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ANDREIA CRISTINA TRAVASSOS DA COSTA

**DEPLEÇÃO DE MASSA LIVRE DE GORDURA EM DPOC  
E SUA RELAÇÃO COM MANIFESTAÇÕES  
EXTRAPULMONARES DA DOENÇA**

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Dissertação apresentada ao Programa de Pós-Graduação em Ciências da Reabilitação (Programa Associado entre Universidade Estadual de Londrina [UEL] e Universidade Norte do Paraná [UNOPAR]), como requisito parcial à obtenção do título de Mestre em Ciências da Reabilitação.

Orientadora: Profa. Dra. Nidia A. Hernandes.

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Londrina, 09 de agosto de 2016.

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“Foi o tempo que dedicastes à tua rosa que a fez tão importante”

(Antoine de Saint-Exupéry)

COSTA, Andreia Cristina Travassos. **Depleção de massa livre de gordura em DPOC e sua relação com manifestações extrapulmonares da doença.** 2016. 91f. Dissertação de mestrado (Programa de Pós-Graduação em Ciências da Reabilitação – Programa Associado entre UEL e UNOPAR) – Universidade Estadual de Londrina, Londrina, 2016.

## RESUMO

**Introdução:** A doença pulmonar obstrutiva crônica (DPOC) esta associada a diversas manifestações extrapulmonares, dentre estas a depleção de massa livre de gordura (MLG) que gera impactos clínicos importantes. Existem diversos pontos de corte para classificação de depleção de MLG em pacientes com DPOC. Entretanto, não se sabe se tais critérios discriminam manifestações extrapulmonares da doença. Além disso, nenhum desses pontos de corte foram desenvolvidos para a população brasileira. **Objetivos:** Desenvolver um ponto de corte para determinar depleção de massa livre de gordura específico para pacientes com DPOC brasileiros, verificar sua validade, assim como sua associação, e de outros pontos de corte publicados previamente, com mortalidade, capacidade de exercício, qualidade de vida, atividade física e estilo de vida sedentário. **Métodos:** Para determinar um novo ponto de corte, 57 pacientes com DPOC foram submetidos à impedância bioelétrica para determinação da MLG. Um novo ponto de corte foi obtido a partir do melhor valor de índice de massa livre de gordura (IMLG) para discriminação de boa capacidade de exercício (teste de caminhada de seis minutos - TC6min -  $\geq 82\%$ pred). Para verificar a capacidade discriminativa de todos os pontos de corte, uma nova amostra foi composta (n=96). Além do novo ponto de corte, foram também avaliados aqueles propostos por: Schols *et al.*, Schutz *et al.*, Kyle *et al.*, Coin *et al.*, Vestbo *et al.* e Franssen *et al.* Todos foram testados para discriminar: baixa capacidade de exercício (TC6min  $< 82\%$ pred; e  $< 350$ m), inatividade física (tempo gasto em atividade física  $< 30$  min), sedentarismo ( $\geq 8$ h:30min em atividades  $< 1,5$  METS) e baixa qualidade de vida (escore total St. George's Respiratory Questionnaire  $\geq 38,2$  pontos). Para a análise estatística, foram utilizadas curvas ROC com valor de área sob a curva (AUC), calculados valores preditivos positivo (VPP), negativo (VPN), sensibilidade (S), especificidade (E) e acurácia (AC). Regressão de Cox e método Kaplan-Meier foram utilizados para verificar associação entre os pontos de corte e mortalidade. **Resultados:** O novo ponto de corte obtido foi um IMLG de  $20,35 \text{ kg/m}^2$  (AUC=0,565, S=0,36; E=0,81) para homens e  $14,65 \text{ kg/m}^2$  (AUC=0,744, S=0,88; E=0,60) para mulheres. O ponto de corte de Schols *et al.* discriminou melhor sedentarismo (VPP=63%, VPN=50% e AC=62%) e capacidade de exercício pelo critério TC6min  $< 350$ m (VPP=85% e AC=73%), enquanto o novo ponto de corte discriminou melhor capacidade de exercício pelo critério  $< 82\%$ predito (VPN=67%, AC=62%) e qualidade de vida (VPN=57%, AC=53%). Somente o novo ponto de corte apresentou associação com mortalidade (HR=2,123,  $P=0,039$ , log rank=0,035). **Conclusão:** Um novo ponto de corte para determinação de depleção de MLG foi desenvolvido para homens e mulheres brasileiros com DPOC. O ponto de corte de Schols *et al.* foi discriminativo para sedentarismo e capacidade de exercício (valores absolutos do TC6min). Entretanto, o novo ponto de corte foi o único a apresentar associação com mortalidade por todas as causas e maior poder discriminativo para capacidade de exercício (valores relativos do TC6min) e qualidade de vida em DPOC.

**Palavras-chave:** Doença pulmonar obstrutiva crônica. Composição corporal. Estado nutricional. Valores de referência. Prognóstico.

COSTA, Andreia Cristina Travassos. **Fat-free mass depletion in COPD and its relationship with extrapulmonary disease manifestations.** 2016. 91p. Dissertação de mestrado (Programa de Pós-Graduação em Ciências da Reabilitação – Programa Associado entre UEL e UNOPAR) – Universidade Estadual de Londrina, Londrina, 2016.

## ABSTRACT

**Introduction:** Chronic obstructive pulmonary disease (COPD) is associated with extrapulmonary manifestations, among them depletion of fat-free mass (FFM) which leads to important clinical impacts. Several cut off points to determine FFM depletion in COPD are known. However, it is unclear whether these criteria can discriminate extrapulmonary disease manifestations. Furthermore, none cut off point was developed for the Brazilian population. **Objectives:** To develop a cut off point for FFM depletion specific for Brazilian COPD patients, to validate it and to verify its association and of previously published cut off points with mortality, exercise capacity, health related quality of life, physical activity and sedentary lifestyle. **Methods:** In order to determine a new cut off point, 57 COPD patients underwent bioelectrical impedance to determine FFM. A new cut off point was obtained from the best fat-free mass index (FFMI) value for discrimination of preserved exercise capacity (6-minute walk test - 6MWT -  $\geq 82\%$  pred). To verify the discriminative capacity of all cut off points, a new sample was composed (n=96). In addition to the new cut off point, those proposed by Schols et al., Schutz et al., Kyle et al., Coin et al., Vestbo et al. and Franssen et al. were also evaluated. All cut off points were tested to discriminate: low exercise capacity (6MWT  $< 82\%$  pred, and  $< 350\text{m}$ ), physical inactivity (time spent on physical activity  $< 30$  min), sedentary lifestyle ( $\geq 8\text{h}$ : 30min in  $< 1.5$  METS activities) and low quality of life (total score St. George's Respiratory Questionnaire  $\geq 38.2$  points). For statistical analysis, it was constructed a ROC curve with area under the curve (AUC) value, it was calculated positive predictive value (PPV), negative (NPV), sensitivity (Se), specificity (Sp) and accuracy (AC). Cox regression and Kaplan-Meier method were used to assess the association between the cut off points and mortality. **Results:** The new cut off points obtained were: FFMI of  $20.35 \text{ kg/m}^2$  (AUC=0.565, Se=0.36, Sp=0.81) for men and  $14.65 \text{ kg/m}^2$  (AUC=0.744, Se=0.88; Sp=0.60) for women. The cut off point of Schols et al. was the best to discriminate sedentarism (PPV=63%, NPV=50% and AC=62%) and poor exercise capacity assessed by walked distance in absolute value (PPV=85% and AC=73%), while the new cut off point was the best to discriminate poor exercise capacity assessed by walked distance in % of predicted (NPV=67%, AC=62%) and quality of life (VPN=57%, AC=53%). Only the new cut off point was associated with mortality (HR=2.123,  $P=0.039$ , log rank=0.035). **Conclusion:** A new cut off point to detect FFM depletion was developed for Brazilian men and women with COPD. The cut off point of Schols et al. was discriminative for sedentarism and exercise capacity (6MWT in absolute value). However, the new cut off point was the only one that presented association with all-cause mortality and had the highest discriminating power for exercise capacity (6MWT in relative value) and quality of life in patients with COPD.

**Keywords:** Chronic obstructive pulmonary disease. Body composition. Nutritional status. Reference values. Prognosis.

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## LISTA DE SIGLAS E ABREVIATURAS

ATS	American Thoracic Society
AUC	Area Under the Curve
BIA	Bioelectrical Impedance
BMI	Body Mass Index
COPD	Chronic Obstructive Pulmonary Disease
DEXA	Absortometria de raios-x de dupla energia
DPOC	Doença Pulmonar Obstrutiva Crônica
ERS	European Respiratory Society
FEV <sub>1</sub>	Forced Expiratory Volume in the First Second
FFM	Fat-free Mass
FFMI	Fat-free Mass Index
GOLD	Global initiative for chronic obstructive disease
IMC	Índice de Massa Corpórea
IMLG	Índice de Massa Livre de Gordura
K	Cohen's Kappa Value
MET	Metabolic Equivalents
MLG	Massa Livre de Gordura
MVPA	Moderate to Vigorous Physical Activity
NPV	Negative Predictive Value
OMS	Organização Mundial da Saúde
PPV	Positive Predictive Value
ROC	Receiver operation characteristics
SGRQ	Saint George's Respiratory Questionnaire
6MWT	Six Minute Walking Test
6MWD	Six Minute Walking Distance

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## 1 INTRODUÇÃO

A doença pulmonar obstrutiva crônica (DPOC) é considerada comum, prevenível e tratável, caracterizada por uma limitação persistente ao fluxo aéreo, geralmente progressiva e associada à resposta inflamatória crônica das vias aéreas e pulmões às partículas e gases nocivos<sup>1</sup>. A DPOC é uma das principais causas de morbidade e mortalidade no mundo. Dados da Organização Mundial de Saúde (OMS) apontam que a DPOC foi a terceira principal causa de morte no mundo na última década, responsável por cerca de 5,6% de todas as mortes<sup>2</sup>.

Embora seja considerada uma doença primariamente pulmonar, está relacionada a diversas características extrapulmonares, dentre estas o declínio da massa muscular, que não se explica apenas pelo peso corporal ou índice de massa corpórea (IMC)<sup>3</sup>.

A massa corporal total pode ser dividida em massa gorda e massa livre de gordura (MLG). Os músculos são os principais representantes da MLG, sendo que esta é responsável pelo componente metabólico ativo do corpo<sup>3,4</sup>. Por esse motivo, sua falta ou perda é prejudicial.

A depleção de MLG é frequentemente encontrada em pacientes com DPOC e resulta de fatores como inflamação sistêmica, atrofia por desuso, desnutrição e uso de corticosteróides<sup>5</sup>. Sabe-se que pacientes com DPOC moderada à grave apresentam uma alta prevalência de depleção muscular, independente de apresentarem peso corporal normal<sup>6,7</sup>. Tem sido descrito que a prevalência de depleção muscular em pacientes com DPOC varia de 10 a 15% em pacientes com peso corporal normal até acima de 35%, considerando pacientes elegíveis à reabilitação pulmonar<sup>3,6,8,9</sup>.

A depleção muscular em DPOC gera impactos clínicos significativos já que está associada a pior qualidade de vida<sup>9</sup> e capacidade de exercício<sup>6,10-12</sup>. Em uma população de indivíduos saudáveis, demonstrou-se que aqueles que eram ativos fisicamente apresentaram menor chance de ter baixo índice de massa livre de gordura (IMLG) ao contrário dos indivíduos sedentários, indicando que a MLG também está relacionada à atividade física e sedentarismo<sup>13</sup>.

Menores valores de MLG indicam também pior prognóstico, com maiores índices de mortalidade independentemente do IMC<sup>3,14</sup>. Considerando todos esses fatores, a avaliação da massa livre de gordura torna-se de suma importância durante o manejo de pacientes com DPOC.

A avaliação rotineira da MLG em pacientes com DPOC permite que se detecte precocemente depleção muscular nesses indivíduos. Essa avaliação pode ser realizada por meio de diferentes métodos, mas nem todos são aplicáveis na prática clínica por diversos fatores, como tempo de realização, alto custo e necessidade de mão de obra qualificada, bem como recursos tecnológicos e suporte técnico<sup>15</sup>. Por esses motivos, a escolha do método de avaliação deve não apenas se basear na precisão, mas também na praticidade e no custo<sup>16</sup>. A impedância bioelétrica é um método simples, não invasivo, de rápida realização e que não depende da colaboração do indivíduo. Trata-se de um método validado e amplamente utilizado na avaliação da composição corporal de pacientes com DPOC<sup>15-17</sup>. Entretanto, estudos que comparam esta técnica à métodos de referência são controversos, demonstrando que, embora a impedância bioelétrica apresente boa correlação com os métodos padrão ouro, existe uma ampla variabilidade entre estes<sup>15-18</sup>, o que pode ser atribuído ao uso de diferentes fórmulas para se estimar a massa livre de gordura. Rutten *et al.*<sup>7</sup> desenvolveram uma equação baseada nas variáveis idade, gênero, altura, peso e impedância. Além disso, os autores observaram que a MLG estimada por esta equação apresentou forte relação ( $r^2=0,90$ ) com a obtida pelo DEXA, além de uma diferença média de 0,57kg (limites de concordância de -5,6 a 6,7kg) em homens e de 0,68kg (limites de concordância de -4,2 a 5,5kg) em mulheres com DPOC. Até o momento, nenhuma fórmula específica para pacientes DPOC brasileiros foi desenvolvida.

Atualmente, existem diversos pontos de corte descritos para a determinação de depleção muscular à partir da quantificação de MLG. Entretanto, a literatura demonstra que a escolha do ponto de corte para o diagnóstico de depleção pode influenciar a prevalência deste achado<sup>3,7</sup>.

Dentre os pontos de corte disponíveis na literatura, Schols *et al.*<sup>6</sup> desenvolveram valores distintos para homens e mulheres com DPOC moderada à grave, baseados na porcentagem de peso ideal. Schutz *et al.*<sup>19</sup>, Kyle *et al.*<sup>20</sup>, Coin *et al.*<sup>21</sup>, Vestbo *et al.*<sup>3</sup> e Franssen *et al.*<sup>22</sup> desenvolveram

valores de referência a partir de populações de indivíduos aparentemente saudáveis.

Idealmente, um valor de referência para detecção de depleção de MLG deveria levar em consideração determinantes fisiológicos, como idade, gênero e etnia, assim como parâmetros funcionais<sup>22,23</sup>. Além disso, é importante se conhecer o quanto tal valor de referência se relaciona com outros desfechos clínicos da doença, bem como seu poder preditivo prognóstico.

Dessa forma, os objetivos do estudo que compõe a presente dissertação foram desenvolver um ponto de corte para determinar depleção de MLG específico para pacientes com DPOC brasileiros, verificar sua validade, assim como sua associação, e de outros pontos de corte publicados previamente, com mortalidade, capacidade de exercício, qualidade de vida, atividade física e estilo de vida sedentário.

## 2 REVISÃO DE LITERATURA – CONTEXTUALIZAÇÃO

### 2.1 DOENÇA PULMONAR OBSTRUTIVA CRÔNICA

A DPOC é considerada comum, prevenível e tratável, caracterizada por limitação persistente ao fluxo aéreo, geralmente progressiva e associada à resposta inflamatória crônica das vias aéreas e pulmões às partículas e gases nocivos. A limitação crônica ao fluxo aéreo é causada pela combinação de obstrução das vias aéreas de pequeno calibre (bronquiolite obstrutiva) e destruição do parênquima pulmonar (enfisema)<sup>1</sup>. O processo inflamatório crônico presente na DPOC provoca alterações estruturais que culminam em diminuição do diâmetro das vias aéreas de pequeno calibre. A destruição do parênquima pulmonar leva à perda das ligações alveolares com as vias aéreas de pequeno calibre e diminuição da elasticidade pulmonar. Todas essas alterações diminuem a capacidade das vias aéreas de se manterem abertas durante a expiração<sup>1</sup>.

A DPOC é uma das principais causas de morbidade e mortalidade no mundo. Dados da OMS apontam que a DPOC foi a terceira principal causa de morte no mundo na última década, responsável por cerca de 5,6% de todas as mortes<sup>2</sup>. A prevalência de DPOC em indivíduos com 40 anos ou mais varia de 9-10%<sup>24</sup>. Entretanto, estima-se que a prevalência e morbidade relacionada à DPOC tenda a aumentar nas próximas décadas, principalmente devido à exposição contínua aos fatores de risco e ao padrão de envelhecimento da população mundial<sup>1</sup>. No Brasil, a DPOC foi causa de 35545 óbitos em 2013<sup>25</sup>.

O tabagismo é o principal fator de risco para o desenvolvimento e progressão da doença<sup>26</sup>. Entretanto, existem predisponentes de risco que estão associados à interação entre fatores genéticos e ambientais. Pode-se, então, listar como fatores de risco para DPOC: causas genéticas, tabagismo, exposição à poeira, vapor, fumo e produtos químicos no ambiente de trabalho, exposição à biocombustíveis como carvão, estrume animal e resíduos de madeira, poluição do ar, envelhecimento, infecções, asma, gênero e fatores socioeconômicos<sup>27</sup>.

Os sintomas característicos da DPOC são tosse crônica, produção de expectoração e dispneia<sup>28,29</sup>. Entretanto, esta doença também

está associada a importantes manifestações extrapulmonares que geram impacto significativo no prognóstico e sobrevida desses pacientes<sup>30</sup>.

Sabe-se que a inflamação e o estresse oxidativo em pacientes com DPOC estende-se não apenas às vias aéreas, mas também ao sistema sanguíneo periférico, indicando que a inflamação sistêmica pode ser considerada uma peça-chave entre o comprometimento pulmonar e as manifestações sistêmicas<sup>31,32</sup>. Mediadores inflamatórios presentes na circulação sanguínea desses pacientes estão associados ao surgimento e piora de comorbidades como doenças cardíacas isquêmicas, insuficiência cardíaca, osteoporose, anemia, diabetes, síndrome metabólica e depressão<sup>1</sup>. Além disso, podem contribuir para a perda de massa muscular esquelética e caquexia, umas das manifestações sistêmicas da doença.

## 2.2 COMPOSIÇÃO CORPORAL EM DPOC

Tendo em vista que a DPOC é uma doença com manifestações sistêmicas, recentemente têm sido propostas novas descrições relacionadas à doença que levam em consideração não apenas o comprometimento pulmonar primário. Atualmente, tem-se demonstrado que o peso corporal e composição corporal desses pacientes discriminam novos fenótipos da doença e são preditores de desfecho, independentes da função pulmonar<sup>33,34</sup>.

O baixo peso corporal e a perda de peso involuntária são comuns em DPOC, com uma prevalência que varia entre 10 a 20% dos pacientes com doença moderada a grave<sup>8,34</sup>. Estes pacientes também apresentam declínio progressivo da massa muscular esquelética e anormalidades bioenergéticas, que culminam na perda de peso corporal<sup>35</sup>.

É bem reconhecido que o IMC é um forte preditor de mortalidade em DPOC<sup>36</sup>, sendo que pacientes com comprometimento leve a moderado e IMC de normal a sobrepeso apresentam menor risco de mortalidade. Em pacientes com doença grave, essa relação parece ser ainda mais forte, sendo que um IMC baixo aumenta em sete vezes a chance de morte<sup>37</sup>. Entretanto, ainda não se sabe se a “vantagem prognóstica” relacionada ao IMC é conferida pelo excesso de gordura ou pela preservação da massa livre de gordura em

pacientes com IMC maior<sup>33</sup>, já que a obesidade esta relacionada a um maior risco cardiovascular<sup>38</sup>.

Em um modelo de dois compartimentos, a massa corporal total pode ser dividida em massa gorda e massa livre de gordura (MLG), sendo que esta é responsável pelo componente metabólico ativo do corpo<sup>17,39</sup> e, por isso, é comumente usada como uma medida indireta da massa muscular. A depleção de MLG é frequentemente encontrada em pacientes com DPOC e resulta de fatores como inflamação sistêmica, atrofia por desuso, desnutrição e uso de corticosteroides sistêmicos<sup>5</sup>.

Sabe-se que em DPOC a prevalência de depleção muscular é alta independentemente de haver peso corporal normal, já que mesmo nesses pacientes existe uma prevalência de depleção de MLG que varia de 10 a 15%<sup>3,6-8</sup>. Rutten *et al.*<sup>7</sup> avaliaram a composição corporal de 1087 indivíduos com DPOC moderada a grave e encontraram uma taxa de depleção da MLG de 37% nos homens e 59% nas mulheres, quando avaliada por meio da impedância bioelétrica.

A depleção de MLG é uma característica clínica importante já que está associada à pior qualidade de vida<sup>9</sup>, reduzida força muscular periférica e pior capacidade de exercício, tanto máxima quanto submáxima<sup>6,10-12</sup>. Além disso, indivíduos saudáveis fisicamente ativos apresentam menores chances de ter um baixo índice de MLG, ao contrário de indivíduos sedentários<sup>13</sup>, evidenciando a associação entre MLG e sedentarismo.

Menores valores de MLG estão fortemente relacionados também a um pior prognóstico de pacientes com DPOC. Schols *et al.*<sup>14</sup> demonstraram que o IMLG, ou seja, a relação entre massa livre de gordura e a estatura ao quadrado, é um forte preditor de mortalidade independente do IMC e da massa gorda. Adicionalmente, Vestbo *et al.*<sup>3</sup> demonstraram que um baixo IMLG aumenta significativamente as chances de mortalidade, mesmo em pacientes com peso corporal normal. Tais achados indicam que tal índice é um preditor de mortalidade ainda mais forte que o IMC. Por isso avaliação da composição corporal em pacientes com DPOC torna-se indispensável.

### 2.3 AVALIAÇÃO DA COMPOSIÇÃO CORPORAL

A avaliação da composição corporal pode ser realizada por meio de diferentes métodos, mas nem todos são aplicáveis na prática clínica, por diversos fatores, como: tempo de realização, alto custo e necessidade de mão de obra qualificada, bem como recursos tecnológicos e suporte técnico<sup>15</sup>. Por esses motivos, a escolha do método de avaliação deve não apenas se basear na precisão, mas também na praticidade e no custo<sup>16</sup>.

Existem diversas técnicas para avaliação da composição corporal classificadas em métodos diretos, indiretos e duplamente indiretos. A dissecação de cadáveres é a única metodologia considerada direta para tal fim, o que justifica a impossibilidade de uso de uma forma direta para avaliação da composição corporal. Os métodos indiretos não envolvem manipulação dos componentes, pois eles partem de princípios químicos e físicos que visam à extrapolação das quantidades de gordura e massa magra corporais. Dentre esses métodos, pode-se citar densitometria, pletismografia, tomografia computadorizada, ressonância magnética, diluição isotópica e absorptometria de raios X de dupla energia (DEXA).

A densitometria, também conhecida como pesagem subaquática ou pesagem hidrostática, é baseada no Princípio de Arquimedes, segundo o qual o corpo mergulhado em um fluido, sofre por parte deste, uma força vertical para cima, cuja intensidade é igual ao peso do fluido deslocado pelo corpo. Dessa forma, o volume corporal é definido pela diferença entre o peso corporal do indivíduo fora e submerso na água, sendo que corpos mais densos tendem a afundar e os menos densos a flutuar<sup>40</sup>.

Para o cálculo da densidade corporal leva-se em consideração: a massa corporal do indivíduo fora da água, a massa do indivíduo completamente submerso, a densidade da água de acordo com a temperatura, o volume residual pulmonar e volume gastrointestinal. A aferição do volume residual envolve equipamento de alto custo e difícil acesso, desta forma, este pode ser obtido por meio de equações de predição. Uma vez obtido, o valor de densidade corporal é convertido em porcentagem de gordura corporal por meio de equações. Esta técnica é considerada padrão-ouro para avaliação da composição corporal, já que é um método muito preciso<sup>41</sup>. Entretanto, seu uso

para avaliações de campo é limitado, já que o indivíduo avaliado necessita de adaptação ao meio aquático, além de técnicos altamente treinados, equipamentos laboratoriais caros e é frequente a impossibilidade de medida direta do volume residual.

A pletismografia estima o volume corporal por meio do deslocamento de ar. Neste caso, o volume corporal é definido pela subtração do volume da câmara vazia pelo volume da câmara com o indivíduo dentro dela. Uma vez, definido o volume corporal é possível aplicar os princípios da densitometria para determinar a composição corporal por meio do cálculo da densidade corporal. Este método tem ótima correlação com o método de pesagem hidrostática<sup>42,43</sup>. Embora, seja mais rápido e fácil, necessite menos da cooperação do avaliado e tenha menor duração em relação à pesagem hidrostática<sup>43</sup>, exige equipamento de alto custo e treinamento técnico.

A tomografia computadorizada é um exame de imagem, que por meio da radiação de feixes de raio-x, permite separar a gordura corporal dos demais tecidos e avaliar de maneira mais precisa a densidade muscular e a área de secção transversa do músculo<sup>44,45</sup>. Entretanto, tem como desvantagens a exposição à radiação, alto custo e diferenças entre equipamentos<sup>45</sup>.

Por outro lado, a ressonância magnética que também é um método de imagem não envolve exposição à radiação e é considerada, juntamente à tomografia computadorizada, como método padrão-ouro para avaliação da massa muscular. Entretanto, este método não pode ser utilizado em indivíduos com implantes metálicos e também envolve equipamento de alto custo, o que dificulta seu uso na prática clínica<sup>44</sup>.

A diluição isotópica é um método invasivo para avaliação da água corporal total. É necessário a ingestão de isótopos, os quais são distribuídos igualmente por toda água corporal. Por meio de constantes de hidratação, variáveis como a massa livre de gordura são obtidas<sup>43</sup>.

A absorptometria de raios-x de dupla energia é considerada uma técnica avançada para medir a densidade do osso e a composição corporal. O princípio básico desta técnica é a utilização de uma fonte de raio x com um filtro que converte um feixe de raio x em picos fotoelétricos que atravessam o corpo<sup>40</sup>. A atenuação desses picos fotoelétricos permite a obtenção da massa

gorda, conteúdo mineral ósseo e massa magra que inclui a massa do tecido muscular, conectivo e de órgãos, além da água corporal. Sendo assim, esse método exige maior custo, não é portátil e fornece medidas indiretas da massa muscular<sup>45</sup>.

Existem ainda, métodos duplamente indiretos para avaliação da composição corporal que são aqueles validados a partir de um método indireto<sup>40</sup>.

A impedância bioelétrica é um método duplamente indireto e tem como princípio a medida da resistência total do corpo à passagem de uma corrente elétrica, já que os componentes corporais oferecem resistência diferenciada à passagem dessa corrente. Ossos e gordura contêm pequena quantidade de água e são meios de baixa condutividade, enquanto a massa muscular e outros tecidos ricos em água e eletrólitos são bons condutores<sup>39,40</sup>. Por um sistema tetrapolar, no qual dois eletrodos são posicionados na região dorsal da mão direita e dois na região dorsal do pé direito, o aparelho irá identificar os níveis de resistência e reatância do organismo à corrente elétrica. Por meio da avaliação da quantidade total de água pode-se prever a massa gorda e a massa livre de gordura<sup>40</sup>. Sendo assim, alterações no estado de hidratação do indivíduo constituem a principal limitação deste método. A fim de se obter resultados mais precisos, alguns procedimentos anteriores à impedância bioelétrica devem ser adotados, dentre estes: manter-se em jejum de pelo menos 4 horas, não ingerir bebidas alcoólicas 12 horas antes do exame e urinar pelo menos 30 minutos antes do exame.

Além disso, como se trata de um método indireto, são necessárias equações preditivas que, por meio dos valores de resistência e dados antropométricos, fornecem um valor de MLG. Para ser válido, esse método depende de que a equação utilizada seja específica para a população a ser avaliada<sup>39,46,47</sup>. Existem diversas fórmulas descritas na literatura para predição da MLG em indivíduos com DPOC, sendo que cada uma leva em consideração diferentes variáveis<sup>7,16,17,48</sup>. Rutten *et al.*<sup>7</sup> desenvolveram uma equação baseada nas variáveis idade, gênero, altura, peso e impedância. Além disso, os autores observaram que a MLG estimada por esta equação apresentou forte relação ( $r^2=0,90$ ) com a obtida pelo DEXA, além de uma diferença média de 0,57kg (limites de concordância -5,6 a 6,7kg) em homens e de 0,68kg (limites

de concordância -4,2 a 5,5kg) em mulheres com DPOC. Até o momento, nenhuma fórmula específica para pacientes DPOC brasileiros foi desenvolvida.

Por fim, embora a impedância bioelétrica seja um método amplamente utilizado na avaliação da composição corporal de pacientes com DPOC<sup>17</sup>, confortável, não invasiva, de rápida realização e que não requer alto grau de habilidade do avaliador, estudos que comparam esta técnica à métodos de referência são controversos.

Schols *et al.*<sup>17</sup> obtiveram uma forte correlação ( $r=0,93$ ) entre a medida da impedância/altura<sup>2</sup> com a água corporal total obtida pelo método de diluição de deutério. Lerario *et al.*<sup>15</sup> demonstraram que, embora tenha apresentado baixa concordância e subestimado em 0,61kg a massa livre de gordura, a impedância bioelétrica obteve boa correlação ( $r=0,95$ ) com a MLG avaliada pelo DEXA. No estudo de Steiner *et al.*<sup>16</sup>, a impedância bioelétrica subestimou a massa livre de gordura avaliada pelo DEXA em 0,72kg havendo baixa concordância entre estes métodos. Kilduff *et al.*<sup>18</sup> observaram uma diferença média entre a MLG obtida pela impedância bioelétrica e aquela obtida pela pletismografia próxima de zero, além de observarem um amplo limite de concordância entre os métodos, sendo que neste estudo essas diferenças inter-métodos apresentaram impacto clínico significativo. Rutten *et al.*<sup>7</sup> atribuem essas diferenças ao uso de fórmulas não acuradas para predição de MLG; sendo assim, esses autores desenvolveram uma nova fórmula que apresentou boa correlação e limites de concordância com o método de referência (DEXA), como já citado.

Para normalizar a MLG pelo tamanho corporal, esta pode ser expressa como IMLG. A medida da MLG expressa pelo índice tem a vantagem de compensar as diferenças de altura entre os indivíduos. Além disso, pode identificar indivíduos com IMC normal, mas que possuem baixa quantidade de MLG ou identificar indivíduos que apresentam IMC alto por possuírem maior quantidade de MLG e não por serem obesos. Por fim, o índice de massa livre de gordura permite comparar indivíduos jovens com indivíduos de maior idade e de diferentes etnias<sup>23,47</sup>.

## 2.4 VALORES DE REFERÊNCIA PARA ÍNDICE DE MASSA LIVRE DE GORDURA

De acordo com estudos prévios, o IMLG é um forte preditor de fraqueza muscular periférica<sup>49</sup>, capacidade de exercício<sup>6,10-12</sup>, qualidade de vida<sup>9</sup> e mortalidade<sup>3,14</sup>.

Existem na literatura diversos valores de referência para classificar depleção muscular em pacientes com DPOC, a partir do IMLG (Quadro 1). Schols *et al.*<sup>6</sup> desenvolveram pontos de corte de 16kg/m<sup>2</sup> para homens e 15kg/m<sup>2</sup> para mulheres, a partir de uma população de pacientes com DPOC moderada à grave. Tais pontos de corte foram baseados na porcentagem de peso ideal. Por outro lado, Schutz *et al.*<sup>19</sup> desenvolveram percentis baseados no gênero e idade a partir de uma população de indivíduos suíços, aparentemente saudáveis, com idade entre 24 e 98 anos. Kyle *et al.*<sup>20</sup> desenvolveram valores de acordo com o IMC em indivíduos saudáveis com idade entre 15 e 98 anos. Os pontos de corte para detectar depleção muscular propostos por Vestbo *et al.*<sup>3</sup> também foram baseados em percentis a partir de uma grande coorte de indivíduos da Dinamarca. Coin *et al.*<sup>21</sup> desenvolveram percentis para IMLG a partir de uma população de indivíduos italianos com idade entre 20 a 80 anos. Por fim e mais recentemente, Franssen *et al.*<sup>22</sup> publicaram percentis de acordo com gênero, idade e IMC, a partir de uma população do Reino Unido.

**Quadro 1 - Pontos de corte para depleção de massa livre de gordura.**

Referência	Característica da população	Critério de desenvolvimento	Valor de IMLG	País de origem
Schols <i>et al.</i> 1993	253 indivíduos com DPOC moderada a grave: - 203 homens - 52 mulheres  Idade - 53 - 73 anos	Pontos de corte baseados na porcentagem de peso ideal	Para homens: 16 kg/m <sup>2</sup>  Para mulheres: 15kg/m <sup>2</sup>	Holanda
Schutz <i>et al.</i> 2002	5635 indivíduos saudáveis: - 2986 homens - 2649 mulheres	Pontos de corte em percentis de acordo com gênero e idade	Percentil 10%  Para homens: 16,9 - 17,6kg/m <sup>2</sup>	Suíça

	Idade - 18 - 98 anos		- Para mulheres: 13,7 - 14,7kg/m <sup>2</sup>	
Kyle <i>et al.</i> 2004	6733 indivíduos saudáveis: - 3549 homens - 3184 mulheres  Idade 15-98 anos	Intervalos de IMLG de acordo com o gênero e IMC	IMC normal  Para homens: 16,7 - 19,7kg/m <sup>2</sup>  Para mulheres 14,6 - 16,7kg/m <sup>2</sup>	Suíça
Vestbo <i>et al.</i> 2006	10049 indivíduos do estudo de <i>Copenhagen City Heart</i>  Idade ≥ 20 anos	Percentil de acordo com gênero	Percentil 10%  Para homens: 17,05 kg/m <sup>2</sup>  Para mulheres: 14,62 kg/m <sup>2</sup>	Dinamarca
Coin <i>et al.</i> 2008	1866 indivíduos saudáveis - 1435 mulheres - 431 homens  Idade 20 a 80 anos	Percentis de acordo com idade e gênero	Percentil 10%  Para homens: 17,3 - 17,9kg/m <sup>2</sup>  Para mulheres: 13,8 - 14,6kg/m <sup>2</sup>	Itália
Franssen <i>et al.</i> 2014	186885 indivíduos do estudo UK biobank - 86008 homens - 100975 mulheres  Idade 45 - 69 anos	Percentis de acordo com gênero, idade e IMC	Percentil 10% para indivíduos com IMC normal  Para homens: 17,2 - 17,5kg/m <sup>2</sup>  Para mulheres: 14,5 - 14,6kg/m <sup>2</sup>	Reino Unido

Diante de tal variedade de valores de referência descritos para a detecção de depleção, a escolha de um determinado ponto de corte deve levar em consideração alguns critérios, por exemplo, se este foi desenvolvido para a população a ser estudada. Além disso, um bom ponto de corte para depleção de massa muscular deve ser desenvolvido considerando-se gênero, idade e suas implicações funcionais<sup>22,23</sup>.

Sendo assim, a investigação da acurácia diagnóstica desses valores de referência em populações específicas torna-se importante. Além

disso, faz-se necessário investigar a relação entre a depleção detectada por esses pontos de corte e manifestações clínicas da doença, bem como o impacto prognóstico da depleção. Se todos esse pontos forem considerados, a escolha de um determinado ponto de corte tornar-se-á mais precisa.

### 3 ARTIGO CIENTÍFICO

(Formatado de acordo com as normas do periódico *Respiratory Medicine* -  
Anexo B)

**Are the available cut-off values for detection of fat-free mass depletion discriminative for Brazilian patients with COPD? Development of a new cut-off point and its relationship with mortality and extrapulmonary disease manifestations**

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## ABSTRACT

**Introduction:** None cut-off point for fat-free mass index (FFMI) was developed for the Brazilian population and it is unknown if the available ones are able to discriminate extrapulmonary disease manifestations. **Objectives:** To develop a cut-off point for FFM depletion for Brazilian patients with COPD, to validate it and to verify its association and of previously published cut-off points with extrapulmonary disease manifestations. **Methods:** A new cut-off point was obtained from the best FFMI value for discrimination of preserved exercise capacity in patients with COPD (n=57). The discriminative capacity was assessed in a new sample (n=96). In addition to the new cut-off point, other previously published were tested to discriminate low exercise capacity, physical inactivity, sedentary lifestyle and low quality of life. A ROC curve with area under the curve (AUC) value was done, as well as discriminative capacity was calculated. Cox regression and Kaplan-Meier method assessed the association between the cut-off points and mortality. **Results:** The new cut-off points for FFMI were 20.35kg/m<sup>2</sup> for men (AUC=0.565, Se=0.36, Sp=0.81) and 14.65kg/m<sup>2</sup> for women (AUC=0.744, Se=0.88; Sp=0.60). The new cut-off point was the best to discriminate poor exercise capacity assessed by walked distance in % predicted and quality of life. Only the new cut-off point was associated with mortality (HR=2.123; 95% CI: 1.03 - 4.33, *P*=0.039, log rank *P*=0.035). **Conclusion:** Only the new cut-off point was associated with all-cause mortality and had the highest discriminating capacity for exercise capacity (6MWT in relative value) and quality of life in patients with COPD.

**Keywords:** Pulmonary Disease, Chronic Obstructive. Body Composition. Nutritional Status. Reference Values. Prognosis.

**ABBREVIATIONS**

ATS	American Thoracic Society
AUC	Area Under the Curve
BIA	Bioelectrical Impedance
BMI	Body Mass Index
COPD	Chronic Obstructive Pulmonary Disease
ERS	European Respiratory Society
FEV <sub>1</sub>	Forced Expiratory Volume in the First Second
FFM	Fat-free Mass
FFMI	Fat-free Mass Index
GOLD	Global initiative for chronic obstructive pulmonary disease
K	Cohen's Kappa Value
MET	Metabolic Equivalent
MVPA	Moderate to Vigorous Physical Activity
NPV	Negative Predictive Value
PPV	Positive Predictive Value
ROC	Receiver operation characteristics
SGRQ	Saint George's Respiratory Questionnaire
6MWT	Six Minute Walking Test

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease characterized by persistent airflow limitation, usually progressive and associated with enhanced chronic inflammatory response in the airways and lung to noxious particles or gases<sup>1</sup>. Although COPD is essentially a pulmonary disease, it is associated with several extrapulmonary manifestations that are referred as the systemic effects of the disease<sup>2</sup>.

Among systemic manifestations of COPD, there is wasting of body cell mass which represents the actively metabolizing tissue, being muscle mass its largest element<sup>3</sup>. Wasting of body cell is recognised, in particular, by loss of fat-free mass (FFM)<sup>2</sup> which corresponds to a heterogeneous compartment that is mainly represented by skeletal mass, but also includes organ mass and connective tissue<sup>4</sup>.

Depletion of FFM is common in patients with COPD, being often diagnosed based on low fat-free mass index (FFMI), i.e. FFM normalized by height. Its prevalence can reach 35% in patients eligible for pulmonary rehabilitation<sup>5,6</sup> and also can be found among those with normal weight (prevalence ranging from 10 to 15%)<sup>5,7</sup>.

Low FFM plays an important role in the disease severity since it is related to several dysfunctions, including impaired peripheral muscle strength<sup>5,6</sup>, health-related quality of life<sup>6</sup> and poor exercise capacity<sup>8-11</sup>. It was shown that FFM is also related to sedentarism and physical activity levels<sup>12-14</sup>. In addition, it is also known that FFM is an important determinant of prognosis in patients with COPD<sup>15</sup>. Vestbo et al.<sup>7</sup> demonstrated that a FFMI below the 10<sup>th</sup> percentile of the general population significantly increased all-cause and COPD-cause mortality, even in patients with normal body mass index.

Hence, it is important to include FFM assessment in the routine management of patients with COPD to early detect its depletion. However, the choice of the cut-off point to define FFM depletion is still a doubt for researchers and clinicians, since there are several values available in the literature.

Prevalence and predictive value of FFM depletion depends on the choice of the cut-off point, especially in men<sup>7,16</sup>. Additionally, it is known that reference

values to detect FFM depletion should ideally take into account socio-demographic variables, such as gender, age and ethnicity<sup>4,17</sup>. Thus, it is reasonable to consider that reference values used for diagnosis of FFM depletion should be those developed specifically for the studied population.

Thus, the present study aimed to develop a cut-off point for FFM depletion specific for Brazilian patients with COPD, to validate it and to verify the association of this and other previously published cut-off points with mortality, exercise capacity, health related quality of life, physical activity and sedentary lifestyle.

## **MATERIAL AND METHODS**

### **Sample and protocol study**

A retrospective cohort study with a cross-sectional analysis was conducted with patients diagnosed with COPD recruited during the initial evaluation for admission in a physical training program at the Laboratory of Research in Respiratory Physiotherapy, State University of Londrina (Brazil). The study used baseline data regarding body composition, exercise capacity, physical activity, sedentary behaviour and quality of life from a study previously published elsewhere<sup>18</sup> which investigated the effects of two different exercise programs in patients with COPD. The present study was approved by the institutional ethics committee (996.413), and all participants gave informed consent.

Inclusion criteria were the diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD)<sup>1</sup>, clinical stability without infections and exacerbations within the last three months prior the study, absence of severe and/or unstable cardiac disease and of musculoskeletal comorbidities which could interfere with carrying out the proposed assessments. Exclusion criterion was fat-free mass missing data.

Firstly, in order to develop a FFMI-based cut-off point to detect FFM depletion for Brazilian patients with COPD, a cross-sectional analysis (sample1, n=57) was performed with subjects undergoing assessment of body composition, lung function and exercise capacity. Additionally, to test the

discriminative capacity of the new cut-off point and the others previously described by Schutz et al.<sup>19</sup>, Kyle et al.<sup>20</sup>, Franssen et al.<sup>17</sup>, Schols et al.<sup>8</sup>, Coin et al.<sup>21</sup> and Vestbo et al.<sup>7</sup>, another sample of 96 subjects (sample 2) who were also followed up for mortality was composed. Subjects were classified as “depleted” or “non-depleted” according to all cut-off points to test their capacity to discriminate poor exercise capacity, poor health-related quality of life, physical inactivity, sedentary lifestyle and its association with all-cause mortality.

## **Assessments**

### Lung function

Lung function was assessed by spirometry using a portable spirometer (SpiroBank G<sup>®</sup>, MIR, Italy) in order to confirm COPD diagnosis. The test was performed according to the American Thoracic Society (ATS) - European Respiratory Society (ERS) guidelines<sup>22</sup> and the predicted values were calculated for the Brazilian population<sup>23</sup>.

### Body composition

Body weight was measured on a calibrated scale to the nearest 0.1 kg (Filizola model 31, Filizola, Brazil) while patients were barefoot and wearing light clothes. Body height was measured to the nearest 0.5 cm while patients were barefoot and standing with their backs and heels touching a vertical bar (Filizola model 31, Filizola, Brazil). Body mass index (BMI) was calculated as weight divided by height squared ( $\text{kg/m}^2$ ).

Body composition was assessed by using single-frequency bioelectrical impedance (800 $\mu\text{A}$  at 50Hz) analyser (BIA) (Biodynamics 310TM, Biodynamics Corp., USA) according to the protocol of Lukaski et al.<sup>24</sup> and manufacturer's recommendations. Participants were instructed to do not ingest coffee, tea, chocolate or alcoholic beverages and do not exercise for at least 12 hours prior the test. All body composition measurements were performed at the same period of the day. Furthermore, patients fasted for 4 hours prior to the test and

urinated immediately before the evaluation. During the measurements, patients were lying in supine position. Distal electrodes were positioned in the middle dorsal surface of the right hand and foot, proximal to metacarpal-phalangeal and metatarsal-phalangeal joints, respectively. Proximal electrodes were positioned between the distal prominences of the radius and ulna and between the medial and lateral malleoli at the ankle, also on the right side. FFM was calculated from the impedance using a specific formula derived for patients with COPD<sup>16</sup>. Fat-free mass index was calculated by dividing FFM by height squared ( $m^2$ ).

#### Health-related quality of life

Health-related quality of life was assessed by the Saint George's Respiratory Questionnaire (SGRQ) which is validated for the Brazilian population<sup>25</sup>. The questionnaire is divided into three domains: symptoms (8 items), activity (16 items), and impacts (26 items), resulting in a total score varying from zero (no impairment) to 100 points (maximum impairment). A total score  $\geq 38.2$  points<sup>26</sup> was suggested to classify subjects as having poor health-related quality of life.

#### Exercise capacity

Functional exercise capacity was assessed by the 6-minute walking test (6MWT), which was performed according to ATS recommendations<sup>27</sup>. The best of two tests was considered for analysis. Reference values used were those described by Britto et al.<sup>28</sup>. Walked distances  $< 82\%$  predicted<sup>29</sup> and  $< 350m$ <sup>30</sup> were classified as poor exercise capacity.

#### Sedentary lifestyle and physical activity in daily life

Sedentarism variables and physical activity level were assessed by two activity monitors (SenseWear armband, BodyMedia, USA and DynaPort Activity Monitor, McRoberts, The Netherlands). Participants wore the devices

simultaneously over 2 weekdays (Tuesday and Wednesday) during 12 hours per day.

Subjects were classified as having low physical activity level according to the cut-off point of 30 minutes/day spent in moderate to vigorous physical activity (MVPA), i.e., physical activity intensity greater than 3 metabolic equivalents (MET)<sup>31</sup>. Time spent per day in activities requiring < 1.5 MET was used to discriminate sedentarism; participants were considered sedentary if they spent more than 8 hours and 30 minutes in such activities<sup>32</sup>.

### Mortality data

Vital status was checked by telephone contact and officially confirmed by checking the dataset of the Centre Information on Mortality, which is the responsible organ for registering all death events in the municipality. These data were collected after formal authorization provided by the city's Health Secretary. Follow up period was from the baseline assessment until August, 2015 or until the date of death. Survival time was defined as the time from the baseline assessment to the date of death or the last contact (August, 2015). The outcome was all-cause mortality.

### Statistical analysis

The statistical analysis was performed using the statistical package SPSS 20.0 (SPSS Inc., USA). The normality in data distribution was evaluated using the Shapiro-Wilk test. Results were described as mean  $\pm$  standard deviation (SD) or median [interquartile range 25%-75%] or absolute and relative frequency. Firstly, in the sample 1 of 57 subjects, a receiver operation characteristics (ROC) curve with area under the curve (AUC) value was used to determine a cut-off value of FFM depletion (variable used: FFMI) with the best sensitivity and specificity to predict good exercise capacity (6MWT  $\geq$  82%predicted), an important clinical feature of the disease, in women and men separately. Then, subjects in sample 2 (n=96) were classified as "depleted" or "non-depleted" according to the new cut-off value determined by the ROC curve, and by the previously published cut-off values. Cox's proportional-hazard

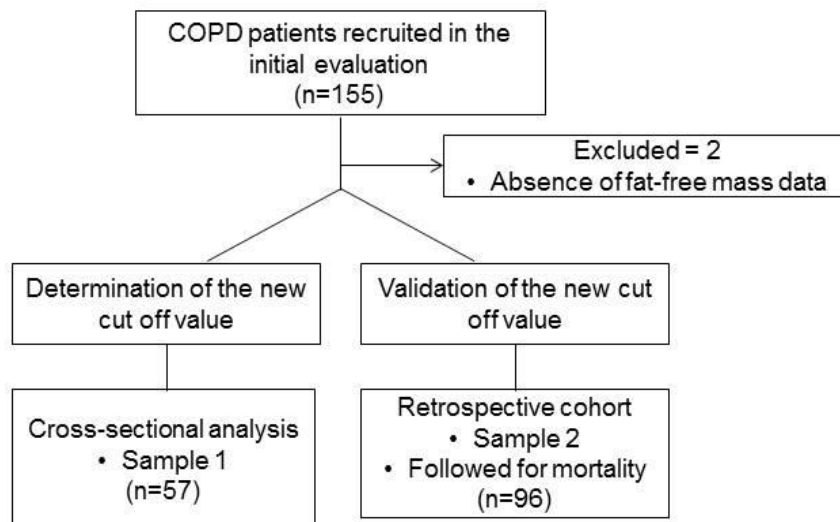
regressions estimated the association between mortality and FFM depletion. Kaplan-Meier curves with the Log-Rank tests were performed to analyse the differences of survival over time between depleted and non-depleted patients, classified according to all cut-off values mentioned above.

The statistical approaches used to investigate the clinical applicability of each cut-off value in discriminating poor exercise capacity (6MWT < 82% predicted and < 350m walked distance), poor health-related quality of life (SGRQ total score  $\geq$  38.2), physical inactivity (< 30 minutes MVPA) and sedentary lifestyle ( $\geq$ 8:30hs/day in activities < 1.5 MET) were tested by positive predictive values (PPV), negative predictive values (NPV), and accuracy, according to recommended equations<sup>33</sup>. The Cohen's kappa (k) test was used to determine whether there was agreement between the classification ("depleted" or "non-depleted") and the clinical characteristics, as well as to show the strength of agreement<sup>34</sup>. Comparisons between the study samples were done using Student's T-test, Mann-Whitney or Chi-square test, as appropriate. Significance level was set at  $P < 0.05$ .

The Power and Sample Size Calculation program (version 3.1.2) was used to calculate the statistical power of Cox regression analysis using a Chi-square test. A sample composed by 96 patients presented a power of 98% to detect a significant difference ( $\alpha = 0.05$ ) between the failure rate (patients dying) among controls (non-depleted) and experimental subjects (depleted).

## RESULTS

From the eligible candidates, two patients were excluded due to incomplete data regarding fat-free mass. To determine a new cut-off value to detect FFM depletion which is discriminative for good exercise capacity, a sample of 57 patients was composed (sample 1). To validate all cut-off values, another sample was studied (n=96) (sample 2). Subjects of sample 2 were enrolled in an exercise training program as part of an interventional study<sup>18</sup> previously mentioned and 56 patients (58.5%) completed the program (figure 1).

**Figure 1:** Flowchart of study groups' formation

Characteristics of both samples are described in table 1. Subjects of sample 1 had less marked pulmonary impairment, better exercise capacity and quality of life. There was no difference in body composition variables.

**Table 1.** Characteristics of the studied subjects in both samples.

	<b>Sample 1 (n=57)</b>	<b>Sample 2 (n=96)</b>	<b>P</b>
<b>Anthropometrics</b>			
Male/Female, n	29/28	53/43	0.60
Age, yrs	67 ± 8	66 ± 8	0.37
BMI, kg/m <sup>2</sup>	26 [22-29]	26 [21-31]	0.88
<b>Pulmonary function</b>			
GOLD (II/III/IV), n	34/14/9	27/47/20	0.001
FEV <sub>1</sub> /FVC, %	55 [45-69]	51 [41-66]	0.69
FEV <sub>1</sub> , %pred	54 [35-62]	41 [31-52]	0.006
<b>Body composition</b>			
FFM, kg	45 ± 9	45 ± 9	0.73
FFMI, kg/m <sup>2</sup>	17.7 ± 2.5	17.5 ± 2.3	0.67

**Exercise capacity**

6MWT, m	470 ± 70	434 ± 80	0.005
6MWT, %pred	88 ± 13	80 ± 14	0.001

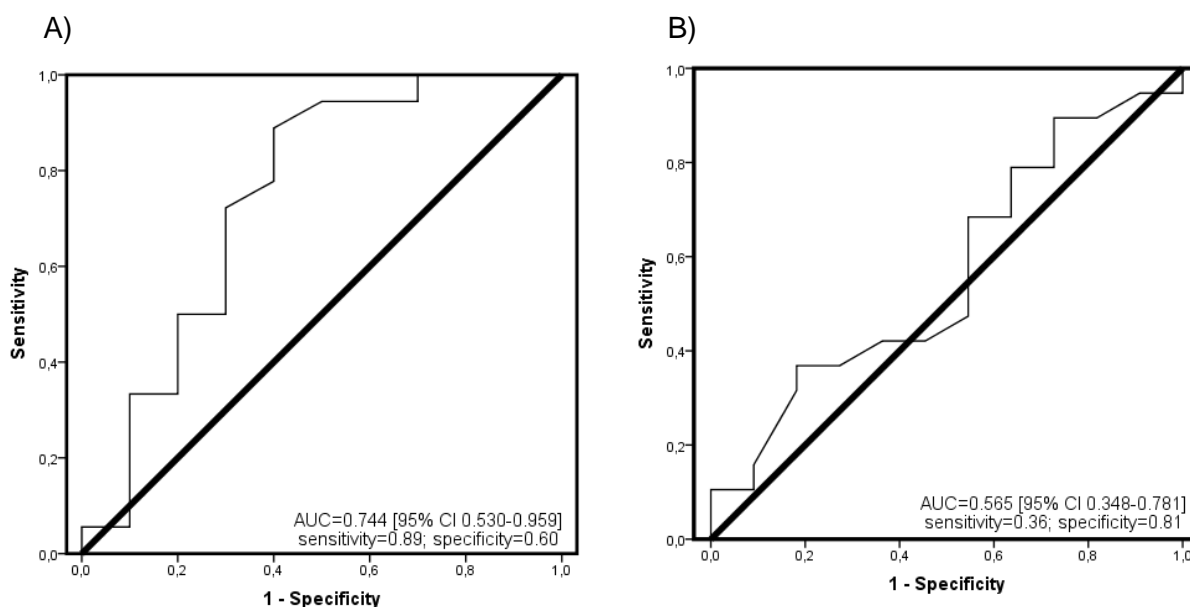
**Health-related quality of life**

SGRQ, pts	42 ± 18	52 ± 16	0.001
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BMI: body mass index; GOLD: Global initiative for chronic obstructive pulmonary disease; FEV<sub>1</sub>: forced expiratory volume in the first second; FVC: forced vital capacity; FFM: fat-free mass; FFMI: fat-free mass index; 6MWT: six-minute walking test; SGRQ: Saint George's respiratory questionnaire; pts: points.

The FFMI cut-off values which best discriminate good exercise capacity were 14.65 kg/m<sup>2</sup> for women (AUC=0.744 [95% CI 0.530-0.959]; sensitivity=0.89; specificity=0.60) and 20.35 kg/m<sup>2</sup> for men (AUC=0.565 [95% CI 0.348-0.781]; sensitivity=0.36; specificity=0.81) (figure 2).

**Figure 2:** ROC curve of the best FFMI cut-off value to discriminate good exercise capacity in women (A) and men (B) with COPD.



The discriminative capacity of the cut-off values for poor exercise capacity, poor health-related quality of life, physical inactivity and sedentary lifestyle are shown in table 2. Agreement between the classification in depleted

and non-depleted according to all cut-off values and the clinical characteristics of the disease was also demonstrated. The cut-off value described by Schols et al.<sup>8</sup> demonstrated the best PPV for all variables and it was more discriminative for sedentary lifestyle and poor exercise capacity (absolute walked distance [in meters] in the 6MWT), while the new cut-off value demonstrated the best NPV and accuracy for poor exercise capacity (6MWT walked distance in % predicted) and poor health-related quality of life. Cohen's Kappa demonstrated poor to fair agreement between the cut-offs classification and clinical features.

**Table 2.** Discriminative capacity of the studied cut-off values for FMM depletion in the sample 2.

	<b>PPV</b>	<b>NPV</b>	<b>Accuracy</b>	<b>K</b>
<b>Exercise capacity</b>				
<b>(6MWT&lt; 82%pred)</b>				
New cut-off value	0.56	0.67	0.62	0.245
Schutz et al.	0.78	0.30	0.51	0.082
Kyle et al.	0.56	0.60	0.58	0.172
Franssen et al.	0.78	0.41	0.57	0.185
Schols et al.	0.91	0.21	0.52	0.118
Coin et al.	0.76	0.35	0.53	0.113
Vestbo et al.	0.80	0.32	0.53	0.119
<b>Exercise capacity</b>				
<b>(6MWT&lt;350m)</b>				
New cut-off value	0.44	0.63	0.48	0.043
Schutz et al.	0.72	0.22	0.51	0.082
Kyle et al.	0.50	0.68	0.53	0.111
Franssen et al.	0.71	0.47	0.66	0.144
Schols et al.	0.85	0.21	0.73	0.07
Coin et al.	0.68	0.26	0.60	-0.04
Vestbo et al.	0.73	0.26	0.64	-0.002
<b>Physical inactivity</b>				
<b>(MVPA&lt;30minutes)</b>				
New cut-off value	0.41	0.60	0.50	0.01

Schutz et al.	0.66	0.22	0.44	-0.108
Kyle et al.	0.46	0.47	0.46	-0.063
Franssen et al.	0.76	0.35	0.55	0.119
Schols et al.	0.87	0.15	0.50	0.022
Coin et al.	0.64	0.30	0.46	-0.059
Vestbo et al.	0.52	0.54	0.53	0.058
<b>Sedentary lifestyle</b>				
<b>(sedentary time <math>\geq 8h30'</math>)</b>				
New cut-off value	0.60	0.36	0.46	-0.023
Schutz et al.	0.60	0.33	0.53	-0.056
Kyle et al.	0.61	0.37	0.49	-0.100
Franssen et al.	0.62	0.39	0.55	0.015
Schols et al.	0.63	0.50	0.62	0.074
Coin et al.	0.62	0.38	0.54	0.007
Vestbo et al.	0.69	0.25	0.46	-0.057
<b>Quality of life</b>				
<b>(SGRQ<math>\geq 38.2</math>)</b>				
New cut-off value	0.38	0.57	0.53	-0.04
Schutz et al.	0.66	0.25	0.33	-0.04
Kyle et al.	0.38	0.51	0.48	-0.07
Franssen et al.	0.66	0.32	0.39	0.000
Schols et al.	0.85	0.16	0.30	0.000
Coin et al.	0.66	0.30	0.37	-0.01
Vestbo et al.	0.66	0.25	0.33	-0.04

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PPV: positive predictive value; NPV: negative predictive value; K: Cohen's kappa; 6MWT: six-minute walking test; MVPA: moderate to vigorous physical activity; SGRQ: Saint George's respiratory questionnaire.

The results of the univariate Cox regression analysis showed that only the new cut-off value presented association with all-cause mortality in this sample of Brazilian patients with COPD. According to the new cut-off, depleted patients were approximately 2 times more likely to die compared to non-depleted patients (HR: 2.12; 95% CI: 1.03 - 4.33) (table 3).

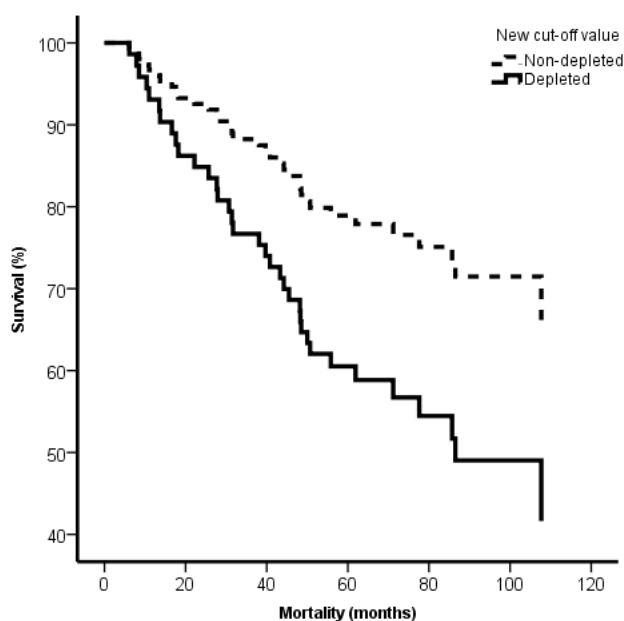
**Table 3.** Univariate Cox regression of the association between the cut-off values and mortality in COPD.

Cut-off point	HR	95% CI	<i>P</i>
New cut-off	2.12	1.03 - 4.33	0.039
Schutz et al.	1.10	0.53 - 2.30	0.791
Kyle et al.	1.08	0.55 - 2.10	0.818
Franssen et al.	0.80	0.38 - 1.68	0.571
Schols et al.	1.53	0.66 - 3.51	0.316
Coin et al.	1.33	0.66 - 2.69	0.415
Vestbo et al.	1.39	0.68 - 2.85	0.359

HR: Hazard ratio; CI: Confidence interval

The Kaplan-Meier plot for the new cut-off value is shown in figure 3. In this analysis, mortality was significantly associated with FFM depletion, classified according to the new cut-off value (log rank  $P=0.035$ ). The median follow up time was 63.4 months [IQR 25%-75% 47.5-88.5] and the minimum and maximum follow-up period was 6 and 112 months, respectively. During the follow up period, 37 patients died; 19 of them from respiratory causes, 4 from cardiac, 4 from gastrointestinal, 5 from neoplastic, 1 from diabetes and 2 from other causes.

**Figure 3:** Kaplan-Meier plot of survival in patients with COPD classified as depleted or non-depleted according to the new cut-off value.



## DISCUSSION

This study developed FFMI-based values for depletion of FFM in Brazilian men and women with COPD which better discriminate poor exercise capacity. By using a functional outcome that is closely related to depletion of FFM, a cut-off point of 14.65 kg/m<sup>2</sup> for women and 20.35 kg/m<sup>2</sup> for men was found. Moreover, the new cut-off was the only capable of discriminating mortality in comparison to previously published cut-off values.

Depletion of FFM is closely associated with impaired maximal and submaximal exercise capacity in COPD. It contributes to impaired peak exercise capacity, decrease in peak oxygen pulse and earlier anaerobic metabolism<sup>35</sup>. Teopompi et al.<sup>11</sup> found that the contribution of FFM depletion in the reduction of exercise capacity, poor cardiovascular response and leg fatigue is irrespective of ventilatory constraints. Moreover, it is known that FFMI is associated with the 6MWT<sup>36</sup>. In the study of Van de Boel et al.<sup>37</sup>, FFMI explained from 41% to 48% of the variability of peak workload in COPD, whereas in male patients it explained 16% of the 6MWT variability. Lainscak et al.<sup>38</sup> found a moderate correlation between FFMI and 6MWT ( $r=0.42$ ); these authors also found that dyspnoea symptoms and 6MWT explained 53% of FFMI variance. Similar findings were demonstrated by Sabino et al.<sup>9</sup> who showed that 6MWT was significantly associated with FEV<sub>1</sub>/FVC, weight, BMI, FFMI and maximal inspiratory pressure. Therefore, these variables were used in a backward stepwise multiple linear regression analysis, which showed that FFMI was the only significant independent predictor of 6MWT (partial  $r=0.52$ ). Taking into consideration the evidences of a close relationship between exercise capacity and FFMI, the authors in the present study considered developing cut-off values for FFMI based on functional performance; thus, it could ensure a more accurate diagnosis of FFM depletion in Brazilian patients with COPD.

FFM depletion is also associated with impaired quality of life in patients with COPD. Depleted patients had higher scores (greater impairment) in the activity and impact domains in the SGRQ<sup>6</sup>. Additionally, it is known that healthy physically active subjects are less likely to have low FFMI opposed to their sedentary counterparts<sup>12</sup>. Moreover, physically active patients with COPD had greater FFMI and lower proportion of FFM depletion<sup>14</sup>. Therefore, decreased

FFMI may lead to all these adverse implications, which requires that an accurate cut-off point should be discriminative for all these clinical features.

The proportion of muscle wasting in patients with COPD is largely dependent on the cut-off points used for its classification<sup>16</sup>. Vestbo et al.<sup>7</sup> using two approaches to classify depletion of FFM found a difference in this proportion of 8.8% in women and 12.2% in men. It is possible to hypothesize that these differences may arise when using a non-appropriate cut-off point for a specific population.

Some cut-off points for FFMI have already been described to characterize depletion. Schols et al.<sup>8</sup> developed the cut-offs of  $FFMI < 16 \text{ kg/m}^2$  for men and  $15 \text{ kg/m}^2$  for women, based on the percentage of ideal body weight in a population of moderate to severe patients with COPD from the Netherlands. Schutz et al.<sup>19</sup> developed percentiles of FFMI based on age and gender from an apparently healthy sample aged 24-98 years in Switzerland. Kyle et al.<sup>20</sup> demonstrated FFMI ranges according to BMI in healthy Swiss men and women across the age ranging from 15 to 98 years. Vestbo et al.<sup>7</sup> established the cut-offs of  $FFMI < 17.0 \text{ kg/m}^2$  for men and  $14.62 \text{ kg/m}^2$  for women based on the 10<sup>th</sup> percentile of a large cohort of subjects from Copenhagen. The cut-offs of Coin et al.<sup>21</sup> are also based in percentiles of FFMI according to age and gender from a sample of apparently healthy Italian adults aging 20 to 80 years old. Recently, Franssen et al.<sup>17</sup> developed new reference values for FFMI based on percentiles according to gender, age and BMI from the UK Biobank's population. Despite the fact that several cut-off points have already been described, none of them were developed based on clinical outcomes and so far the present authors have no knowledge of any value developed for the Brazilian population.

In the present study, subjects classified as depleted according to Schols et al.<sup>8</sup> were more likely (i.e. higher PPV) to present poor exercise capacity, lower physical activity level, sedentarism and poor health-related quality of life. This finding could be related to the fact that patients classified as depleted according to this cut-off point were the ones with the lowest value of FFMI (i.e.  $FFMI < 16 \text{ kg/m}^2$  for men and  $15 \text{ kg/m}^2$  for women). It could be hypothesized that the lower the FFMI the higher extrapulmonary manifestations. Supporting this hypothesis, in this study the cut-off point of Schols et al.<sup>8</sup> was also more

accurate to detect higher sedentary behaviour and poor exercise capacity by absolute distance walked in the 6MWT.

Noteworthy, as the new cut-off value is more rigorous for men with COPD than the previous ones, it will identify those male patients with a less pronounced decrease in FFMI, i.e. less severe physical impairments. As a consequence, it was more accurate to detect poor exercise capacity by the 6MWT in percentage of predicted, since relative values are more rigorous than absolute walked distance to diagnose poor exercise capacity.

Patients with COPD with lower values of FFMI (i.e.  $\text{FFMI} < 16 \text{ kg/m}^2$  for men and  $15 \text{ kg/m}^2$  for women) do need nutritional support to benefit from pulmonary rehabilitation programs<sup>39,40</sup>. The use of the new cut-off point, that is stricter and able to identify patients with a lower decrease in FFMI, might be used to facilitate the treatment of depleted patients. Since it was already demonstrated that for patients with moderate to severe COPD, with normal weight and an average FFMI of  $18 \text{ Kg.m}^{-2}$ , a balanced exercise program of both endurance and strength training could act as an anabolic stimulus, promoting improvements in FFM, maximum  $\text{VO}_2$ , peak work rate and quadriceps strength<sup>41</sup>. It means that the new cut-off point would identify patients, especially the male ones, at a time in which the depletion could be reversed with only exercise-training (i.e., without nutritional support).

The new cut-off point presented the best value of accuracy to detect poor quality of life; however, even presenting the highest value, it showed poor discriminative capacity. Unlike FFMI, quality of life is a subjective outcome that is influenced by other factors which were not evaluated in the present study. The poor discriminative capacity could be explained considering that, although depletion of FFMI has a negative impact on quality of life<sup>6</sup>, there are several other factors (e.g. physical activity, symptoms, exacerbations) contributing to a poor health-related quality of life<sup>26,42</sup>. Similar results were found regarding physical activity which is also an outcome influenced by several factors, not only explained by fat-free mass index. Although Andersson et al.<sup>14</sup> found that fat-free mass depletion was less prevalent among physically activity subjects, the explanatory value of FFMI towards physical activity level was relatively low. Waschki et al.<sup>13</sup> found that the decrease in  $\text{FEV}_1$  and increase in the SGRQ score were associated with the decrease in physical activity level, while

changes in 6MWT and FFM were not. On the other hand, the same authors found that the sustained level of physical inactivity is related to a progression of muscle depletion. This complex relationship between fat-free mass and physical activity may explain the poor discriminative capacity of the new cut-off point with respect to this outcome. Finally, it is important to highlight that the agreement between the studied cut-offs values and clinical features varied from poor to fair. This confirmed our hypothesis that although FFM depletion is associated with several disease manifestations, the criterion used to detect it may influence in clinical interpretations.

It is well established in the literature that BMI is consistently associated with mortality in patients with COPD<sup>43,44</sup>. Hallin et al.<sup>45</sup> followed patients with COPD after admission due to acute exacerbation and founded highest mortality rate in patients with BMI < 20kg/m<sup>2</sup>. In a long-term mortality trial, weight loss was associated with increased all-cause and COPD-mortality<sup>46</sup>. However, both high fat mass and low FFMI are also independent predictors of all-cause mortality<sup>47</sup>. A study demonstrated that underweight and overweight patients who decreased FFMI in a period of one year had higher mortality risk<sup>48</sup>. Additionally, it was also shown that FFMI is a stronger predictor of mortality than BMI<sup>7,49</sup>. Schols et al.<sup>15</sup> found higher 3-year mortality risk in depleted COPD patients even in those with normal BMI, as well as patients with low BMI but normal FFMI had lower mortality risk. Then, it becomes clear that depletion of FFM leads to higher mortality risk in COPD patients, which highlights the importance of choosing a cut-off point that, above all, can predict unfavourable prognosis in these patients.

In the present study, the new cut-off value was the only that presented association with all-cause mortality. It is known that COPD is frequently associated with a variety of comorbidities, suggesting that there is a common pathophysiologic pathway for the co-occurrence of several chronic conditions<sup>50</sup>. It is also known that low FFM is associated with presence of comorbidities in COPD. Thus, we could infer that a decreased FFMI could not only impact on COPD-related mortality but also on other causes of mortality which could be consequence of the multiple comorbidities associated with the disease. The participants that composed the present retrospective cohort were enrolled in an exercise training program, as part of an interventional study<sup>18</sup>. Part of them

concluded the program and it could interfere in the analysed survival rate. However, the authors do not believe that it influenced the results regarding mortality since it was not observed significant changes in FFM and FFMI after the intervention ( $P>0.05$ , data not shown), indicating that FFM and FFMI was not influenced by the effects of exercise training in this cohort. Furthermore, when we compared the subgroup of patients who completed the exercise program with those who dropped out, they had similar time to death ( $P>0.05$ , data not shown).

As previously mentioned, reference values to detect FFM depletion should consider some determinants, as ethnicity<sup>4</sup>. The new cut-off point developed for Brazilian COPD patients in the present study considered also functional aspects of this population which could explain the fact that it was the only reference value which presented association with mortality. However, it should be important to test its clinical applicability in other samples to confirm this hypothesis.

An interesting finding in this study was that the sample composed in order to validate the new cut-off point was different from that used to develop it in aspects such as disease severity, exercise capacity and quality of life (table 1). The authors consider that it strengthens our results since we can infer that the new cut-off point had good discriminative capacity for extrapulmonary manifestations of COPD even in a sample with different clinical profile, reinforcing the external validity of the cut-off value developed.

Some limitations of the current study need to be considered. Firstly, the results of the present study may not be applicable to patients with mild disease, since the samples were composed of patients with moderate to severe impairment (GOLD stages II to IV). Secondly, a gold standard method was not used for measurement of body composition. However, bioelectrical impedance has been extensively used for this assessment in COPD patients because it is practical, simple and reliable when using a validated equation to assess patients with stable water and electrolytes balance<sup>10,51</sup>. For the present study, it was used a validated prediction equation specific for patients with COPD, incorporating gender, height, weight and the measured impedance<sup>16</sup>. However, it is not possible to affirm that all patients were free of any level of oedema and that consequently the hydric status did not interfere in the measurements,

although the protocol was standardized and all subjects had body composition measurements assessed at the same conditions.

## **CONCLUSION**

A new cut-off point to detect FFM depletion was developed for Brazilian men and women with COPD. These values were 20.35 kg/m<sup>2</sup> for men and 14.65 kg/m<sup>2</sup> for women. Moreover, it was the only cut-off which presented association with all-cause mortality and was also accurate to detect poor exercise capacity (6MWD in relative value) and quality of life.

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## **DECLARATION OF INTEREST**

The authors disclose no conflict of interest.

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#### 4 CONCLUSÃO GERAL

Como já demonstrado, a depleção muscular é um determinante de desfechos clínicos desfavoráveis em DPOC. Este estudo demonstrou a capacidade discriminativa de vários pontos de corte descritos na literatura para alguns desses desfechos, como capacidade de exercício, qualidade de vida, atividade física e sedentarismo. Tais resultados facilitam a escolha do ponto de corte o que favorece um diagnóstico preciso e facilita o manejo desses pacientes que devem ser encaminhados para suplementação nutricional e modalidades específicas de treinamento.

Um novo ponto de corte para detecção de depleção muscular, baseado em valores de IMLG, foi desenvolvido para pacientes com DPOC brasileiros, sendo valores distintos para homens e mulheres. Este novo ponto de corte foi o único a apresentar associação com mortalidade e também foi o mais acurado para detectar baixa capacidade de exercício e qualidade de vida. Embora o ponto de corte proposto por Schols *et al.*<sup>6</sup> não tenha apresentado associação com mortalidade, este apresentou boa capacidade para discriminar sedentarismo e também baixa capacidade de exercício.

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## APÊNDICES

## APÊNDICE A

### TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Prezado(a) Senhor(a):

O(A) Sr(a) está sendo convidado para participar de um projeto de pesquisa chamado “*Efeitos de um programa de exercício físico de longa duração sobre aspectos pulmonares e sistêmicos em pacientes com Doença Pulmonar Obstrutiva Crônica (DPOC)*”, cujo pesquisador responsável é o Prof. Dr. Fábio de Oliveira Pitta, do Departamento de Fisioterapia da Universidade Estadual de Londrina (UEL). O estudo analisará principalmente as melhoras obtidas após 6 meses de treinamento utilizando-se dois tipos diferentes de exercício físico.

Justificativa: O presente estudo contribuirá para solucionar uma questão não resolvida e que tem sido alvo de grande debate: levando em conta que a longa duração do programa de treinamento físico é fundamental no processo de conscientizar pacientes com DPOC a aumentar sua atividade física diária, será necessário que o treinamento físico realizado durante esse programa de longa duração seja feito em alta intensidade, ou um programa de baixa intensidade de treinamento já atingiria o objetivo? Se programas de longa duração, porém com baixa intensidade de treinamento, trouxerem benefícios importantes no aumento da atividade física diária, isso poderá trazer mudança no entendimento atual sobre protocolos de exercício em pacientes com DPOC, que hoje são realizados sob alta intensidade de treinamento.

Objetivo: Comparar os efeitos de dois protocolos de treinamento físico em um programa de reabilitação de longa duração (6 meses) em pacientes com DPOC: um protocolo de alta intensidade (baseado em treinamento de endurance e força) e um protocolo de baixa intensidade (baseado em exercícios respiratórios e de readequação do complexo tóraco-pulmonar).

Procedimentos: Os pacientes incluídos realizarão uma série de testes que incluirá avaliação da função pulmonar, capacidade máxima e funcional de

exercício, força muscular periférica e respiratória, atividade física na vida diária, composição corporal, função autonômica cardíaca, qualidade de vida, estado funcional e sensação de dispnéia. A realização dos testes requer uma visita de aproximadamente 2 horas ao Hospital Universitário Regional Norte do Paraná, em Londrina, além do uso do pequeno aparelho na cintura durante dois dias (12 horas por dia, apenas durante o dia e não de noite). Após a avaliação inicial, os pacientes serão divididos em dois grupos: um grupo realizará um programa de exercícios físicos direcionado ao aumento da mobilidade torácica realizado 3 vezes por semana, durante 24 semanas ; e outro grupo realizará um programa de treinamento de endurance e força de membros superiores e inferiores realizado 3 vezes por semana, durante 24 semanas. Ao final do programa de treinamento, os participantes serão reavaliados seguindo os mesmos testes realizados na avaliação inicial.

Custos: A pesquisa é gratuita e portanto não envolve qualquer custo por parte dos indivíduos. Não haverá qualquer gratificação financeira pela participação. No entanto, em caso de eventuais danos ocorridos exclusivamente por causa deste estudo, o Sr(a) terá direito a tratamento médico completo oferecido pela instituição.

Riscos: Nenhum dos procedimentos utilizados constitui risco direto para a integridade física ou moral dos participantes. Além disso, os participantes poderão abandonar o estudo a qualquer momento que se achar conveniente, sem qualquer prejuízo em nenhum sentido.

Sigilo: Embora os resultados da pesquisa possam ser divulgados em publicações e eventos científicos, a identidade dos participantes será sempre preservada de maneira sigilosa, ou seja, em segredo.

Caso o(a) Sr(a) aceite esse convite e concorde voluntariamente em participar do estudo assinando este termo de consentimento, consideramos que o Sr(a) acredita que foi suficientemente informado(a) pelo(a) pesquisador(a) \_\_\_\_\_ sobre a pesquisa, os procedimentos

envolvidos nela, assim como os possíveis riscos e benefícios decorrentes dessa

participação. Ressaltamos novamente que o Sr(a) pode retirar seu consentimento a qualquer momento, sem que isto leve a qualquer prejuízo em nenhum sentido.

Local e data: \_\_\_\_\_

Nome do participante: \_\_\_\_\_

Assinatura do participante ou responsável: \_\_\_\_\_

Nome do pesquisador: \_\_\_\_\_

Assinatura do pesquisador: \_\_\_\_\_

Colocamo-nos à disposição para qualquer esclarecimento que se fizer necessário nos telefones (43) 3371 2288 ou 3371 2252 ou pessoalmente no Ambulatório de Fisioterapia Respiratória do Hospital Universitário Regional Norte do Paraná: Av. Robert Koch, 60 – Vila Operária – Londrina – PR (perguntar pelo Professor Fábio de Oliveira Pitta). Em caso de dúvida, o Comitê de Ética em Pesquisa da Universidade Estadual de Londrina / Hospital Universitário pode ser contactado pelo telefone (43) 3371 2490.

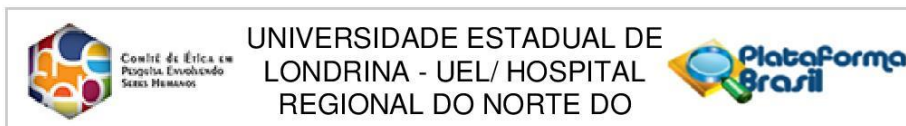
Atenciosamente,

Prof. Fábio de Oliveira Pitta  
Coordenador do Projeto

## **ANEXOS**

## ANEXO A

### Parecer do comitê de ética em pesquisa



#### PARECER CONSUBSTANCIADO DO CEP

##### DADOS DO PROJETO DE PESQUISA

**Título da Pesquisa:** ESTUDO SOBRE (IN)ATIVIDADE FÍSICA DA VIDA DIÁRIA E MORTALIDADE EM PACIENTES COM DPOC

**Pesquisador:** KARINA COUTO FURLANETTO

**Área Temática:**

**Versão:** 2

**CAAE:** 41437014.0.0000.5231

**Instituição Proponente:** CCS - Departamento de Fisioterapia

**Patrocinador Principal:** Financiamento Próprio

##### DADOS DO PARECER

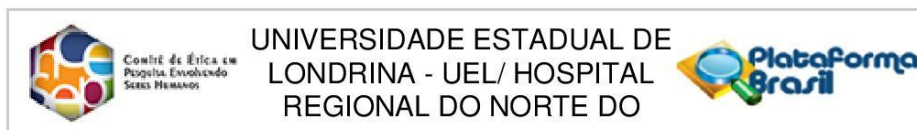
**Número do Parecer:** 996.413

**Data da Relatoria:** 20/03/2015

##### Apresentação do Projeto:

Trata-se de um projeto de pesquisa sob coordenação da Prof. Karina Couto Furlanetto, do Departamento de Fisioterapia da Universidade Estadual de Londrina (UEL). É um "estudo de coorte com análise retrospectiva de prontuários de pacientes com DPOC [doença pulmonar obstrutiva crônica], incluídos em um programa de reabilitação pulmonar nos anos de 2006 a 2014. Na avaliação inicial, os pacientes foram submetidos à avaliação do nível de atividade física na vida diária (AFVD) por meio de acelerômetros, além de avaliações da função pulmonar, força muscular respiratória, capacidade de exercício, força muscular periférica, qualidade de vida, estado funcional e sensação de dispneia. Os dados atuais referentes ao estado vital serão coletados por meio do acesso ao banco de dados do Núcleo de Informação de Mortalidade (NIM) da Autarquia Municipal de Saúde do Estado do Paraná. Caso o paciente tenha ido a óbito, serão coletadas informações sobre a data de morte e a etiologia no referido banco de dados. Após coletadas essas informações, os dados serão analisados levando-se em consideração dois grupos: grupo sobrevivente e grupo não sobrevivente". O estudo parte da seguinte hipótese: "[...] o tempo gasto em sedentarismo ou em atividade física seja um importante fator de predição de mortalidade em pacientes com DPOC".

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**UF:** PR **Município:** LONDRINA  
**Telefone:** (43)3371-5455 **E-mail:** cep268@uel.br



Continuação do Parecer: 996.413

#### **Objetivo da Pesquisa:**

##### **Objetivo Primário:**

Definir um ponto de corte para tempo gasto em sedentarismo em pacientes com DPOC, e investigar sua associação com a mortalidade, comparando este ponto de corte a outros fatores preditores de mortalidade já estabelecidos na literatura.

##### **Objetivo Secundário:**

- Identificar um ponto de corte para tempo gasto em sedentarismo em pacientes com DPOC a partir da recomendação de 30 minutos de atividade física de intensidade moderada a vigorosa (AFMV).
- Investigar a associação desse novo ponto de corte com a mortalidade nesses pacientes.
- Avaliar o poder de predição de mortalidade de diferentes desfechos de (in)atividade física de vida diária medida objetivamente em pacientes com DPOC e compará-los com o poder de predição de desfechos previamente conhecidos como preditores de mortalidade da doença.
- Determinar a variável de (in)atividade física de vida diária com maior poder de predição de mortalidade em pacientes com DPOC.

#### **Avaliação dos Riscos e Benefícios:**

Como não há a previsão de participantes no projeto, apenas a consulta de prontuários, não há riscos para participantes. Com relação aos benefícios, são para a área de estudos.

#### **Comentários e Considerações sobre a Pesquisa:**

A pesquisadora sanou todas as pendências, como indicado a seguir, in verbis:

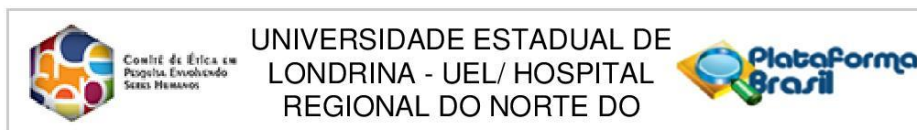
1) TCLE para os participantes da pesquisa prospectiva finalizada, que figurarão como participantes na nova pesquisa;

R: A nova pesquisa é um estudo retrospectivo que dispensa o TCLE, devido à metodologia proposta. Os dados sobre mortalidade dos participantes da nova pesquisa NÃO serão coletados por meio de contato telefônico ou visita domiciliar, e sim em prontuários, por meio do acesso ao banco de dados do Núcleo de Informação de Mortalidade (NIM) da Autarquia Municipal de Saúde do Estado do Paraná (adequações no sistema da Plataforma Brasil foram realizadas).

2) TCLE para os responsáveis por informações sobre a morte dos participantes da pesquisa prospectiva finalizada, que figurarão como participantes na nova pesquisa;

R: A nova pesquisa não realizará ligações telefônicas ou visitas domiciliares. Os dados atuais referentes ao estado vital serão coletados por meio do acesso ao Núcleo de Informação em Mortalidade (NIM) da Autarquia Municipal de Saúde.

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Continuação do Parecer: 996.413

3) Folha de rosto assinada pela coordenação do Programa de Doutorado em Ciências da Reabilitação UEL/UNOPAR;

R: Acredito que houve um mal entendido quanto à instituição proponente do projeto de pesquisa devido ao anexo da autorização emitido pela Autarquia. Este projeto não foi cadastrado na UEL como projeto de pós-graduação e sim no meu nome, como docente do departamento de Fisioterapia. Eu também sou aluna de doutorado do programa de Ciências da Reabilitação orientada pelo professor Fabio Pitta, que é colaborador desse projeto, e quando a solicitei a autorização na Autarquia Municipal de Saúde do Estado do Paraná, também forneci essa informação. Os dados coletados neste projeto de pesquisa provavelmente renderão um segundo artigo durante o período do meu doutorado e talvez um segundo artigo da aluna Leila Donária (citado na autorização da Autarquia), por isso achei pertinente informá-los, mas o ESTUDO SOBRE (IN)ATIVIDADE FÍSICA DA VIDA DIÁRIA E MORTALIDADE EM PACIENTES COM DPOC, não é projeto de doutorado ou mestrado e sim do departamento de Fisioterapia. Gostaria gentilmente de solicitar que fosse mantida a folha de rosto previamente enviada para que fosse levado adiante como está, pois este projeto contabiliza carga horária docente na UEL e já está até na pauta da próxima reunião de departamento.

4) Apresentação do "Termo de Sigilo e Confidencialidade";

R: Inclui o "Termo de Sigilo e Confidencialidade" (em anexo no sistema).

5) Indicação de um membro da equipe que propiciará acolhimento ou indicação do tipo de encaminhamento a ser dado no caso dos participantes se sentirem emocionalmente abalados por conta da abordagem da questão da morte.

6) Roteiro das perguntas que serão feitas aos participantes, especialmente aquelas que tratarão sobre óbitos.

R (questões 5 e 6): Visto que os dados serão coletados em prontuários, as questões 5 e 6 também não se aplicam ao presente estudo.

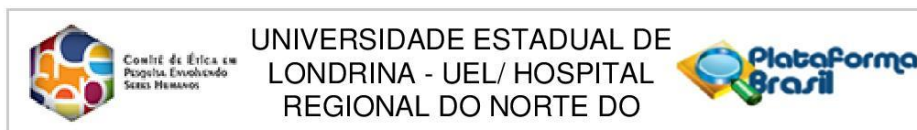
**Considerações sobre os Termos de apresentação obrigatória:**

Foram contemplados todos os termos de apresentação obrigatória.

**Recomendações:**

Não há.

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Continuação do Parecer: 996.413

**Conclusões ou Pendências e Lista de Inadequações:**

Não há.

**Situação do Parecer:**

Aprovado

**Necessita Apreciação da CONEP:**

Não

**Considerações Finais a critério do CEP:**

Prezado (a) Pesquisador (a),

Este é seu parecer final de aprovação, vinculado ao Comitê de Ética em Pesquisas Envolvendo Seres Humanos da Universidade Estadual de Londrina. É sua responsabilidade imprimi-lo para apresentação aos órgãos e/ou instituições pertinentes.

Coordenação CEP/UEL.

LONDRINA, 24 de Março de 2015

---

**Assinado por:**

**Alexandrina Aparecida Maciel Cardelli  
(Coordenador)**

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## ANEXO B

### Normas de formatação do periódico *Respiratory Medicine*

#### **Your Paper Your Way**

We now differentiate between the requirements for new and revised submissions. You may choose to submit your manuscript as a single Word or PDF file to be used in the refereeing process. Only when your paper is at the revision stage, will you be requested to put your paper in to a 'correct format' for acceptance and provide the items required for the publication of your article.

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Respiratory Medicine is an internationally-renowned, clinically-oriented journal, combining cutting-edge original research with state-of-the-art reviews dealing with all aspects of respiratory diseases and therapeutic interventions, but with a clear clinical relevance. The journal is an established forum for the publication of phased clinical trial work at the forefront of interventional research. As well as full-length original research papers, the journal publishes reviews, correspondence, and short reports. The Journal also publishes regular supplements on areas of special interest.

#### **Ethics in publishing**

Please see our information pages on Ethics in publishing and Ethical guidelines for journal publication.

#### **Declaration of interest**

All authors must disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding. If there are no conflicts of interest then please state this: 'Conflicts of interest: none'.

## **Submission declaration and verification**

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## **Authorship**

All authors should have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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### **Clinical trial results**

In line with the position of the International Committee of Medical Journal Editors, the journal will not consider results posted in the same clinical trials registry in which primary registration resides to be prior publication if the results posted are presented in the form of a brief structured (less than 500 words) abstract or table. However, divulging results in other circumstances (e.g., investors' meetings) is discouraged and may jeopardise consideration of the manuscript. Authors should fully disclose all posting in registries of results of the same or closely related work.

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#### *Reporting clinical trials*

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#### *Registration of clinical trials*

Registration in a public trials registry is a condition for publication of clinical trials in this journal in accordance with International Committee of Medical Journal Editors recommendations. Trials must register at or before the onset of

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#### *Language (usage and editing services)*

Please write your text in good English (American or British usage is accepted, but not a mixture of these). Authors who feel their English language manuscript may require editing to eliminate possible grammatical or spelling errors and to conform to correct scientific English may wish to use the English Language Editing service available from Elsevier's WebShop.

## **Submission**

Our online submission system guides you stepwise through the process of entering your article details and uploading your files. The system converts your article files to a single PDF file used in the peer-review process. Editable files (e.g., Word, LaTeX) are required to typeset your article for final publication. All correspondence, including notification of the Editor's decision and requests for revision, is sent by e-mail.

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Submissions are allocated to a handling editor, typically an Associate Editor. Should the paper be considered suitable for peer review, appropriate reviewers will be recruited. Authors are required to provide the name and full contact details of 2 potential reviewers, though choice of reviewers is at the discretion of the handling editor.

The final decision-making responsibility lies with the handling editor, who reserves the right to reject the paper despite favourable reviews depending on the priorities of the journal.

## **Reviews**

The journal welcomes submission of state-of-the-art reviews on important topics with a clinical relevance. Potential review authors are encouraged to contact the Deputy Editor Dr N. Hanania [hanania@bcm.tmc.edu](mailto:hanania@bcm.tmc.edu) in advance with their review proposals.

## **Case Reports**

Case reports will no longer be considered for publication in Respiratory Medicine, but instead should be directed to the sister publication Respiratory Medicine Case Reports. Please note that this is a separate publication. Case reports should be submitted for consideration by Respiratory Medicine Case Reports via <http://ees.elsevier.com/rmcr/>. Respiratory Medicine Case Reports is

an open access journal and all authors will be required to pay a £250 processing fee to cover the costs of publishing the article, which authors will be required to pay once an article has passed peer review.

### **<Brief Communications**

These should be submitted as detailed above but should not exceed 1000 words, and may normally contain only one illustration or table. Brief communications containing new information may be selected for rapid peer review and publication at the discretion of the editor and editorial board.

## **NEW SUBMISSIONS**

Submission to this journal proceeds totally online and you will be guided stepwise through the creation and uploading of your files. The system automatically converts your files to a single PDF file, which is used in the peer-review process.

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### *References*

There are no strict requirements on reference formatting at submission. References can be in any style or format as long as the style is consistent. Where applicable, author(s) name(s), journal title/book title, chapter title/article title, year of publication, volume number/book chapter and the pagination must be present. Use of DOI is highly encouraged. The reference style used by the journal will be applied to the accepted article by Elsevier at the proof stage. Note that missing data will be highlighted at proof stage for the author to correct.

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There are no strict formatting requirements but all manuscripts must contain the essential elements needed to convey your manuscript, for example Abstract, Keywords, Introduction, Materials and Methods, Results, Conclusions, Artwork and Tables with Captions.

If your article includes any Videos and/or other Supplementary material, this should be included in your initial submission for peer review purposes.

Divide the article into clearly defined sections.

### *Figures and tables embedded in text*

Please ensure the figures and the tables included in the single file are placed next to the relevant text in the manuscript, rather than at the bottom or the top of the file.

## **REVISED SUBMISSIONS**

### *Use of word processing software*

Regardless of the file format of the original submission, at revision you must provide us with an editable file of the entire article. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article. The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the [Guide to Publishing with Elsevier](#)). See also the section on Electronic artwork.

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Subdivision - unnumbered sections

Divide your article into clearly defined sections. Each subsection is given a brief heading. Each heading should appear on its own separate line. Subsections should be used as much as possible when cross-referencing text: refer to the subsection by heading as opposed to simply 'the text'.

## Introduction

State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

## *Material and methods*

Provide sufficient detail to allow the work to be reproduced. Methods already published should be indicated by a reference: only relevant modifications should be described.

## *Results*

Results should be clear and concise.

## *Discussion*

This should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section is often appropriate. Avoid extensive citations and discussion of published literature.

## *Conclusions*

The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.

## *Appendices*

If there is more than one appendix, they should be identified as A, B, etc. Formulae and equations in appendices should be given separate numbering: Eq. (A.1), Eq. (A.2), etc.; in a subsequent appendix, Eq. (B.1) and so on. Similarly for tables and figures: Table A.1; Fig. A.1, etc.

### **Essential title page information**

- **Title.** Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible.
- **Author names and affiliations.** Please clearly indicate the given name(s) and family name(s) of each author and check that all names are accurately spelled. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower-case superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.
- **Corresponding author.** Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. **Ensure that the e-mail address is given and that contact details are kept up to date by the corresponding author.**
- **Present/permanent address.** If an author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

### **Structured abstract**

A structured abstract, by means of appropriate headings, should provide the context or background for the research and should state its purpose, basic procedures (selection of study subjects or laboratory animals, observational and

analytical methods), main findings (giving specific effect sizes and their statistical significance, if possible), and principal conclusions. It should emphasize new and important aspects of the study or observations.

A list of three to six keywords should be supplied: full instructions are provided when submitting the article online.

### *Abbreviations*

Define abbreviations that are not standard in this field in a footnote to be placed on the first page of the article. Such abbreviations that are unavoidable in the abstract must be defined at their first mention there, as well as in the footnote. Ensure consistency of abbreviations throughout the article.

### *Acknowledgements*

Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).

### *Formatting of funding sources*

List funding sources in this standard way to facilitate compliance to funder's requirements:

Funding: This work was supported by the National Institutes of Health [grant numbers xxxx, yyyy]; the Bill & Melinda Gates Foundation, Seattle, WA [grant number zzzz]; and the United States Institutes of Peace [grant number aaaa].

It is not necessary to include detailed descriptions on the program or type of grants and awards. When funding is from a block grant or other resources

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If no funding has been provided for the research, please include the following sentence:

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### *Units*

Follow internationally accepted rules and conventions: use the international system of units (SI). If other units are mentioned, please give their equivalent in SI.

### *Math formulae*

Please submit math equations as editable text and not as images. Present simple formulae in line with normal text where possible and use the solidus (/) instead of a horizontal line for small fractional terms, e.g.,  $X/Y$ . In principle, variables are to be presented in italics. Powers of  $e$  are often more conveniently denoted by  $\exp$ . Number consecutively any equations that have to be displayed separately from the text (if referred to explicitly in the text).

### *Footnotes*

Footnotes should be used sparingly. Number them consecutively throughout the article. Many word processors build footnotes into the text, and this feature may be used. Should this not be the case, indicate the position of footnotes in the text and present the footnotes themselves separately at the end of the article.

## Artwork

### *Electronic artwork*

#### *General points*

- Make sure you use uniform lettering and sizing of your original artwork.
- Preferred fonts: Arial (or Helvetica), Times New Roman (or Times), Symbol, Courier.
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- Use a logical naming convention for your artwork files.
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A detailed [guide on electronic artwork](#) is available.

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[1] J. van der Geer, J.A.J. Hanraads, R.A. Lupton, The art of writing a scientific article, *J. Sci. Commun.* 163 (2010) 51–59.

Reference to a book:

[2] W. Strunk Jr., E.B. White, *The Elements of Style*, fourth ed., Longman, New York, 2000.

Reference to a chapter in an edited book:

[3] G.R. Mettam, L.B. Adams, How to prepare an electronic version of your article, in: B.S. Jones, R.Z. Smith (Eds.), *Introduction to the Electronic Age*, E-Publishing Inc., New York, 2009, pp. 281–304.

Reference to a website:

[4] Cancer Research UK, Cancer statistics reports for the UK. <http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/>, 2003 (accessed 13.03.03).

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