). The participants underwent an assessment of sociodemographic and clinical characteristics and their functional exercise capacity with the 6MWT, following international recommendations. Five equations were analyzed. The distance covered by the patients (503±102 meters) was relatively close to the distances predicted by the reference equations (82-94% of the predicted), although statistically lower ( $p < 0.05$  for all).

**Keywords** | Lung Neoplasms; Reference Values; Exercise Tolerance.

**RESUMO** | O objetivo deste estudo foi verificar o impacto da utilização de diferentes equações de referência brasileiras para a distância percorrida no teste da caminhada de 6 minutos (TC6min) na avaliação da capacidade funcional de exercício em pacientes com câncer de pulmão (CP). Este estudo transversal incluiu 48 pacientes com CP (idade média de 60±12 anos). Os participantes foram submetidos à avaliação de características sociodemográficas, clínicas

e da sua capacidade funcional de exercício com o TC6min, seguindo recomendações internacionais. Foram analisadas cinco equações. A distância percorrida pelos pacientes (503±102 metros) foi relativamente próxima às distâncias previstas pelas equações de referência (82-94% do previsto), embora estatisticamente inferior ( $p < 0,05$  para todas).

**Descritores** | Neoplasias Pulmonares; Valores de Referência; Tolerância ao Exercício.

**RESUMEN** | El objetivo de este estudio fue verificar el impacto de diferentes ecuaciones de referencia brasileñas para la distancia recorrida en la prueba de caminata de 6 minutos (PC6min) en la evaluación de la capacidad de ejercicio funcional en pacientes con cáncer de pulmón (CP). Este estudio transversal incluyó a 48 pacientes con CP (promedio de edad de 60±12 años). Se evaluó las características sociodemográficas, clínicas y la capacidad funcional de los participantes para ejercitarse en la PC6min según los criterios internacionales. Se analizaron cinco ecuaciones. La distancia recorrida por los pacientes (503±102 metros) estuvo relativamente cerca de las distancias predichas por las ecuaciones de referencia (82-94% del predicho), aunque son estadísticamente menores ( $p < 0,05$  para todas).

**Palabras clave** | Neoplasias Pulmonares; Valores de Referencia; Tolerancia al Ejercicio.

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## INTRODUCTION

Lung cancer (LC) is among the types of cancer with the highest morbidity and mortality rate in different parts of the world<sup>1,2</sup>. Due to the changes caused by cancer, such as weight loss, symptoms such as dyspnea and fatigue, and the consequences of the treatments used, such as surgery and/or chemotherapy, patients with LC tend to have a vastly compromised physical and mental condition. In the study by Granger et al.<sup>3</sup>, the authors observed that patients with non-small cell LC walked less, presenting a smaller number of steps in the daily life, shorter distance covered in the 6-minute walk test (6MWT), worst quadriceps strength and worse health-related quality of life at the time of diagnosis compared to healthy individuals. Physical impairments were noticed even after the main treatments were used in this population, such as lung resection surgery or chemotherapy<sup>4</sup>.

A systematic review of measurement outcomes in patients with non-small cell LC showed that the 6MWT is the most used test for the assessment of functional exercise capacity<sup>3</sup>. This analyzes the maximum distance that an individual can walk in a six-minute period and allows the measurement of the integrated response of all the systems involved during exercise (for example, cardiovascular, respiratory and musculoskeletal)<sup>5</sup>.

For the interpretation of the 6MWT result, a widely used strategy is to compare the values obtained from the population of interest with the reference values calculated from equations developed from a sample of healthy individuals. In Brazil, several reference equations are available in literature<sup>6-9</sup>, but with different characteristics, such as the variables taken into account in the equation and the coefficient of determination ( $R^2$ ). Moreover, divergent results have been shown in the comparison between different equations in other populations<sup>10,11</sup>.

Given the above, the purpose of the present study was to verify the impact of using different Brazilian reference equations for the distance covered in the 6MWT in the functional exercise capacity assessment in patients with LC. It is believed that there is disagreement in the results of the equations. Such research becomes relevant, as it may contribute to a more accurate assessment of the functional exercise capacity of these patients, which may allow a better assessment of the impact of different interventions, as well as a better prognostic

evaluation. For example, if it is observed that one of the Brazilian reference equations presents significant divergent results in relation to the others, this may be associated with an incorrect identification of patients with low functional exercise capacity by this equation, which may lead to the establishment of an improper prognosis or inadequate prescription of therapy (for example, physical exercise).

## METHODOLOGY

### Study design and participants

This is a cross-sectional study, which is a sub-analysis of a larger study that aimed to assess the impact of pulmonary resection by LC on inflammatory markers one month after surgery<sup>12</sup>. This research was carried out at the Thoracic Surgery outpatient clinic of Messejana Dr. Carlos Alberto Studart Gomes Hospital, in the city of Fortaleza (CE), Brazil, from July 2012 to July 2014. For the present study, only preoperative evaluation was used, and patients with a diagnosis of non-small cell LC, candidates for pulmonary resection surgery and ages 18 years-old or older were included; and patients with advanced LC or with cognitive or motor changes that made evaluations impossible were excluded. All participants signed the Free and Clarified Consent Term and the research was approved by the Research Ethics Committee of the Messejana Hospital with the Opinion No. 277,681. The article was presented according to the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)<sup>13</sup>.

### Evaluations

Evaluations of sociodemographic and clinical data (age, gender, body mass index (BMI), cancer staging, current smoking and previous lung disease), lung function (spirometry), health-related quality of life (medical outcomes study 36-item short form health survey – SF-36), and functional exercise capacity (6MWT) were carried out. Spirometry was performed in accordance with national recommendations<sup>14</sup>, and for the present analysis, the following parameters were used: forced expiratory volume in the first second (FEV1), forced vital capacity (FVC) and the relation between both<sup>15,16</sup>.

SF-36 contains 36 items that are grouped into eight dimensions (functional capacity, pain, physical aspects, emotional aspects, social aspects, mental health, vitality and general state of health). The results can be organized into a summarized physical and mental coefficient. The SF-36 items are coded, grouped and transformed on a scale from 0 to 100, which represents a worse or better general state of health, respectively, for each dimension or summarized coefficient. The translated and validated version for usage in Brazil was used<sup>17</sup>.

The 6MWT was performed according to the recommendations of the American Thoracic Society<sup>18</sup>. All patients were instructed to walk the longest distance possible on a 30-meter course for a period of six minutes and without running. The test was performed twice, but the one used for analysis was the test with the longest distance. The distance covered for the 6MWT was calculated according to the following reference equations for the Brazilian population: Iwama et al.<sup>6</sup>, Dourado et al.<sup>7</sup>, Soares and Pereira<sup>8</sup> and Britto et al.<sup>9</sup>, which, from this point on, will be described only by the name of the first author. The study by Britto et al.<sup>9</sup> generated two equations, which will be described as Britto 1 and Britto 2. Based on the comparison of the distance covered by the patients with the lower limit of normality established from each equation, the participants were classified into reduced or preserved functional exercise capacity.

**Statistical analysis**

The analysis of the obtained data was performed using the software SPSS 22.0 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.), and the software GraphPad Prism® 7.02 (GraphPad Software Inc., La Jolla (CA) USA) was used for the elaboration of the graphs. The occurrence of missing data was described when present and the analysis were produced considering only the available data. The Shapiro-Wilk test was used as a test of normality. Numerical data were presented as mean ± standard deviation, mean (95% confidence interval) or median (interquartile range). Categorical data were expressed as absolute and/or relative frequency. The chi-squared test was applied to compare categorical variables. In order to compare continuous variables, the paired Student’s t-test (or Wilcoxon) or the repeated measurement ANOVA (Tukey’s post-test) were used. In order to

assess the consensus between the different equations for the reduced functional exercise capacity classification, the Kappa coefficient was applied. Significance level less than 5% was adopted (p<0.05).

**RESULTS**

**Sample characteristics**

It was included 48 patients with a diagnosis of non-small cell LC. Table 1 describes the characteristics of these patients. It can be seen that the sample covers elderly patients, and that the majority was composed of female patients (56%). The mean BMI was compatible with overweight. Regarding staging, stage Ia or Ib (52%) prevailed, and 23% reported previous lung disease. The physical dimension of quality of life proved to be more compromised than the mental one.

Table 1. Sociodemographic and clinical characteristics of the sample (n=48)

Characteristic	N	Value
Age, years	48	60±12
Gender, n (%)		
Male	48	21 (44)
Female		27 (56)
BMI, kg/m <sup>2</sup>	48	25,6±3,2
Tobacco load, pack-years	37	35±17
Current smoking, n (%)	48	5 (10)
Stage, n (%)		
Ia or Ib	48	25 (52)
Ila, Ilb or IIIa		23 (48)
Previous lung disease, n (%)	48	11 (23)
FEV <sub>1</sub> , % predicted	48	86±18
FEV <sub>1</sub> / FVC, %	48	80 (73-86)
SPC, %	48	46±7
SMC, %	48	51 (42-62)

Data expressed as absolute and relative frequency, mean ± standard deviation, or median (interquartile range). BMI: body mass index; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; SPC: summarized physical coefficient; SMC: summarized mental coefficient.

Table 2 describes the results to the 6MWT. It was identified that the average distance covered in the test by the group was 503±102 meters. It was also observed that

there was a considerable and statistically significant heart rate (HR) increase ( $p < 0.001$ ), but no change in SpO<sub>2</sub> after the test ( $p = 0.10$ ). There was a slight but statistically significant increase in the symptoms of dyspnea and fatigue ( $p < 0.001$  for both).

Table 2. Responses to the 6-minute walk test in lung cancer patients (n=48)

Variables	N	Value
6MWT distance, meters	47	503±102
HR before, bpm	37	78±16
HR after, bpm	37	111±22
Delta HR, bpm	37	34±21
SpO <sub>2</sub> before, %	37	97 (95-98)
SpO <sub>2</sub> after, %	37	97 (94-98)
Borg D before, score	37	0 (0-0)
Borg D after, score	37	1 (0-2)
Borg F before, score	37	0 (0-0)
Borg F after, score	37	1 (0-2)

Data expressed as mean ± standard deviation or median (interquartile range). 6MWT: 6-minute walk test; HR: heart rate; SpO<sub>2</sub>: Peripheral oxygen saturation; Borg D: dyspnea score on the modified Borg scale; Borg F: fatigue score on the modified Borg scale.

### Predicted distances in the 6MWT

Figure 1 shows the comparison between the distance covered by the patients and the one predicted by the Brazilian equations. It can be noted that the distance covered by the patients was statistically lower than that predicted by all equations ( $p < 0.05$ ). In addition, it was observed that the distance predicted by Iwama<sup>6</sup> (538 ± 37 meters) was shorter than that predicted by Dourado<sup>7</sup> (593 ± 56 meters); the one predicted by Dourado<sup>7</sup> was greater than the distances predicted by Soares<sup>8</sup> (521 ± 50 meters), Britto 1<sup>9</sup> (549 ± 38 meters) and Britto 2<sup>9</sup> (545 ± 53 meters); and that predicted by Soares<sup>8</sup> was lower than that predicted by Britto 1<sup>9</sup>. The average difference (95% confidence interval) between the values reached by the patients and the predicted values of Iwama<sup>6</sup>, Dourado<sup>7</sup>, Soares<sup>8</sup>, Britto 1<sup>9</sup> e Britto 2<sup>9</sup> was: 35 (11, 58) meters; 104 (80, 128) meters; 32 (5, 58) meters; 46 (21, 70) meters; and 58 (31, 84) meters, respectively.

The distance covered by the patients represented 93±15% of the predicted by Iwama<sup>6</sup> (statistically greater than Britto 1); 82 ± 13% of predicted by Dourado<sup>7</sup> (lower than all others); 94±15% of the predicted by Soares<sup>8</sup> (greater than Britto 1); 91±15% of the predicted by Britto 1<sup>9</sup>; and 89±15% of the predicted by Britto 2<sup>9</sup>.

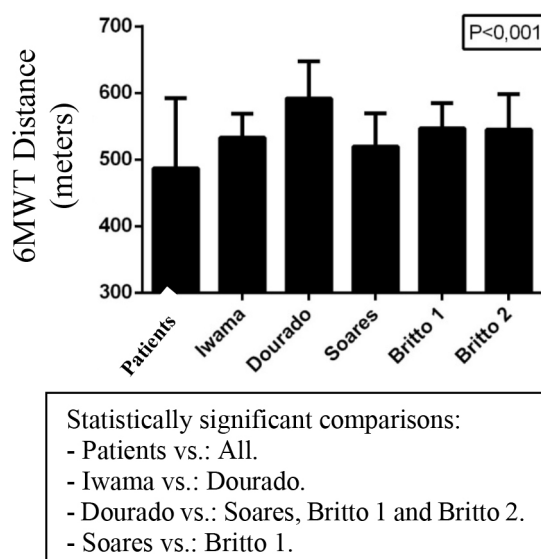


Figure 1. Comparison between the distance covered by patients with lung cancer and those predicted by the Brazilian equations (n=47 for Iwama<sup>6</sup> and Britto 1<sup>9</sup>; n=35 for Dourado<sup>7</sup>, Soares<sup>8</sup> and Britto 2<sup>9</sup>).

### Classification according to the functional exercise capacity

Figure 2 shows the proportion of patients with LC classified as “with low functional exercise capacity” according to the different Brazilian equations. It is noticed that in Dourado<sup>7</sup> it was where the equation presented a higher percentage (56%), followed by Britto 2<sup>9</sup> (29%), Soares<sup>8</sup> (19%), Iwama<sup>6</sup> and Britto 1<sup>9</sup> (17% for both). Only 7 patients (15%) were classified as having reduced functional exercise capacity by all equations, while 20 patients (42%) were classified in at least one of the equations. This last percentage is lower than the one calculated from the study by Dourado<sup>7</sup> due to the occurrence of missing data (check subtitle in Figure 1).

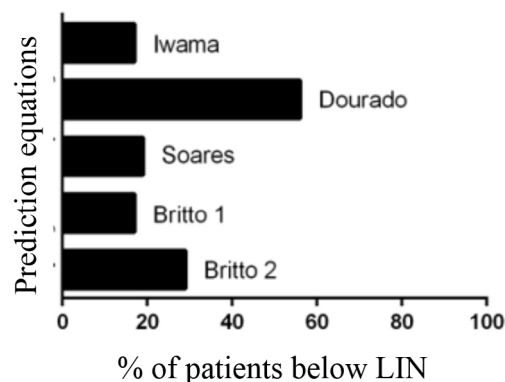


Figure 2. Proportion of lung cancer patients classified as “with low functional exercise capacity” according to Brazilian equations (n=48)

The consensus by the Kappa coefficient between pairs of equations for the reduced functional exercise capacity classification varied between 0.32 and 0.92. The equations that showed the highest consensus (i.e., kappa > 0,75) were: Iwama<sup>6</sup> and Soares<sup>8</sup>: 0.92; Iwama<sup>6</sup> and Britto 1<sup>9</sup>: 0.85; Iwama<sup>6</sup> and Britto 2<sup>9</sup>: 0.85; Soares<sup>8</sup> and Britto 1<sup>9</sup>: 0.92; and Soares<sup>8</sup> and Britto 2<sup>9</sup>: 0.77.

## DISCUSSION

This study investigated the applicability of different Brazilian reference equations for the distance covered in the 6MWT in patients with LC. It was observed that the distance predicted by Dourado<sup>7</sup> was greater than all the others, and that there was no difference in the comparison between the distances predicted by Iwama<sup>6</sup>, Soares and Pereira<sup>8</sup> and one of the equations proposed by Britto<sup>9</sup>. It was also noted a good consensus between the predicted equations by these last studies for the reduced functional exercise capacity classification. These findings may impact the interpretation of the distance covered in the 6MWT by patients with LC.

The main document of the American Thoracic Society (ATS) and European Respiratory Society (ERS) for the use of the 6MWT in patients with respiratory diseases makes it clear that the reference equations can be used for the results' interpretation, but that it must be verified in local populations whenever possible<sup>5</sup>. The comparison with predicted values shows how limited a given population is, and this strategy has been widely used in the literature on LC. In the study by Cavalheri et al.<sup>4</sup>, it was observed that patients with non-small cell LC had an average of 80% of the predicted distance covered in the 6MWT a few weeks after curative care. In the study by Granger et al.<sup>3</sup>, it was found an average distance of 84% of the predicted at the time of the diagnosis of LC, but with a reduction to 69% of the predicted after six months. These values are similar or lower to those found in the present study. The identification of impairments in the functional exercise capacity of patients with LC is essential for the development of monitoring and treatment strategies for these individuals.

Few Brazilian studies have aimed to investigate and compare the applicability of the different equations for the distance covered in the 6MWT. In the study by Santos et al.<sup>19</sup>, the authors noticed that the distance covered by healthy elderly people was lower than that predicted

by Dourado<sup>7</sup>, greater than that predicted by Soares and Pereira<sup>8</sup> and with no difference in comparison with the values by Iwama<sup>6</sup>. In the study by Machado<sup>10</sup>, the authors investigated the usage and applicability of different equations (national and international) in a sample of patients with chronic obstructive pulmonary disease (COPD). It was observed that the values in percentage of the predicted calculated from the equations by Iwama<sup>6</sup> and the two equations by Britto<sup>9</sup> were similar. It has also been noted that the values calculated from the Dourado<sup>7</sup> equation were lower than all the others and that those calculated from the Soares<sup>8</sup> equation were higher than all the others. In the present study, the value calculated from the Dourado<sup>7</sup> equation was also lower than all the others. In the same study by Machado et al.<sup>10</sup>, the authors found a good consensus in the reduced functional exercise capacity classification between the equations by Iwama<sup>6</sup> and the two equations by Britto<sup>9</sup>. This study obtained similar results, but there was no good consensus between the two equations proposed by Britto<sup>9</sup>.

Considering the findings of this study and previous studies, it can be observed that the equation proposed by Dourado<sup>7</sup> is the one that presents results that are more divergent from the others. This study applied the 6MWT to 98 healthy individuals and generated an equation that included the variables age, weight, height and gender that collectively explained 54% of the variance of the distance covered in the test. Still taking into account the different studies, it can be said that the equations that present more similar results are the ones proposed by Iwama<sup>6</sup> and the Britto<sup>9</sup> equation, which does not use heart rate. The study by Iwama<sup>6</sup> evaluated 134 healthy individuals and generated an equation that included only age and gender, which explained 30% of the variance in the distance covered in the 6MWT. Britto's<sup>9</sup> study included a multicenter sample of 617 healthy individuals and generated two equations. The equation with results similar to the one proposed by Iwama<sup>6</sup> included age, gender and BMI, explaining 46% of the variance. This equation proposed by Britto<sup>9</sup> and the equation proposed by Iwama<sup>6</sup> seem to be the most applicable for patients with LC. The equation proposed by Soares<sup>8</sup> was not suggested based on the findings by Santos et al.<sup>19</sup>, who realized that it led to values statistically lower than those of a sample of healthy individuals, while the Britto 2<sup>9</sup> equation was not advised for including the delta of heart rate during the test, which might not be statistically adequate. However, for a more robust recommendation, further studies are needed to investigate the ability of the

different equations to discriminate groups of patients with different characteristics, by comparing them with other outcomes (e.g., mortality, physical activity in daily life, etc.).

This study had some limitations. The reduced sample size and the occurrence of some missing data may have compromised the power of some analysis, as well as the external validity of the findings. Additionally, the number of patients classified as “reduced functional exercise capacity” was small, which may also have compromised external validity. Nonetheless, it is believed that the external validity has not been so affected since the results of the 6MWT (as a percentage of predicted) observed in this study for patients with LC (i.e., 82–94%) were close to those observed in previous studies (i.e., 80–84%)<sup>3,4</sup>. Finally, reference equations for non-Brazilian populations were not included, as performed in other studies<sup>10,11</sup>. It was decided to analyze only the Brazilian equations, considering that they are the most adequate to be used in Brazil.

## CONCLUSION

Our study found that 17–56% of lung cancer patients have low functional exercise capacity according to the different Brazilian reference equations. Most of the investigated reference equations exhibited similar results. The equation proposed by Dourado et al.<sup>7</sup> was the one that presented the most divergent results, while those proposed by Iwama et al.<sup>6</sup> and one equation by Britto et al.<sup>9</sup> (the one that does not include heart rate) were the ones that led more similar results. It is suggested that one of these last two equations be used when lung cancer patients are being evaluated.

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