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Comprometimento nutricional de pacientes hospitalizados por exacerbação da doença pulmonar obstrutiva crônica: desnutrição e sarcopenia

Dissertação de Mestrado

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Dissertação de Mestrado apresentada ao Programa de Pós-Graduação em Ciências da Nutrição da Universidade Federal de Ciências da Saúde de Porto Alegre, como requisito parcial para obtenção do título de Mestre em Ciências da Nutrição.

Orientadora: Profª Dra. Flávia Moraes Silva

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Os produtos desta dissertação compreendem dois artigos científicos originais, conforme detalhado abaixo:

- **Malnutrition in acute exacerbated patients with chronic obstructive pulmonary disease - comparative analysis of the accuracy of AND-ASPEN, ESPEN, and GLIM Consensus: a cohort study**, submetido ao periódico *Journal of the Academy of Nutrition and Dietetics* (ISSN: 2212-2672; fator de impacto: 4,92; qualis A2), cujas diretrizes podem ser consultadas em https://jandonline.org/content/authorinfo.
- **Prevalence, associated factors, and prognostic value of sarcopenia in patients with acute exacerbated chronic obstructive pulmonary disease**, submetido ao periódico *Nutrition* (ISSN: 0899-9007; fator de impacto: 3.59; qualis A1), cujas diretrizes podem ser consultadas em https://www.elsevier.com/journals/nutrition/0899-9007/guide-for-authors.

SUMÁRIO

LISTA DE ABREVIATURAS

Termos em português

ASG - Avaliação subjetiva global

AUC - Área sobre a curva ROC

CP - Circunferência da panturrilha

CVF - Capacidade vital final

DPOC - Doença pulmonar obstrutiva crônica

FAM - Força do aperto de mão

IBRANUTRI - Inquérito brasileiro de avaliação nutricional hospitalar

IC - Intervalo de confiança

IMC - Índice de massa corporal

IMLG - Índice de massa livre de gordura

UTI - Unidade de terapia intensiva

VEF1 - Volume expiratório forçado em 1 segundo

VM - Ventilação mecânica

Termos em inglês

%BWL - Percent of body weight loss

AECOPD - Acute exacerbated chronic obstructive pulmonary disease

AND-ASPEN - Academy of Nutrition and Dietetics–American Society for Parenteral and Enteral Nutrition ESPEN - European Society for Clinical Nutrition and Metabolism

AUC - Area under the curve

BIA - Bioimpedance analysis

BMI - Body mass index

BODE - Body-mass index, airflow Obstruction, Dyspnea, and Exercise

BOLD - Burden of obstructive lung diseases

CC - Calf circumference

CCI - Charles comorbidity index

CI - Confidence interval

COPD - Chronic obstructive pulmonary disease

CRP - C-reactive protein

DEXA - Dual x-ray absormetry

ERS - European Society of Respirology

EWGSOP - European Work Group on Sarcopenia in Older People

FEV^1 - Forced expiratory volume in 1 second

FFMI - Fat-free mass index

FVC - Forced vital capacity.

GLIM - Global Leadership Initiative of Malnutrition

GOLD - Global Initiative of Chronic Obstructive Lung Disease

HR - Hazard ratio

HSG - Handgrip strength

ICU - Intensive care units

LOS - Length of stay

mMRC - Modified medical resarch council

MRC - Medical resarch councial

NPV - Negative predictive value

OR - Odds ratio

PPV - Positive predictive value

ROC - Receiver operating characteristic

SGA - Subjective Global Assessment

SPPB - Short physical performance battery

RESUMO

Introdução: A doença pulmonar obstrutiva crônica (DPOC) caracteriza-se por seu caráter progressivo e irreversível e pela presença de inflamação crônica, a qual é intensificada nos quadros de exacerbação. Isso contribui para um intenso catabolismo proteico e, consequentemente, para o comprometimento do estado nutricional de pacientes com DPOC. O objetivo desse estudo foi avaliar a prevalência de desnutrição por diferentes ferramentas integrativas e a validade concorrente e preditiva dessas em predizer desfechos intra-hospitalares. Além disso, foi avaliada a prevalência de sarcopenia, os fatores associados a essa condição e a sua associação com desfechos clínicos em pacientes com DPOC hospitalizados por exacerbação da doença.

Metodologia: Estudo de coorte prospectiva com pacientes internados por exacerbação da DPOC em um hospital público terciário brasileiro. A coleta de dados foi realizada em até 72 horas após a admissão hospitalar. O diagnóstico de desnutrição foi realizado pela ferramentas Avaliação Subjetiva Global (ASG), *Global Leadership Initiative of Malnutrition* (GLIM), *Academy of Nutrition and Dietetics–American Society for Parenteral and Enteral Nutrition* (AND-ASPEN) e *European Society for Clinical Nutrition and Metabolism* (ESPEN). O diagnóstico de sarcopenia foi realizado de acordo com o consenso proposto pelo *European Work Group on Sarcopenia in Older People* (EWGSOP 2) considerando força do aperto de mão (FAM) e índice de massa livre de gordura (IMLG) ou circunferência da panturrilha (CP) reduzidos. Os desfechos avaliados foram tempo de internação hospitalar e mortalidade intra-hospitalar. Testes estatísticos apropriados foram aplicados e p valores <0,05 foram considerados significativos. O protocolo de pesquisa foi aprovado pelo Comitê de Ética do Hospital e todos os pacientes deram seu consentimento.

Resultados: Foram incluídos no estudo 241 pacientes (68,3 ± 10,2 anos e 53,5% mulheres). A prevalência de desnutrição variou entre 20,2% a 54,4%, de acordo com a ferramenta utilizada. O diagnóstico de desnutrição pela AND-ASPEN apresentou melhor acurácia (AUC = 0,837; IC95% 0,783-0,841) e concordância com a ASG (k = 0,674). Além disso, foi preditor de tempo de internação hospitalar prolongado (>14 dias) (OR = 1,73; IC95% 1,01-3,37). Em 208 pacientes foi possível estabelecer o diagnóstico de sarcopenia, sendo identificada em 16,3%. Os fatores associados à presença de sarcopenia foram os estágios 2 e 3 de severidade da doença (OR = 4,69; IC95% 1,30- 16,91) e a presença de desnutrição (OR = 16,46 IC95% 3,50- 77,41). Quando empregada a CP reduzida associada a força do aperto de mão (FAM) reduzida para diagnóstico de sarcopenia, foi identificada prevalência de 20,3% e esse diagnóstico apresentou acurácia satisfatória, (AUC = 0,886; IC 95% 0,811-0,961) e alta concordância (kappa = 0,703, p<0,001) com o diagnóstico realizado a partir da FAM e IMLG reduzidos.

Conclusão: Desnutrição e sarcopenia foram identificados em 20-50% e 16-20% dos pacientes, respectivamente, variando conforme diagnóstico aplicado. A ferramenta da AND-ASPEN apresentou validade preditiva e concorrente satisfatórias em diagnosticar desnutrição no paciente hospitalizado por DPOC exacerbado. Fatores como desnutrição e estágio da DPOC foram associados à presença de sarcopenia, a qual pode ser diagnosticada com a CP como medida de massa muscular quando IMLG não estiver disponível.

Palavras-chaves: doença pulmonar obstrutiva crônica, desnutrição, sarcopenia, hospitalização, mortalidade.

ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) is characterized as a progressive and irreversible limitation of air, and by the presence of systemic inflammation, which is intensified in exacerbation periods. This scenario contributes to an intense protein catabolism and deterioration of the nutritional status of COPD patients. Therefore, the aim of this study was to evaluate the prevalence of malnutrition assessed by different integrative nutritional tools and the concurrent and predictive validity of these to predict in-hospital outcomes. Besides, the sarcopenia prevalence and its associated factors were assessed, as well as the association of it with clinical outcomes in acute exacerbated COPD (AECOPD) patients.

Methodology: Prospective cohort study with AECOPD patients hospitalized in a tertiary public Brazilian hospital. The data collection was performed within the first 72 hours after hospital admission. Malnutrition diagnosis was established by Subjective Global Assessment (SGA), Global Leadership Initiative of Malnutrition (GLIM), Academy of Nutrition and Dietetics–American Society for Parenteral and Enteral Nutrition (AND-ASPEN) and European Society for Clinical Nutrition and Metabolism (ESPEN) criteria. The sarcopenia diagnosis was defined according to the European Work Group on Sarcopenia in Older People (EWGSOP 2) consensus, which considers reduced handgrip strength (HGS) and reduced fat-free mass index (FFMI) or reduced calf-circumference (CC). Length of hospital stay (LOS) and in-hospital mortality were considered as clinical outcomes. Appropriated statistical tests were performed and p values <0.05 were considered significant. The local Ethics Committee approved the study protocol and all patients gave their consent.

Results: Two hundred and forty-one patients were included (68.3 ± 10.2 years old and 53.5% of women). The malnutrition prevalence varied from 20.2% to 54.4%. The AND-ASPEN diagnosis showed better accuracy (AUC = 0.837; 95%CI 0.783-0.841) and concordance with SGA (k = 0.674). Besides, malnutrition by AND-ASPEN was predictor of prolonged LOS (>14 days) (OR = 1.73; 95%CI 1.01-3.37). It was possible to evaluate sarcopenia in 208 patients, with a prevalence of 16.3%. Moderate and severe stages of the disease (OR= 4.69; 95%CI 1.30-16.91) and malnutrition (OR= 16.46; 95%CI 3.50-77.41) were found to be significantly associated to presence of sarcopenia. When low CC associated with reduced HGS was used for the sarcopenia diagnosis, 20.3% of patients presented sarcopenia and this diagnosis showed satisfactory accuracy (AUC = 0.886; 95%CI 0.811-0.961) and high concordance (kappa = 0.703, p<0.001) with the one assessed with reduced FFMI and HSG.

Conclusion: Malnutrition and sarcopenia were identified in 20-50% and 16-20%, respectively, depending on the diagnosis applied. The AND-ASPEN nutritional tool showed satisfactory predictive and concurrent validity to diagnose malnutrition in AECOPD patients. Factors as malnutrition and stage of the disease were associated with the presence of sarcopenia in this sample, which can be diagnosed with reduced CC as marker of muscle mass when the FFMI is not available.

Key words: chronic obstructive pulmonary disease, malnutrition, sarcopenia, hospitalization, mortality.

REFERENCIAL TEÓRICO

Aspectos gerais da doença Pulmonar Obstrutiva Crônica (DPOC)

A DPOC é uma doença crônica, tratável e prevenível, caracterizada pela persistente limitação do fluxo de ar, geralmente progressiva e associada à inflamação crônica das vias aéreas inferiores. É causada principalmente pela exposição a longo prazo a partículas e/ou gases nocivos[1].

A limitação persistente do fluxo aéreo é ocasionada pela destruição do parênquima pulmonar, definido como enfisema pulmonar, e pela inflamação das vias aéreas, denominada bronquite crônica. Tais alterações podem ocorrer de forma concomitante ou isolada, variando de indivíduo para indivíduo[2]. Quando isoladas, apresentam sintomas e características distintas. A bronquite manifesta-se pela presença de tosse crônica e produção de muco, e está associada ao aumento da espessura da parede das vias aéreas inferiores. Já a destruição alveolar, o enfisema, gera redução na capacidade expiratória (capacidade de expansão e força de expiração) pela diminuição da elasticidade alveolar, levando, consequentemente, ao aumento da dispneia, hipoxemia e hipercapnia[1-3].

O enfisema está relacionado principalmente à resposta inflamatória gerada pela exposição crônica a partículas nocivas. A liberação de quimiocinas pelo epitélio recruta células pró-inflamatórias que causam danos e reparo celular constantes, ocasionando a obliteração e limitação das vias aéreas inferiores[4]. Além disso, alguns outros mecanismos influenciam o dano celular, como por exemplo o desequilíbrio na razão proetase-antiprotease. As proteases são enzimas responsáveis pela degradação de proteínas no organismo e são contrabalançadas pelas antiproteases que impedem a destruição de tecidos celulares funcionantes. Porém, na DPOC, há diminuição das antiproteases e aumento das proteases, principalmente as responsáveis pela deterioração das estruturas compostas pela elastina, como por exemplo os alvéolos[5]. A deficiência da alfa-1-antitripsina, inibidor importante das proteases séricas, é um dos fatores genéticos que influenciam esse desequilíbrio[6].

A falta de ar (dispneia) é o principal sintoma relatado pelos pacientes com DPOC e a maior causa de incapacidade funcional e ansiedade; porém, são diversos e ainda incertos os seus mecanismos[7]. Sabe-se que a exposição prolongada aos fatores de risco gera resposta inflamatória

anormal, exagerada, local e sistêmica, caracterizada pela presença excessiva de células pró-inflamatórias no sangue, como linfócitos e neutrófilos[8]. Mudanças estruturais celulares ocorrem devido à inflamação constante e levam à destruição do parênquima pulmonar, resultando em estruturas alveolares inelásticas e incapazes de realizar a expiração de forma efetiva[9]. Assim sendo, após a expiração ineficaz, há retenção gasosa, impedindo a inspiração completa e causando os sintomas da dispneia. Por consequência, há diminuição da capacidade funcional desses pacientes[10]. Além disso, a dispneia crônica causa disfunção na musculatura acessória pelo constante esforço respiratório, o que gera um ciclo vicioso visto que essa musculatura é responsável pela realização da expansão pulmonar durante a inspiração[11].

A hipoxemia (diminuição do oxigênio sérico) e hipercapnia (aumento do dióxido de carbono sérico) são outras características importantes presentes na DPOC. Ambas são consequências da troca gasosa deficitária, tanto pela presença de muco e inflamação, quanto pela diminuição do drive respiratório e destruição de vias aéreas inferiores que reduzem a área de trocas gasosas[10]. Essas anormalidades na ventilação alveolar diminuem a razão perfusão/respiração, responsáveis pela hipoxemia crônica[12]. Comparados com indivíduos hígidos, pacientes com DPOC apresentam maior resistência nas trocas e retenção gasosas, hipoxemia e hipercapnia com piora progressiva nos diferentes estágios da doença[12].

A tosse crônica com produção de muco, frequente em pacientes bronquiolíticos, está associada à inflamação crônica em resposta à exposição aos fatores de risco e, também, ao aumento das células caliciformes e glândulas submucosas, responsáveis pela produção e secreção de muco, que são estimuladas pelo fator de crescimento epidermal, e que se encontra em maiores níveis nessa população[13].

Exacerbação da doença pulmonar obstrutiva crônica

Pacientes com DPOC apresentam sintomatologia de tosse, dispneia e produção de muco de forma crônica, porém, o uso de medicação contínua, a participação em programas de reabilitação pulmonar e, em certos casos, o uso de oxigenoterapia domiciliar, são capazes de manter o paciente estável[1]. Todavia, a exposição a infecções virais e/ou bacterianas podem levar à exacerbação dos sintomas respiratórios, com aumento na produção de muco e piora da dispneia que exigem terapias adicionais às convencionais[14].

As exacerbações são classificadas como leves, quando tratáveis apenas com broncodilatadores, moderadas quando há necessidade de associação com antibióticos ou

corticosteroides, e graves, necessitando de hospitalização[15]. Mais de 50% dos pacientes com DPOC experienciam episódios de exacerbação, e, geralmente, mais de um episódio ao ano[16]. A incidência das exacerbações varia ao longo do ano, sendo mais frequentes no período do inverno, em que há aumento de viroses e doenças respiratórias agudas. Ademais, são associadas com maior tempo de recuperação e inflamação sistêmica quando iniciam no inverno[17].

As exacerbações possuem impacto importante na qualidade de vida desses pacientes. Sintomas de ansiedade, depressão e estresse crônico são frequentemente descritos e relacionados com piora na capacidade funcional[17]. Além do prejuízo na saúde mental e funcional, as exacerbações aumentam o risco para doenças cardiovasculares, neurológicas e endócrinas[18]. Outrossim, essas são responsáveis por aumento importante nos custos hospitalares, redução da função pulmonar e maior risco de mortalidade[19,20].

Hospitalizações por exacerbações pioram sintomas de anorexia, são acompanhadas de febre, aumento do catabolismo proteico e, assim, balanço energético negativo[21]. Esse cenário gera impacto negativo no estado nutricional e aumento da disfunção muscular desses pacientes que podem perdurar por tempo prolongado. Aproximadamente 80% de pacientes com múltiplas internações apresentam disfunção muscular e essa é relacionada com aumento do risco para internação, gerando outro ciclo vicioso[22].

Fatores de risco associados com a DPOC

O principal fator de risco para DPOC é o fumo, porém, mesmo em fumantes pesados, a sua prevalência é inferior a 50%[23]. Portanto, observa-se associação com outros fatores, como fumo passivo, exposições ocupacionais (poluentes orgânicos, inorgânicos ou agentes químicos), estado socioeconômico, genética, sexo e idade[24-26]. Indivíduos com histórico de fumo, tanto de cigarro quanto tabaco, maconha e cachimbo, apresentam pior função pulmonar e maior risco de mortalidade[27,28]. A exposição passiva ao cigarro também está relacionada com piora nos sintomas respiratórios[29]. O uso de cigarro durante a gestação causa danos ao desenvolvimento pulmonar do feto e aumento do risco para parto prematuro[30]. Crianças prematuras, com baixo peso ao nascer, que manifestaram dificuldades no desenvolvimento pulmonar, ou até mesmo que apresentaram episódios recorrentes de infecções pulmonares apresentam maior risco de desenvolvimento de DPOC na fase adulta[31,32].

Frequentemente, a idade mais avançada e o sexo masculino são associados com o maior risco de DPOC, porém, ainda não está claro na literatura se a associação com a idade se dá pelo maior tempo de exposição às partículas poluentes ou pela mudança natural do parênquima pulmonar que propicia o desenvolvimento da doença[33]. Em relação ao sexo, percebe-se, atualmente, um equilíbrio na prevalência entre homens e mulheres. Aliás, mulheres parecem ser mais suscetíveis ao efeito do tabaco quando expostas a mesma quantidade e tempo de uso[34-36].

Diagnóstico

O diagnóstico da DPOC é feito pela avaliação do teste de espirometria. Pacientes com histórico de exposição a fatores de risco e sintomas de dispneia, tosse e secreção são encaminhados para exame para verificação do volume de ar expirado forçadamente após um ponto máximo de inspiração (CVF) e o volume de ar expirado durante o primeiro segundo (VEF1). A partir disso, é realizada uma razão entre esses dois valores e, se VEF1/CVF < 0,7 após uso de broncodilatador é confirmado diagnóstico de DPOC (Figura 1)[1].

A avaliação do nível de limitação do fluxo de ar é recomendada a fim de quantificar o seu impacto na qualidade de vida e risco para possíveis exacerbações. Pontos de corte específicos, propostos pela *Global Initiative Of Chronic Obstructive Lung Disease* (GOLD), classificam a doença em quatro estágios crescentes (GOLD 1, 2, 3 e 4) conforme os valores da espirometria (Tabela 1)[1].

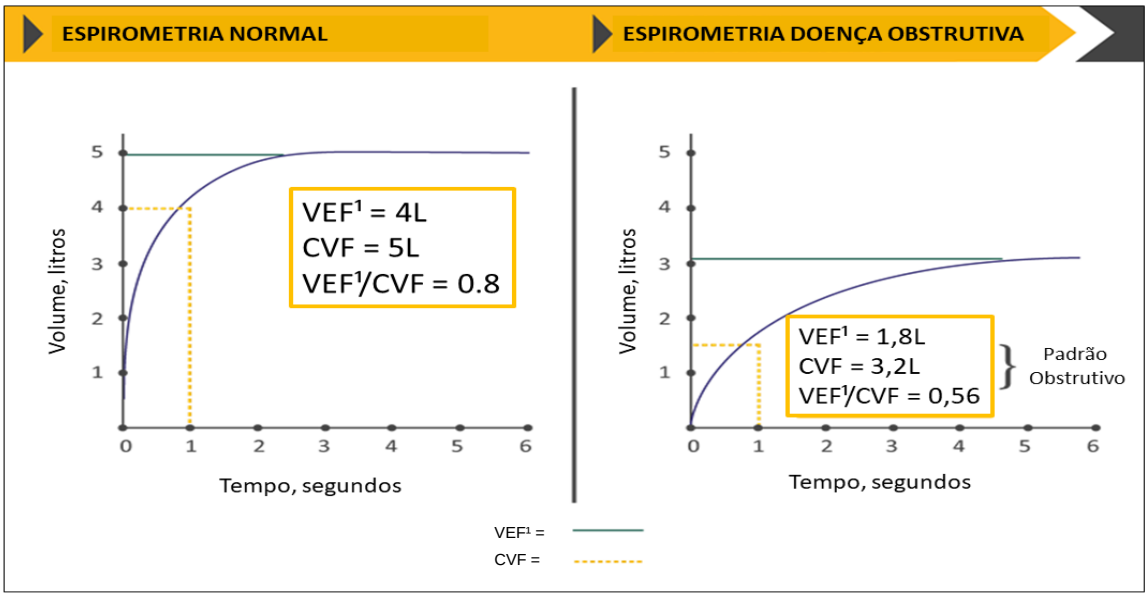

Figura 1. Espirometria de indivíduo hígido x indivíduo com diagnóstico de DPOC.
Fonte: Adaptado do *Global Initiative Of Chronic Obstructive Lung Disease*, 2020.[1]

Para avaliação completa, recomenda-se o uso de ferramentas que mensuram os sintomas e o quanto esses refletem na qualidade de vida. Como por exemplo, a escala para avaliação da dispneia proposta pela *Medical Resarch Councial* (MRC) que diferencia em quatro estágios a falta de ar, sendo o último quartil caracterizado pela presença de falta de ar tão intensa ao ponto de não conseguir sair de casa[37].

Tabela 1. Classificação dos estágios da DPOC pelos valores de espirometria.

Classificação	**Estágio**	**VEF¹ (espirometria)**
GOLD 1	Leve	VEF¹ ≥ 80% do predito
GOLD 2	Moderado	50% ≤VEF¹ < 80% predito
GOLD 3	Severo	30% ≤ VEF¹ < 50% predito
GOLD 4	Muito severo	VEF¹ < 30%

Fonte: Adaptado do *Global Initiative Of Chronic Obstructive Lung Disease*, 2020[1].
Abreviaturas: VEF¹ = volume expiratório forçado no primeiro segundo.

Epidemiologia

Sabe-se que a DPOC ainda é subdiagnosticada, principalmente nos países em desenvolvimento em que o uso da espirometria não é rotina devido ao seu alto custo[1]. Ainda assim, possui prevalência variando de 50% em fumantes pesados e 3 a 11% em não fumantes[38,39]. Estudo multicêntrico realizado em diversas cidades latinas evidenciou prevalência de 14,9% no Brasil, representado pela cidade de São Paulo, sendo, 25,3% DPOC estágio 0, 10,1% estágio 1, 4,6% estágio 2, 0,9 e 0,2% estágio 3 e 4, respectivamente[40].

De acordo com o *Burden Of Obstructive Lung Diseases* (BOLD) a prevalência global de DPOC em homens é de 11,8% e em mulheres de 8,5%[41]. Atualmente, a DPOC é a terceira causa de morte global[42]. Em 2010, o número de casos de DPOC foi de 384 milhões com prevalência global de 11,7%[43]. Cerca de três milhões de mortes são registradas anualmente por DPOC no mundo, e, com o aumento do fumo e envelhecimento da população, é estimado que em 2060 haverá aumento dessa estimativa para mais de cinco milhões[44,45].

Comorbidades associadas

Além de disfunções pulmonares, pacientes com DPOC apresentam comorbidades sistêmicas que influenciam na qualidade de vida, hospitalizações e mortalidade. Dentre elas estão as doenças cardiovasculares, síndrome metabólica, depressão, ansiedade, câncer, osteoporose e disfunções do músculo esquelético[46]. Frequentemente as internações por exacerbação são acompanhadas por comorbidades que acarretam piores complicações, maior tempo de internação e risco de mortalidade intra-hospitalar[47]. Aliás, estudos sugerem que há maior probabilidade desses pacientes irem a óbito pelas comorbidades do que pelo DPOC, sendo extremamente relevante a severidade e estágio do DPOC que podem inverter essa hipótese[48-50].

A disfunção musculoesquelética é uma das comorbidades sistêmicas que mais influencia na sobrevivência e qualidade de vida dessa população. É caracterizada pela perda de força e diminuição da resistência muscular que levam à fadiga. Diferentes mecanismos explicam o desenvolvimento da disfunção muscular[51]. A inflamação sistêmica gera maior estresse oxidativo, e, por consequência, aumento no catabolismo proteico[9]. Além disso, a deficiência da alpha 1-antritripsina leva ao aumento das proteases que podem intensificar a degradação proteica[5,6]. O esforço ventilatório decorrente da dispneia crônica causa anorexia e, assim, redução do consumo alimentar[52]. Portanto, com o maior gasto energético pela inflamação, presença de catabolismo

proteico e redução do consumo alimentar, há balanço energético negativo que acarretará déficit do estado nutricional, principalmente na perda de massa magra[52].

Desnutrição em pacientes com DPOC

De acordo com a *American Society of Enteral and Parenteral Nutrition* (ASPEN), a desnutrição é caracterizada por um desequilíbrio nutricional decorrente do consumo inadequado, aumento das necessidades energéticas e alteração na absorção e utilização de nutrientes[53]. Sendo assim, a perda de peso está frequentemente presente e é associada à redução de massa magra e gordura subcutânea[54]. A inflamação sistêmica, o hipermetabolismo e hipercatabolismo geralmente acompanham essa condição[54].

Na população em geral, a desnutrição no ambiente hospitalar varia de 40 a 60%[55]. No Brasil, dados do Inquérito Brasileiro de Avaliação Nutricional Hospitalar (IBRANUTRI) sugerem que 48% dos pacientes internados em hospitais brasileiros apresentam desnutrição[56]. Maior tempo de internação, risco para mortalidade intrahospitalar, reinternação e complicações durante a internação são desfechos frequentemente associados à desnutrição[57]. De fato, o tempo de internação de pacientes com desnutrição foi em média sete dias superior em comparação a pacientes bem nutridos e a incidência de reinternação também foi superior em pacientes desnutridos (OR=4.33 IC95% 2.66-7.06 e OR=3.36 IC95% 1.99-5.65)[58]. Ainda, outro estudo demonstrou cinco vezes mais chances de mortalidade após 90 dias da internação nos indivíduos desnutridos em comparação àqueles sem desnutrição[59].

Dentre aqueles portadores de DPOC, o estado nutricional tem sido relacionado com diferentes desfechos clínicos, tanto pela desnutrição, quanto pela obesidade. A *European Society of Respirology* (ERS) publicou consenso classificando pacientes com DPOC em diferentes fenótipos de acordo com o estado nutricional, avaliados pela massa livre de gordura (MLG), gordura abdominal e visceral, massa óssea, força muscular e características da disfunção pulmonar (Figura 2). Os principais fenótipos são: a caquexia, representada pelo baixo peso e perda de massa magra que está associada ao fenótipo enfisematoso e aumento do risco para mortalidade e redução de performance física; e a obesidade, representada pelo aumento do índice de massa corporal (IMC) e presença de gordura visceral aumentada, associada ao padrão enfisematoso e maior risco para comorbidades cardiovasculares[60].

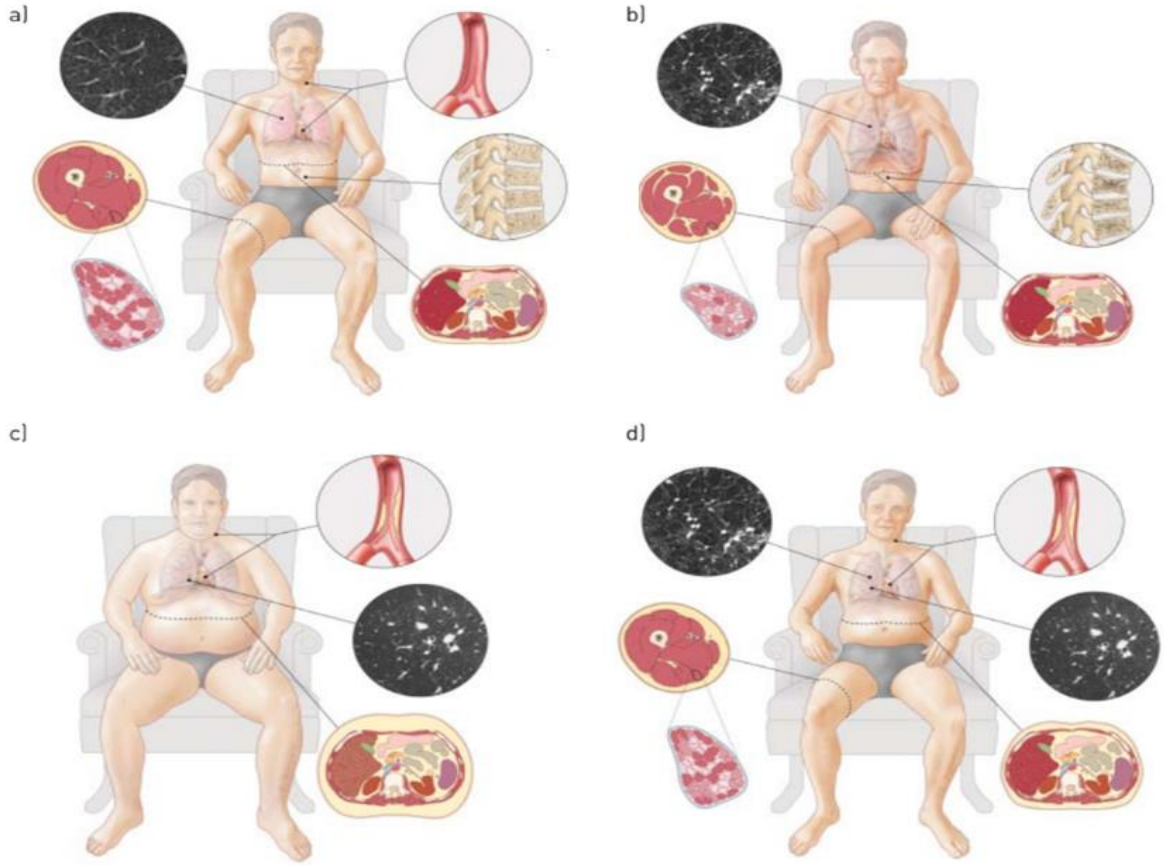

Figura 2. Fenótipos para portadores de DPOC com base no estado nutricional, função pulmonar e presença de disfunção musculoesquelética. a) paciente eutrófico e saudável (referência), com ausência de osteoporose, gordura visceral, placas aterogênicas e presença musculatura adequada. b) paciente com caquexia, presença de enfisema pulmonar, redução de massa magra e infiltração de gordura no músculo e osteoporose. c) paciente obeso, com presença de gordura visceral, placas aterogênicas e bronquiolite. d) paciente obeso sarcopênico, com redução de massa magra, infiltração de gordura no músculo e presença de gordura visceral e placas aterogênicas, não é relacionado a perfil pulmonar específico.

Fonte: Adaptado de *European Society of Respirology Statment*, 2014[60].

A prevalência de desnutrição na DPOC é ampla na literatura, variando de 10-50%[61-65]. Além do mais, cerca de 10% dos pacientes apresentam caquexia, 12% desnutrição sem inflamação, 24% sarcopenia e 14% sarcopenia severa[62]. A etiologia da desnutrição é multifatorial e está presente principalmente nos pacientes com padrão enfisematoso. O fumo, o consumo alimentar insuficiente, a hipoxemia e hipercapnia, o uso crônico de esteroides, comorbidades sistêmicas e a idade são alguns dos fatores que influenciam no desenvolvimento da desnutrição. É importante ressaltar que a exacerbação é uma complicação da DPOC que contribui para o desenvolvimento da desnutrição e que essa, por sua vez, predispõe o paciente a novos episódios de exacerbação (Figura 3)[51].

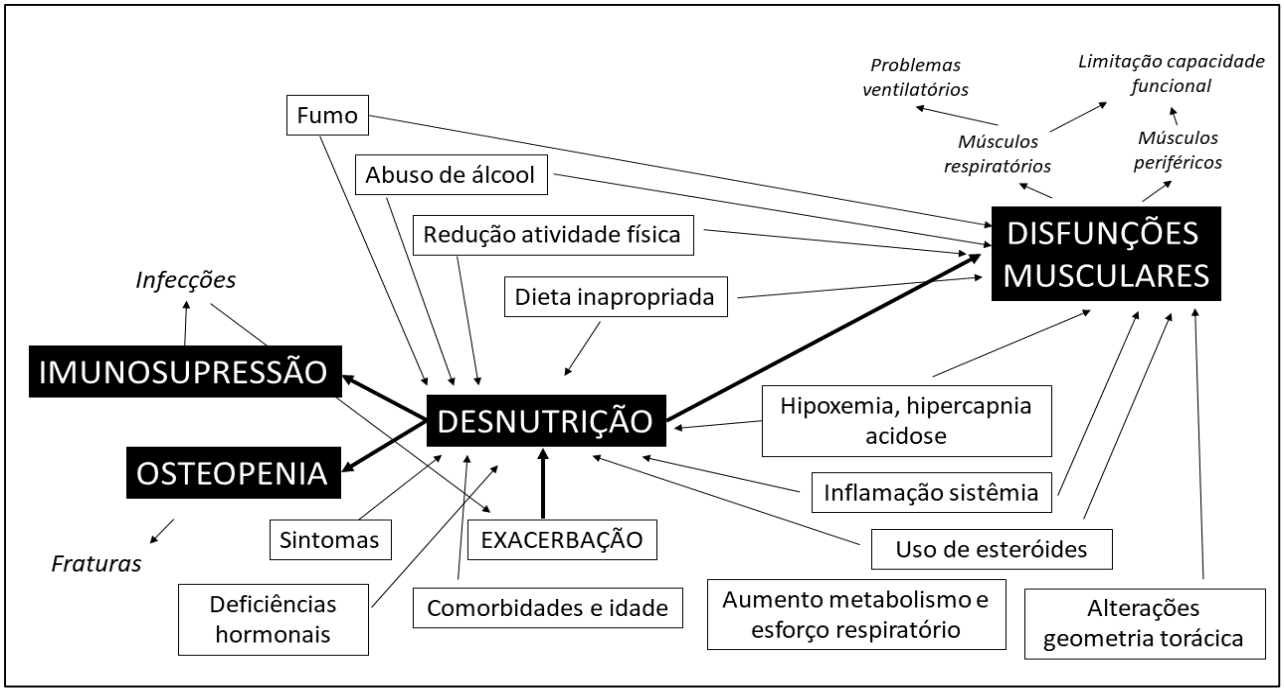

Figura 3. Diferentes fatores que contribuem para a desnutrição e/ou disfunções musculares em pacientes com DPOC e suas consequências.
Fonte: Adaptado de Gea J e colaboradores[51].

A presença de desnutrição nessa população está relacionada com maior incidência de mortalidade, pior função pulmonar, aumento da incapacidade física e piora na qualidade de vida[66-68]. De fato, estudo transversal com 168 pacientes estáveis apontou 74,4% de desnutrição e 89,9% reportaram perda de peso não intencional. A desnutrição foi relacionada com a severidade da doença, consumo insuficiente de proteína e menores valores no questionário de qualidade de vida[69]. Em estudo que compilou dados de diferentes coortes totalizando 287 mil pacientes com DPOC não dependentes de ventilação mecânica (VM) e 15829 dependentes de VM, a presença de desnutrição foi associada a maior incidência de hospitalizações, tempo de internação prolongado e mortalidade (HR = 2,3; IC 95% 2,2- 2,3). Além disso, os custos hospitalares com pacientes desnutridos foram 75% maiores do que com pacientes sem desnutrição[70].

O padrão-ouro para avaliação da composição corporal de indivíduos hígidos é a *dual x-ray absormetry* (DEXA), a qual também é adequada para pacientes com DPOC[71]. Entretanto, seu alto custo dificulta a utilização em diversos estudos científicos e na prática clínica diária. Logo, outros parâmetros estão descritos na literatura para avaliação nutricional nessa população[72]. A albumina sérica e o IMC, por exemplo, foram capazes de predizer desnutrição, e o NRS- 2002 capaz de avaliar risco nutricional em estudo observacional retrospectivo realizado com 438 pacientes com DPOC hospitalizados. Além disso, todas as ferramentas apresentaram associação com desfechos clínicos, como mortalidade hospitalar, mortalidade após 1 ano e reinternação em 30 dias[73].

Sabe-se que a avaliação subjetiva global (ASG) é considerada método de referência para diagnóstico de desnutrição em pacientes hospitalizados[74]. Em pacientes com DPOC, busca da literatura realizada no *Pubmed*® identificou poucos estudos que avaliaram desnutrição a partir dessa ferramenta. Dentre eles, estudo com pacientes com DPOC estáveis demonstrou que pacientes desnutridos apresentaram maior risco para mortalidade em um ano e reinternação hospitalar. Além disso, os pacientes desnutridos apresentaram duas vezes maior tempo de internação hospitalar quando comparados ao bem nutridos[75]. Outro estudo, também realizado com pacientes com DPOC estáveis, demonstrou associação entre a presença de desnutrição diagnosticada pela ASG e piora da função pulmonar, dispneia e qualidade de vida. Porém, os achados desse estudo foram avaliados somente por análises univariadas o que não permite

identificar se a desnutrição é preditor independente dos desfechos clínicos descritos pelos autores[76]. Dentre os estudos conduzidos com pacientes exacerbados, somente um deles avaliou a associação entre desnutrição diagnosticada pela ASG e função pulmonar, sendo demonstrado menores valores de VEF^1, CVF e VEF^1/CVF em pacientes com ASG B e C quando comparados a pacientes com ASG A[77]. Porém, os autores não trazem no estudo a comparação estatística desses dados. Observa-se, portanto, que são escassos os estudos que utilizam a ASG como ferramenta de diagnóstico nutricional, principalmente nos pacientes com DPOC exacerbado e não há dados na literatura em relação à associação estatística entre desnutrição pela ASG e função pulmonar e outros desfechos clínicos.

A fim de desviar o foco do diagnóstico nutricional a partir do IMC, haja vista a limitação do mesmo em diferenciar composição corporal e em identificar alterações do estado nutricional, a *American Society of Parenteral and Enteral Nutrition* (ASPEN) propôs novo critério para diagnóstico de desnutrição mais objetivo, robusto e multifatorial. A desnutrição, conforme proposta pela sociedade, possui etiologia por doença crônica ou aguda e é avaliada pela presença de no mínimo dois dos seis critérios, sendo eles: perda de peso, consumo alimentar reduzido, perda de massa muscular e gordura subcutânea, redução da força do aperto de mão (FAM) e presença de edema/ascite[53]. Ainda, é possível realizar a identificação da severidade da desnutrição avaliado a partir de pontos de cortes pré-estabelecidos dos critérios descritos acima. Até o presente momento, não foram publicados estudos avaliando a desnutrição pela ferramenta proposta pela ASPEN em pacientes com DPOC.

A *European Society of Enteral and Parenteral Nutrition* (ESPEN) publicou consenso em 2015 apresentando um novo critério para diagnóstico de desnutrição na população hospitalizada. Há duas possibilidades de realizar o diagnóstico, a primeira se dá pela presença de IMC < 18,5kg/m², e, a segunda pela perda de peso >10% por tempo indefinido, ou >5% nos últimos três meses associada ao IMC < 20kg/m² em adultos (<70 anos) e < 22kg/m² em idosos maiores de 70 anos ou à redução de massa livre de gordura (IMLG = <15 e <17 kg/m² em mulheres e homens, respectivamente)[78]. Estudo de coorte prospectivo avaliou quais componentes desse critério poderiam predizer desfechos clínicos em indivíduos hospitalizados com DPOC. Foi observado 19% de desnutrição nessa amostra e o único componente capaz de predizer mortalidade foi a perda de peso, porém, após ajuste para função pulmonar, a significância estatística foi perdida[79].

Recentemente, a *Global Clinical Nutritional Community* lançou uma ferramenta para

avaliação de desnutrição em pacientes hospitalizados. Essa é definida por critérios fenotípicos – perda ponderal, IMC reduzido e massa muscular reduzida - e critérios etiológicos – redução do consumo alimentar e presença de inflamação. A presença de pelo menos um critério de cada caracteriza desnutrição. Após, classifica-se a severidade da desnutrição em estágio 1 (desnutrição moderada) e estágio 2 (desnutrição grave) com base nos critérios fenotípicos[80]. Por ser uma ferramenta recente, sua validade ainda não foi testada, mas pode ser promissora para diagnóstico de desnutrição em pacientes com perda de massa muscular e inflamação crônica, como naqueles com DPOC.

Sarcopenia em pacientes com DPOC

Além da desnutrição, pacientes com DPOC apresentam maior risco para desenvolvimento de sarcopenia, decorrente principalmente da disfunção muscular. As alterações musculares características da DPOC são multifatoriais. Um dos possíveis mecanismos para a disfunção muscular nesses pacientes descritos na literatura é a desregulação na sinalização do turnover proteico, o qual é mais proeminente em pacientes com sarcopenia quando comparados a controles. Aumento na sinalização miogênica e do *turnover* levam à degradação proteica e alterações moleculares associadas ao reparo e remodelamento das fibras musculares[81].

De acordo o *European Working Group on Sarcopenia in Older People* (EWGSOP), a sarcopenia é caracterizada pela perda de força associada à redução de massa magra, classificada como sarcopenia severa quando há redução na capacidade funcional associada. O consenso sugere que a força seja avaliada pela aferição da força do aperto de mão (FAM) com dinamômetro calibrado. A massa magra deve ser avaliada pela massa magra apendicular, aferida pelo *dual x-ray absormetr*y (DEXA), bioimpedância elétrica (BIA) ou por tomografia computadorizada. Para avaliação da funcionalidade, recomenda-se a velocidade de marcha, testes de caminhada ou o s*hort physical performance battery* (SPPB) [82].

Revisão sistemática com metanálise de estudos transversais reportou prevalência de sarcopenia na DPOC variando de 7,9 a 66,7% quando estratificada de acordo com a origem da população (hospitalar, comunidade ou clínicas), sendo a estimativa média ponderada da prevalência na população total de 21,6%. Ainda, a chance para desenvolvimento de sarcopenia no paciente com DPOC foi duas vezes maior do que na população em geral (OR= 2,0; IC 95%

1,2 – 3,2). Os principais fatores associados com sarcopenia foram idade, marcadores inflamatórios sistêmicos, IMC, severidade da doença, dispneia e presença de doença cardiovascular[85]. No ambiente hospitalar, não foram encontrados estudos na literatura avaliando a associação da presença de sarcopenia com desfechos clínicos.

A sarcopenia é frequentemente associada à presença de desnutrição. De fato, 24% dos pacientes de uma coorte que avaliou a presença de sarcopenia e desnutrição no DPOC apresentavam ambas doenças concomitantemente[62]. Porém, já é descrita a existência de sarcopenia em pacientes obesos que pode levar a maior risco de desfechos clínicos tão importantes quanto na população desnutrida[86]. Estudo de casos e controles que avaliou a presença de obesidade sarcopênica (OS) em indivíduos com DPOC reportou aumento de 3 vezes na chance de desenvolver OS em indivíduos com DPOC. Ainda, a OS foi associada ao aumento da inflamação sistêmica (OR 1,6; IC95% 1,1-2,5)[87].

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JUSTIFICATIVA

Diante do risco de piores desfechos clínicos associados ao comprometimento do estado nutricional de pacientes com DPOC, a identificação dos métodos mais acurados para diagnóstico nutricional é necessária para que protocolos especializados possam ser construídos e inseridos na rotina de atendimento nas unidades de pneumologia. Considerando que, o IMC, apesar de amplamente empregado em pacientes com DPOC e de seu valor prognóstico reconhecido nessa população, não é capaz de identificar precisamente comprometimento do estado nutricional por não diferenciar os compartimentos corporais e não revelar alterações do estado nutricional. Além disso, se faz necessário a compreensão da relação entre presença de sarcopenia em pacientes hospitalizados por exacerbações e desfechos clínicos, bem como dos fatores clínicos, nutricionais e sociodemográficos associados a maior chance de essa doença musculoesquelética estar presente nos pacientes com DPOC e alternativas mais práticas para o seu diagnóstico na prática clínica. No Brasil, estudos nessa área são escassos e há uma demanda crescente devido ao aumento de exposições a fatores de risco e às projeções estimadas da doença para o futuro, especialmente naqueles com fenótipo exacerbador tendo em vista o pior prognóstico associado às exacerbações.

OBJETIVOS

Objetivo geral

Avaliar a prevalência de alterações do estado nutricional em pacientes com DPOC hospitalizados por exacerbação da doença e a possível associação dessas com desfechos clínicos intra-hospitalares.

Objetivos específicos

Avaliar a prevalência de desnutrição e de sarcopenia em pacientes com DPOC hospitalizados na admissão hospitalar.

Avaliar a validade concorrente de diferentes ferramentas integrativas para diagnóstico de desnutrição em pacientes com DPOC hospitalizados com a ASG como método referência.

Avaliar a associação entre desnutrição e tempo de internação hospitalar e mortalidade intrahospitalar em pacientes com DPOC a fim de verificar a validade preditiva de diferentes ferramentas integrativas para diagnóstico nutricional.

Avaliar fatores associados à presença de sarcopenia em pacientes com DPOC admitidos no hospital por exacerbação da doença.

Avaliar a associação entre sarcopenia e tempo de internação hospitalar, e mortalidade intrahospitalar em pacientes com DPOC.

Avaliar a validade concorrente do diagnóstico de sarcopenia pela circunferência da panturrilha com o IMLG como referência para marcador de massa magra.

ARTIGO 1

Malnutrition in acute exacerbated patients with chronic obstructive pulmonary disease - comparative analysis of the accuracy of AND-ASPEN, ESPEN, and GLIM Consensus: a cohort study

Keywords: malnutrition, COPD, hospitalization, mortality, ROC curve.

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Malnutrition in acute exacerbated patients with chronic obstructive pulmonary disease - comparative analysis of the accuracy of AND-ASPEN, ESPEN, and GLIM Consensus: a cohort study

Research Snapshot

Research Question:

Do new integrative tools for diagnosing malnutrition (e.g., Academy of Nutrition and Dietetics-American Society for Parenteral and Enteral Nutrition [AND-ASPEN], European Society for Clinical Nutrition and Metabolism [ESPEN], and Global Leadership Initiative on Malnutrition [GLIM]) have satisfactory concurrent and predictive validity in acute exacerbated chronic pulmonary obstructive disease (AECOPD) patients?

Key Findings:

In this prospective cohort study AND-ASPEN consensus had the best accuracy and concordance with subjective global assessment (SGA), and it was an independent predictor of prolonged hospitalization. Due to AND-ASPEN satisfactory concurrent and predictive validity, it should be applied for diagnosing malnutrition in AECOPD patients.

Malnutrition in acute exacerbated patients with chronic obstructive pulmonary disease - comparative analysis of the accuracy of AND-ASPEN, ESPEN, and GLIM Consensus: a cohort study

Abstract

Background: Malnutrition in patients with chronic obstructive pulmonary disease (COPD) is prevalent and usually assessed by body mass index, which can lead to misdiagnosis. Subjective global assessment (SGA) is the reference method for malnutrition diagnosis, and new tools have emerged in the last 10 years (e.g., Academy of Nutrition and Dietetics-American Society for Parenteral and Enteral Nutrition [AND-ASPEN], European Society for Clinical Nutrition and Metabolism [ESPEN], and Global Leadership Initiative on Malnutrition [GLIM]).

Objective: To assess the concurrent and predictive validity of integrative tools for diagnosing malnutrition in acute exacerbated COPD (AECOPD) patients.

Design: Prospective cohort study.

Participants/setting: It was conducted in a tertiary Brazilian hospital with AECOPD patients.

Main study factor: Malnutrition was diagnosed by SGA (reference method), AND-ASPEN, ESPEN, and GLIM consensus in the first 72 h of hospital admission.

Main outcomes: Hospital length of stay (LOS) and mortality.

Statistical analysis: Concurrent (ROC curve construction and kappa coefficient) and predictive validity (Logistic/Cox Regression) were tested. P values < 0.05 was considered significant.

Results: In a sample of 241 patients (46.5% males; 68.3 ± 10.2 years old), the prevalence of malnutrition was 50.0% by SGA, 54.4% by AND-ASPEN, 20.2% by ESPEN, and 47.8% by GLIM. AND-ASPEN had the best accuracy (AUC=0.837; 95%CI 0.783-0.841) and concordance (kappa = 0.674) with SGA and it was an independent predictor of prolonged LOS (OR = 1.73; 95%CI 1.01-3.37). ESPEN consensus did not agree with SGA but was associated with prolonged LOS (OR = 2.57 95%CI, 1.27-5.20). The GLIM had good concordance (kappa = 0.533) and accuracy with SGA (AUC = 0.768; 95%CI 0.701-0.835) but was not associated with any clinical outcomes.

Conclusion: The AND-ASPEN consensus was the most accurate integrative tool for diagnosing malnutrition in AECOPD patients and should be included in nutritional protocols of pneumology hospital settings.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by a progressive limitation of breathing, chronic dyspnea, and systemic inflammation. It is prevalent in 11.8% of the men and 8.5% of the women, globally. Annually, around three million deaths due to COPD are registered, and it is estimated that in 2060, there will be close to five million deaths per year [1]. Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a frequent event that affects these patients. It is characterized by an acute increase in basal dyspnea, usually associated with a bacterial or viral infection, which can lead to hospitalization [2].

Malnutrition in COPD patients is highly prevalent, with a prevalence ranging from 20% to 60%, according to the nutritional methods applied for diagnoses [3-9]. The presence of malnutrition has been associated with a decrease in quality of life, reduced pulmonary function, increased incidence of breathlessness, high risk of exacerbation and consequent hospitalization [10-13]. Most of the studies on malnutrition in COPD patients, available in literature, use the body mass index (BMI) for malnutrition diagnosis [3,8,14-20]. However, BMI considers only the total body mass per height and do not differentiate body composition, reduction in food consumption, weight loss, and other variables that encompass malnutrition. Furthermore, BMI do not reflect age-related changes in height or fat/muscle mass in the elderly and is a less reliable marker of nutritional status in this population than in younger age groups. Therefore, it is important to understand that a high BMI do not rule out malnutrition [21].

Because of the limitations with the use of BMI, in hospital settings, the global reference method for malnutrition diagnosis is the Subjective Global Assessment (SGA), as it has been well established as a prognostic method for clinical and surgical patients [22,23]. Its predictive validity has also been demonstrated in COPD patients [5,24-27]. However, because of its subjectivity, its accuracy and reproducibility may be questionable.

In the last 10 years, integrative nutritional tools have been proposed by different nutrition societies. One of them was proposed by the European Society for Clinical Nutrition and Metabolism (ESPEN) and considers BMI < 18.5 kg/m² or unintentional weight loss combined with reduced BMI or reduced fat free mass index (FFMI) as a diagnostic criterion [28]. The American Society of Parenteral and Enteral Nutritional (ASPEN), along with the Academy of Nutrition and Dietetics (AND), proposed a consensus that classifies malnutrition as chronic or acute disease based on unintentional weight loss, reduction in food consumption, reduced

handgrip strength (HGS), loss of muscle mass and subcutaneous fat, edema, and ascites assessed by physical exam [29]. The most recent integrative nutritional tool was proposed by the Global Initiative of Malnutrition (GLIM), and it diagnoses malnutrition by the presence of at least one phenotypic (weight loss, low BMI, and reduced muscle mass) and one etiologic criterion (reduced food consumption, impaired assimilation of nutrients and inflammation) [30].

Till date, the predictive and concurrent validity of these nutritional tools have been scarcely assessed in COPD patients. Only one study evaluated the predictive validity of the ESPEN criteria for malnutrition diagnosis in AECOPD patients, but did not demonstrate any association between malnutrition and the clinical outcomes evaluated (prolonged length of hospital stay [LOS], severity of disease, readmission, and mortality) [6]. Recent AND consensus on the nutrition care process in COPD patients did not describe the guidelines on the nutritional assessment owing to the lack of studies in this field. Besides that, the AND emphasizes the importance of and need for studies in this regard [31]. Thus, the aim of the current study was to evaluate the prevalence of malnutrition in AECOPD patients and to assess the concurrent and predictive validity of the emergent integrative tools that are proposed for diagnosing malnutrition.

Methods

Design

This was a prospective cohort study performed in a public tertiary hospital at Porto Alegre (Rio Grande do Sul, Brazil) approved by the Local Ethical Committee (approval number 3.126.689).

It was conducted according with Brazilian Resolution for ethical in research involving humans (http://www.conselho.saude.gov.br/resolucoes/2012/Reso466.pdf).

Sample

The sample was composed of hospitalized patients with AECOPD according to medical diagnosis in the electronic records. Patients who were lucid, orientated, and able to walk, without amputation of superior and/or inferior members were recruited to the study. Patients with no recorded diagnosis of AECOPD were excluded.

The sample size was calculated using an online calculator considering the results of Ester Marco et al. study, which aimed to identify the association between malnutrition and mortality in hospitalized patients with COPD [6]. Pondering the ratio of well nourished to malnourished patients of 4.0, the relative frequency of positive not exposed (death in well-nourished patients) of 12.1%, and the hazard ratio (HR) of 3.85, the calculated sample, at 80% power and 5% significance, was equal to 179 patients. With an additional of 20% to account for possible loss to follow-up and adjustments for confounders in the multivariate analysis, the estimated sample for this study was 215 patients (http://www.openepi.com/Menu/OE_Menu.htm).

Study Protocol

Data were collected within the first 72 hours after hospital admission by four trained researchers at each patient's bedside between March 2019 and March 2020. The informed consent form was read to the eligible patients and the data collection was started only after they signed the form. Socioeconomic and demographic data, such as age, sex, origin, and ethnicity were collected by a standard form. Medical history, clinical laboratory exams, such as C-reactive protein, and pulmonary functional tests were collected from electronic records.

Those patients with spirometry exam tests available in the last year had the diagnosis of COPD confirmed by the forced expiratory volume in the first second/final vital capacity (FEV_1/FVC) ratio of <70% after bronchodilator use. The disease stage was classified according to Global Initiative for Chronic Obstructive Lung Disease – GOLD in 1 (mild), 2 (moderate), 3 (severe), or 4 (very severe) – considering the FEV_1 values [1]. The modified Medical Research Council scale, validated for the Portuguese language (mMRC) was applied to identify the severity of dyspnea, and those with score greater than three points were considered to have reduced daily activities due to dyspnea [32].

Nutritional assessment encompassed anthropometric, functional, and subjective assessments as well as impedance bioelectrical tests in order to fulfill the criteria of SGA [33], ESPEN [28], ASPEN [29], and GLIM [30] as detailed bellow. Patients were followed until discharge by electronic records to assess the outcomes of interest.

Nutrition assessment

Anthropometric measures, i.e., body weight and height, were recorded, and with these data, the BMI was calculated as body weight/height^2. Usual body weight (previous 6 months) was self-reported, and the percent of body weight loss (%BWL) was calculated as follows: %BWL = (usual body weight - actual body weight)*100/ usual body weight. Body weight and height were measured with patients wearing light clothing and no shoes, with a portable weight balance (Plena®) and portable stadiometer (Sanny®).

Handgrip strength was measured with a calibrated dynamometer Saehan®. Patients were instructed to hold the device with the non-dominant hand, position the elbow at 90º, and press the device with maximal strength. The test was repeated three times with 1 minute rest between each test. The highest value was compared with the reference values and HGS was considered to have reduced based on the cutoff points below the 5th percentile proposed in a Brazilian study [34]. Functional capacity was also subjectively assessed by patient perception and classified as normal, reduced, or bedridden.

Temporal muscle wasting, wasting of pectoral and deltoid muscles (supraclavicular and infraclavicular areas), and of quadriceps and gastrocnemius muscles were assessed by physical examination. The magnitude of wasting was classified as “normal,” “mild,” “moderate,” or “severe.” Physical examination of the orbital region, triceps, and fat overlying the ribs was performed, and the loss of subcutaneous fat was classified as “normal,” “mild,” “moderate,” or “severe”. Generalized or localized fluid accumulation evaluation of the extremities and/or ascites was performed and classified as “normal,” “mild,” “moderate,” or “severe” [35].

A qualitative self-report questionnaire of intake was carried out through the percent of food intake (100%, 75%, 50%, 25%, 0%); patients chose the portion that represented their food intake in the last week, month, and last three months. Patients were also asked about the diet consistency, and the presence of gastrointestinal symptoms in the last 2 weeks.

Bioelectrical impedance analysis was performed to assess the skeletal muscle mass. Each patient was asked to lay in the supine position for 10 minutes; after that, two distal electrodes were placed on the dorsal region of the right hand between the metacarpal and phalanx of the hand and metatarsus and phalanx of the right foot. The two proximal electrodes were placed on the styloid process and malleolus of both the right hand and foot. A frequency of 50-kHz was used to assess data on reactance, resistance, lean mass, and phase angle. The equation proposed by Gonzalez et al. was used to estimate the FFM [36], and the FFM index (FFMI) was calculated as

FFM (kg) divided by body height². The cutoff points adopted to classify reduced muscle mass were <17 kg/m² for men and <15 kg/m² for women [37]. This test was not performed in patients with BMI >35 kg/m^2, in those with a pacemaker or metallic prothesis, and in patients with edema and/or ascites.

Considering the data obtained above, malnutrition was diagnosed according to SGA [33], ESPEN [28], AND-ASPEN [29], and GLIM [30] Consensus. The variables employed in malnutrition diagnosis by each tool are summarized in **Table 1**.

Clinical outcomes

Patients were followed until hospital discharge and the outcomes of interest (LOS, and intra-hospital mortality) were collected from their electronic records. For data analyses, the LOS was categorized by median values, and values equal to or higher than the median were considered prolonged hospitalization.

Statistical analysis

Quantitative variables were described as mean and standard derivation, when parametric, and as median and interquartile range, when non-parametric, and the categorical variables were expressed as absolute and relative frequency. The normality of the quantitative variables was assessed by the Kolmogorov-Smirnov test. To compare the frequency of malnutrition and general features between patients grouped according to the outcomes, student's *t* test, Mann-Whitney *U* test, Chi-square, or Fisher Exact test was performed.

The concurrent validity of AND-ASPEN, ESPEN, and GLIM to identify malnutrition, considering SGA as the reference method, was tested by the kappa (k) coefficient and by the construction of receiver operating characteristic (ROC) curve. The area under the curve (AUC) (95% confidence interval [CI]) was calculated. For kappa classification, the following reference values were considered: <0.20, poor; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; 0.81–0.99, almost perfect; and 1.00, perfect [38]. Data on sensitivity, specificity, and positive and negative predictive values were obtained, using the following cutoffs for interpretation: 90 to 100% high, 80 to ≤89% moderate, ≤79% low [39]. The AUCs of the different nutritional tools applied were compared using the Delong in the MedCalc software [40].

Logistic regression and Cox regression were performed to assess the association between malnutrition and prolonged LOS and in-hospital mortality, respectively (predictive validity of integrative tools for malnutrition diagnosis test). Multivariable analysis was performed considering age, sex, and mMRC score as confounders.

Data were analyzed in IBM SPSS Statistics for Windows, version 20.0 program, and values of $P<0.05$ were considered statistically significant.

Results

General features of the sample

A total of 241 patients were included in the current study. The general features are detailed in **Table 2**. Most of them were female, white, aged above 60 years old, and were from Porto Alegre.

Spirometry test data were available for 140 patients (58%), COPD diagnosis was confirmed for all, and among them, 41.4% were classified as GOLD 3 (the most frequent grade of disease). Reduction in daily activities due to dyspnea according to the mMRC scale was reported in more than two-thirds of the sample.

Nutritional diagnosis could not be carried out by SGA for one patient because the information on weight loss was not reported, and according to this tool, 50% of the sample was malnourished (22.9% with SGA B and 27.1% with SGA C). The ASPEN criteria could not be fulfilled in two patients because of the lack of information on weight loss for one patient and difficulty in evaluating HGS in another patient; in the remaining patients (n = 239), 34.3% presented moderate malnutrition and 20.1% severe malnutrition. The GLIM criteria were applied in 206 patients because data on C-reactive protein was not available for all patients (47; 19.5%) and FFMI was not measured in patients with edema, ascites, or obesity (65; 27.0%). According to this tool, 20.8% presented moderate malnutrition and 26.6%, with severe malnutrition. The ESPEN criteria could be fulfilled in 234 patients and 20.2% of them were diagnosed as malnourished (in seven patients, the information on FFMI was not available and it made impossible to determine the diagnose).

The median of LOS was 11 (7-13) days, and eighteen (7.5%) patients died before hospital discharge.

Concurrent validity of the nutritional assessment tools for malnutrition diagnosis

The AND-ASPEN criteria showed the best concordance with the SGA as well as the highest accuracy, as demonstrated by the kappa value and AUC of ROC curve. These results, as well as the values of sensitivity, specificity, PPV, and NPV for all tools tested are described in **Table 3**. The AUC of the AND-ASPEN consensus was significantly higher than the AUCs of GLIM and ESPEN ($p = 0.040$ and $p < 0.0001$, respectively), and the AUC of ESPEN was lower than that of GLIM ($p = 0.002$).

Predictive validity of the nutritional assessment tools

The association between malnutrition and prolonged LOS or in-hospital death was investigated by bivariate and multivariate analyses to assess the predictive validity of the tools.

According to the bivariate analysis results, presented in **Table 4**, patients with prolonged LOS (≥11 days) were more frequently malnourished according to the AND-ASPEN, ESPEN criteria, and SGA than patients with LOS <11 days. The frequency of malnourished patients by GLIM did not differ between the groups. Females were less frequent in patients with prolonged LOS than in theses with LOS < 11 days (44.4% vs. 63.2%, $p = 0.003$). Higher frequency of mMRC >3 (85.5% vs. 77.6%, $P = 0.158$) was observed in patients with prolonged LOS than in those without. The other general features did not differ between groups (data not showed).

According to the multivariate analysis, adjusted for sex and mMRC score, malnutrition identified by the AND-ASPEN and ESPEN criteria significantly increased the odds for prolonged hospitalization (**Table 5**). Malnourished patients according to the AND-ASPEN and ESPEN criteria had a 2.57- and 1.73-fold higher likelihood of hospitalization for more than 11 days, respectively, than those who were not malnourished.

On comparing the data of survivors and non-survivors, the frequency of malnutrition did not differ between groups, independent of the diagnostic tool used (**Table 4**). All non-survivors showed an mMRC score >3, whereas 80.2% of the survivors showed a high dyspnea score ($P = 0.050$). The other general features did not differ between patients according to in-hospital mortality (data not presented). On multivariate analysis, similar results were obtained, and malnutrition was not a significant predictor of in-hospital death, as presented in **Table 5**.

Discussion

The aim of the present study was to evaluate the prevalence of malnutrition in AECOPD patients and to determine which tool could accurately diagnose malnutrition and predict outcomes. The prevalence of malnutrition varied from 20% to 54%, depending on the tool applied. The AND-ASPEN consensus showed the most satisfactory accuracy and concordance with SGA in identifying malnourished patients. The diagnoses made by the AND-ASPEN and ESPEN criteria were independent predictors of prolonged LOS.

The prevalence of malnutrition in our sample was approximately 50%, excluding the diagnosis by ESPEN since it did not present good concordance with the SGA. The prevalence of malnutrition reported by studies involving patients with COPD varied from 20% to 60% [3-9]. A metanalysis with pulmonary inpatients showed a prevalence of 32% [41]. However, most of the studies on malnutrition in COPD patients used reduced BMI to diagnose malnutrition, and it can justify the underreported prevalence of malnutrition. BMI does not consider different body compositions or weight loss, which is essential for identifying malnourished patients. In fact, malnutrition and loss of muscle mass can be observed in patients with normal BMI. A population-based study with COPD patients showed that 26.1% of the patients with normal BMI had an FFMI lower than the 10th percentile [42]. A recent review of nutritional assessment in COPD patients concluded that the use of BMI for nutritional diagnosis will miss important changes in body composition related to poor clinical outcomes and to under diagnose of malnutrition [43].

SGA is the reference standard for the diagnosis of malnutrition in hospitalized patients. It has already been validated by numerous studies and associated with mortality, prolonged LOS, clinical complications, and worse outcomes in inpatients [22,23]. Regarding COPD, the few studies that applied the SGA involved stable COPD patients and demonstrated malnutrition rates ranging from 13% to 74% [5,24-26]; one study that evaluated malnutrition in AECOPD presented a higher prevalence of 83% [27]. In the present study, 50% of the malnourished patients were identified by the SGA, and this difference can be explained by the subjectivity of the SGA that is strictly dependent on the interpretation of the examiner as well as the methodology of SGA application. Gupta et al. [27] applied a scoring system, while we followed the protocol proposed by Detsky et al. that considers weight loss, food consumption, and physical exam results as the major

components of diagnosis by SGA[33]. Although SGA is considered a predictor of worse outcomes in general clinical and surgical patients, in our study, there was no association between malnutrition diagnosed by this tool and prolonged hospitalization or in-hospital mortality. One study involving stable COPD patients showed a positive association between malnutrition and 30-day mortality [9], while another study involving AECOPD patients did not show such an association [27]. Perhaps, in these patients, as in our sample, exacerbation was the major predictor of death, independent of nutritional status. This aspect should be further investigated in future studies with stable and AECOPD patients.

In the current study, the GLIM criterion demonstrated fair accuracy in identifying malnutrition, and the prevalence was significantly lower than that obtained with the AND-ASPEN; the concordance with SGA was moderate. One study evaluated the sensitivity and specificity of GLIM with SGA as the reference and demonstrated a sensitivity of 61.3% and a specificity of 89.9% [44], similar to this study. We did not find any study available in the literature that assessed the AUC and kappa values of GLIM with SGA as the reference, as we did in this study. Regarding the concurrent validity of the GLIM, malnutrition diagnosed by it was not a predictor of prolonged LOS and in-hospital death in our sample, in contrast to the results of some studies involving hospitalized patients (individuals with hematological malignity had 3.55-fold higher risk of mortality, surgical patients had a 1.29-fold higher chance of complications and 2.15-fold higher risk of death in 30 days, and general inpatients had 3.23-fold higher odds of sarcopenia) [45-47]. In this study, only the FFMI was applied to assess muscle mass, and increased CRP was considered to indicate inflammation, and the adoption of these parameters, which better reflect the phenotypic and etiologic criteria, can explain the divergence in the results.

The ESPEN consensus, in the present study, did not have good concordance and accuracy with the SGA; however, it was associated with prolonged LOS. Another study involving patients in the emergency room of the same hospital as the present study, showed a lack of agreement between the ESPEN and SGA, and predicted worse clinical outcomes in malnourished patients (1.54-fold higher probability of infection and 2.69-fold higher risk of death) [48]. Although the ESPEN consensus had predictive validity in these studies, it did not have adequate ability to diagnose malnutrition in hospitalized patients. Therefore, we do not recommend its use for diagnosing malnutrition in hospitalized COPD patients.

The AND-ASPEN consensus had the most satisfactory accuracy and concordance with SGA and showed a positive association with prolonged LOS in the current study. Other studies with general inpatients demonstrated the accuracy and concordance of the AND-ASPEN with SGA. An American cohort with 404 adults and elderly inpatients showed an AUC of 0.836, which is almost equal to that reported in our study (0.837) [49]. A Brazilian cohort with critical patients demonstrated 78% concordance between the AND-ASPEN and SGA, but the AND-ASPEN was not fulfilled completely because the authors did not assess the HGS [50]; hence, we consider it the most appropriate tool for diagnosing malnutrition in AECOPD patients. In fact, studies with general inpatients that assessed the nutritional status using the AND-ASPEN consensus demonstrated satisfactory predictive validity with regard to hospital discharge [48], hospital costs [41,52], LOS [52], and mortality [53].

Although the SGA is the reference method for diagnosing malnutrition in hospitalized patients, it was scarcely applied in COPD patients. Besides, it is a subjective method that can be prone to many errors, as compared to the AND-ASPEN, which is a more objective tool. The SGA depends strictly on the subjective analysis of the examiners and information about weight loss is self-reported by the patient. Furthermore, the evaluation of reduced food consumption is qualitative. Unlike the SGA, the AND-ASPEN uses objectives criteria to assess these variables, because it considers measured weight and quantitative consumption report, considering different periods in changes reported by patients, ranging from 1 week to 1 year. However, there are a few limitations to the AND-ASPEN like as with SGA, such as the need for trained examiners to perform the physical exam and the need for collaboration between patient and clinician when measuring the variables. Furthermore, it also depends of the availability of a dynamometer to assess the HGS in hospital settings.

There are some limitations to this study. The pulmonary tests were not performed for all patients and the BIA test was not performed with the fasting protocol; however, all patients were evaluated in the same time, a few hours after lunch, and all of them received the same diet at the hospital. However, it is a pragmatic design, since respect fasting protocol is not easy in hospital setting. We grouped moderate and severe malnutrition for analyses considering the sample size to maintain the power to test the hypothesis and because in clinical practice the management of malnutrition is not directed by its severity. The strength of this study is the sample of hospitalized AECOPD patients, a population that has rarely been studied in the literature on

nutritional status. It is known that exacerbation has important implications on the quality of life, pulmonary function, and risk of mortality in COPD patients [54]. In this context, there is an increased need for studies evaluating the nutritional status using accurate methods, instead of BMI, in AECOPD patients and its association with short- and long-term clinical outcomes. Futures studies should be performed to confirm the validity of AND-ASPEN for malnutrition diagnosis in pneumology hospital units. It is also important to determine the time spend with its application, its reproducibility and if an individualized nutritional therapy could modify the incidence of worse outcomes in patients according to the nutrition diagnosis by AND-ASPEN.

Conclusions

Malnutrition was identified in 20–54% of the hospitalized patients with AECOPD, ranging according to the integrative tool applied for nutritional diagnosis. The AND-ASPEN consensus for malnutrition diagnosis was the most accurate integrative tool for this proposes. Therefore, considering its concurrent validity with the SGA and predictive validity for prolonged LOS, this tool should be adopted for nutritional assessment of COPD patients admitted to hospitals, and its validity should be explored by more studies.

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Table 1. Variables employed in the malnutrition diagnosis according to each nutritional tool.

	AND-ASPEN[29]	ESPEN[28]	GLIM[30]	SGA[33]
Involuntary weight loss	X	X	X	X
Muscle mass loss	X			X
Subcutaneous fat loss	X			X
Disease's metabolic stress				X
Gastrointestinal symptoms				X
Reduced food intake	X		X	X
Edema/Ascites	X			X
Reduced HGS	X			
Low BMI		X	X	
Inflammation			X	
Reduced FFMI		X	X	

AND-ASPEN, Academy of Nutrition and Dietetics-American Society of Parenteral and Enteral Nutrition; ESPEN, European Society for Clinical Nutrition and Metabolism; GLIM, Global Leadership Initiative on Malnutrition; SGA, Subjective Global Assessment; HGS, handgrip streght; BMI = body mass index; FFMI = fat free mass index.

Table 2. General characteristics of AECOPD patients admitted in hospital on (n = 241).

Characteristic	
Male	112 (46.5%)
Age (years)	68.3 ± 10.2
Level of education (years of study)	5.0 (3.0-5.0)
White Ethnicity	197 (81.7%)
Origin	
Porto Alegre	137 (56.8%)
Metropolitan region	82 (34%)
Marital status	
Married	107 (44.4%)
GOLD stage (n=140)	
GOLD 1	5 (3.6%)
GOLD 2	52 (37.1%)
GOLD 3	57 (40.7%)
GOLD 4	26 (18.6%)
Spirometry values (n=140)	
FEV¹ (%)	56.8 ± 18.9
FVC (%)	60.4 ± 17.4
FEV/FVC (%)	72.3 ± 22.7
CCI (points)	5.0 (3.0-6.0)

CCI, Charles comorbidity index; GOLD, Global Initiative for Chronic Obstructive Lung Disease; FEV¹, forced expiratory volume in 1 second; FVC, forced vital capacity.

Table 3. Concurrent validity of AND-ASPEN, ESPEN, and GLIM Consensus for malnutrition diagnosis considering SGA as reference in hospitalized ECOPD patients.

	GLIM	**AND-ASPEN**	**ESPEN**
Sensitivity	73.1%	88.2%	38.9%
Specificity	80.4%	79.2%	98.3%
PPV	80.6%	79.2%	95.7%
NPV	72.9%	87.2%	63.4%
ROC curve	0.768 (0.701-0.835)	0.837 (0.783-0.841)	0.691 (0.622-0.760)
	$p<0.001$	$p<0.001$	$p<0.001$
Kappa coefficient	0.533	0.674	0.383
	$p<0.001$	$p<0.001$	$p<0.001$

Abbreviations AND-ASPEN = Academy of Nutrition and Dietetics-American Society of Parenteral and Enteral Nutrition; AUC= area under the curve; ESPEN = European Society for Clinical Nutrition and Metabolism; GLIM = Global Leadership Initiative on Malnutrition; NPV= negative predictive value; PPV= positive predictive value; ROC = receiver operating characteristics SGA= Subjective Global Assessment.

Table 4. Association between malnutrition diagnosed by integrative tools and clinical outcomes in AECOPD patients: bivariate analysis.

Malnutrition	**LOS**		p^1
	<11 days	**≥11 days**	
	(n = 116)	**(n = 125)**	
SGA	50 (43.1%)	70 (56.5%)	0.053
AND-ASPEN	52 (45.2%)	78 (62.5%)	0.009
ESPEN	15 (13.2%)	32 (26.7%)	0.016
GLIM	46 (45.1%)	52 (50.5%)	0.527
Malnutrition	**In-hospital death**		p^1
	Survivals	**Non-survivals**	
	(n = 223)	**(n = 18)**	
SGA	107 (48.2%)	13 (72.2%)	0.086
ASPEN – AND	118 (53.4%)	12 (66.7%)	0.400
ESPEN	46 (21.3%)	1 (5.6%)	0.134
GLIM	90 (47.4%)	8 (53.3%)	0.860

[1] Qui-square test. $p<0.05$.

Moderate and severe malnutrition of AND-ASPEN and GLIM was grouped for this analysis.

Abbreviations: AND-ASPEN = Academy of Nutrition and Dietetics-American Society of Parenteral and Enteral Nutrition; ESPEN = European Society for Clinical Nutrition and Metabolism; GLIM = Global Leadership Initiative on Malnutrition; SGA = Subjective Global Assessment.

Table 5. Association between malnutrition diagnosed by integrative tools and, prolonged LOS and death in-hospital in AECOPD patients: multivariate analysis.

LOS[1] (≥11 days)				
	Crude		**Adjusted**	
	OR (95% CI)		**OR (95% CI)**	
SGA	1.69 (1.01-2.81)	*p* 0.046	1.51 (0.89-2.55)	*p* 0.127
ESPEN	2.38(1.21-4.68)	*p* 0.012	2.57 (1.27-5.20)	*p* 0.008
AND-ASPEN	2.00 (1.19-3.37)	*p* 0.009	1.73 (1.01-2.57)	*p* 0.045
Death in-hospital[2]				
	Crude		**Adjusted**	
	HR (95% CI)		**HR (95% CI)**	
ESPEN	0.17 (0.02-1.24)	*p* 0.080	0.17 (0.023-1.34)	*p* 0.081
SGA	1.18 (0.40-3.50)	*p* 0.768	1.13 (038-3.35)	*p* 0.895

[1] Logistic regression (adjusted for sex and MRC scale) [2]Cox regression (adjusted for MRC scale).
Abbreviations: OR, odds ratio; CI, confidence interval; HR, hazard ratio; AND-ASPEN = Academy of Nutrition and Dietetics-American Society of Parenteral and Enteral Nutrition; ESPEN, European Society for Clinical Nutrition and Metabolism; SGA, Subjective Global Assessment.

ARTIGO 2

Prevalence, associated factors, and prognostic value of sarcopenia in exacerbated chronic obstructive pulmonary disease

Running head: Sarcopenia and AECOPD in hospital setting

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Author Contributions

FMS and BEA contributed to study conception. PPT, KV, and BEA contributed to data acquisition. FMS contributed to data analysis and interpretation. PPT, BEA, and FMS drafted the manuscript. All authors critically revised the manuscript, provided final approval, and agreed to be accountable for all aspects of the work, ensuring its integrity and accuracy.

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Tables: four.

Abstract

Background and objectives: Patients with chronic obstructive pulmonary disease (COPD) frequently have systemic comorbidities. Among these, sarcopenia is associated with worse pulmonary function and clinical outcomes. Acute exacerbation in COPD (AECOPD) can intensify muscle dysfunction. Therefore, the present study aimed to evaluate the prevalence of sarcopenia in AECOPD patients and assess the associated factors and their prognostic value.

Methods: Prospective cohort study in a Brazilian public hospital with AECOPD patients. Sarcopenia was assessed according to the European Working Group of Sarcopenia in Older People Consensus 2 (EWGSOP2): reduced handgrip strength (HGS) combined with low fat-free mass index (FFMI) or calf circumference (CC). Data on clinical, nutritional, and sociodemographic features were collected. The evaluated clinical outcomes were the length of hospital stay (LOS), and in-hospital death.

Results: Among 208 patients (54.8% females, 67.6±10.1 years) evaluated, 16.3% presented sarcopenia. Malnutrition (OR=16.50, 95%CI 3.58-76.08), and disease stages 3-4 (OR = 4.05 95%CI 1.20-13.76) were associated with the presence of sarcopenia. The CC showed satisfactory performance in diagnosing sarcopenia as compared to FFMI as a marker of reduced muscle mass (kappa = 0.703; AUC ROC curve = 0.886; 95%CI 0.81-0.96). Sarcopenia was not associated with clinical outcomes.

Conclusion: Almost 20% of patients presented sarcopenia. Malnutrition and advanced stage of disease were associated with increased chances of this condition in AECOPD patients. Reduced HSG combined with low CC may be an alternative when FFMI could not be obtained for sarcopenia diagnosis.

Key words: sarcopenia, calf circumference, COPD, hospitalization, exacerbation.

Highlights

- Sarcopenia affects almost 15% of patients with exacerbation of chronic obstructive pulmonary disease
- Malnutrition and severe disease stages are factors associated with sarcopenia
- The calf circumference can be applied as muscle mass marker in sarcopenia diagnosis

Introduction

Sarcopenia is a recently described disease characterized by loss of strength, muscle mass, and functionality associated with the aging process [1]. Although it is widely related to aging, recent studies have shown that sarcopenia can also be present in adults or even children with chronic diseases and, when present, can lead to worse clinical outcomes [2-4]. Primary and secondary sarcopenia are defined as those associated with age and disease, respectively[1].

Most chronic diseases are associated with inflammatory processes that can increase protein catabolism. Moreover, people with these diseases tend to be bedridden and have lower functional capacity, which worsens the catabolism process and intensifies skeletal muscle dysfunction. Likewise, patients with chronic obstructive pulmonary disease (COPD) are usually elderly, have frequent breathless symptoms that impede physical ability, and have elevated basal inflammatory response as well as reduced protein consumption due to dyspnea, leading to a potential risk of sarcopenia development [5,6].

A recent metanalysis with clinical, nursing, and population-based COPD patients reported a pooled sarcopenia prevalence of 21.6% [7]. In general patients, the presence of sarcopenia was associated with prolonged length of stay (LOS) [8] and twice the risk of death 12 months post-hospitalization, as demonstrated in a study conducted with 172 elderly patients in a geriatric clinic [9]. To our knowledge, no studies have yet evaluated the prevalence of sarcopenia and its association with clinical outcomes in hospitalized patients with acute exacerbated COPD (AECOPD). This is relevant because the AECOPD is associated with further increased inflammation, dyspnea, anorexia, and prostration, therefore, a higher risk of muscle dysfunction [10]. In stable COPD patients, the presence of sarcopenia was associated with worse dyspnea, higher disease stage, malnutrition, and poor exercise tolerance [11]. Moreover, some clinical factors are related to sarcopenia, including age, elevated levels of systemic inflammatory biomarkers, and low body mass index (BMI) [7].

The European Work Group on Sarcopenia in Older People (EWGSOAP) consensus advocates the use of dual x-ray absorptiometry, computed tomography, or impedance bioelectrical analysis to assess skeletal muscle mass in sarcopenia diagnosis[1]. However, the availability of these methods in hospital settings is frequently limited, making it difficult to

perform sarcopenia diagnosis in hospitalized patients. In contrast, calf circumference (CC), which is also recommended by the EWGSOAP [1], is a more feasible indicator of skeletal muscle mass and it has already been validated as a good predictor of nutritional status in general patients [12]. However, no studies have evaluated the accuracy of CC to diagnose sarcopenia in patients with COPD compared to a reference standard.

Considering the scarce literature on sarcopenia in AECOPD patients, the current study aimed to evaluate the prevalence of sarcopenia in these patients, the factors associated with this condition, and its prognostic value. As a secondary aim, we also tested the accuracy of CC as a marker of reduced muscle mass in the diagnosis of sarcopenia.

Methods

Design

This prospective longitudinal study included COPD patients admitted to a public tertiary hospital in Porto Alegre (Rio Grande do Sul, Brazil) due to severe exacerbation of the disease. The study was performed according to the Brazilian laws on ethical research (http://conselho.saude.gov.br/resolucoes/2012/Reso466.pdf) and was approved by the Hospital's ethics committee (approval number 3.126.689).

Sample

All patients admitted to the hospital due to AECOPD were selected. This study included adult and elderly patients who were lucid and able to stand up, and without edema, severe ascites, or amputation. We excluded subjects with cardiac pacemakers, prostheses, or metallic screws, as well as those with body mass index >35 kg/m^2, which precluded the performance of bioimpedance analysis (BIA).

The calculation of the sample size was performed in an online calculator (http://www.openepi.com/Menu/OE_Menu.htm) based on results of a study by Costa *et al.* that demonstrated an odds of 3.87 for sarcopenia when compared patients in quartiles 3 or 4 of Body-mass index, airflow Obstruction, Dyspnea, and Exercise (BODE) index to patients in quartiles 1 or 2, showing a positive association between sarcopenia and COPD prognosis [13]. Based on this association magnitude, 80% power, and 5% significance level, the estimated required sample size was 244 patients.

Data collection

Data were collected between March 2019 and March 2020. All patients with AECOPD meeting the inclusion criteria were invited to participate in the study within the first 72 hours of hospitalization. After patients agreed to participate and signed the consent form, trained researchers collected the data. Socioeconomic and demographic information including age, sex, ethnicity, education level, smoking habits, and previous morbidity history were collected from electronic records, as well as the results of laboratory exams. The clinical diagnosis of COPD was confirmed in spirometry exams based on the presence of a post-bronchodilator forced expired volume in the first second/ vital forced capacity (FEV_1/VFC) <0.70. The severity of disease was assessed according to the latest Global Initiative of Chronic Obstructive Lung Disease (GOLD) considering the FEV_1 values, as follow: FEV_1 >80% of the predicted value was classified as GOLD 1 (mild), >50% FEV_1 <80% as GOLD 2 (moderate), >30% FEV_1 <50% as GOLD 3 (severe), and FEV_1 <30% as GOLD 4 (very severe)[14]. Spirometry test from the last year was considered. The severity of dyspnea was assessed by the modified Medical Research Council (mMRC) scale and was considered severe for patients scoring 3 points or more[15].

Nutrition assessment

Nutritional data were collected at bedside through a standardized interview with patients. The nutritional diagnosis was performed using Subjective Global Assessment (SGA), as proposed by Detsky et al.[16]. Patients were classified as well nourished (SGA-A), moderately or suspected of being malnourished (SGA-B), and severely malnourished (SGA-C) according to clinical history and physical examination findings. Information on unintentional weight loss in the last 6 months, changes in food intake or consistency, presence of gastrointestinal symptoms, reduction of functional capacity, impact of metabolic demand of disease, loss of fat and muscle mass, and fluid accumulation were considered in the nutritional diagnosis.

Muscle strength was assessed based on handgrip strength (HGS) using a calibrated Saehan® hydraulic dynamometer with subjects in a standing position, their arm at a 90º angle and the elbow by the side of the body. The patients were asked to hold the dynamometer with their non-dominant hand and to press the device with maximal strength,

repeating the procedure three times, with 60 seconds of rest between each trial. The highest value was used to classify muscle strength as reduced or normal according to the reference values proposed by the EWGSOP2 (30 kg for men and 20 kg for women) [1].

CC was measured using an inelastic tape at the calf's greatest girth, with the subject seated with legs making a right angle between knees and ankle. CC was defined as reduced for measurement ≤31 cm, as proposed by the EWGSOP2 consensus [1].

For the performance of the BIA test, weight and height were measured with the subjects in an upright position, without shoes and with little clothes, using a calibrated balance Plena® and a Bodymeter 206, Seca® stadiometer. A Biodynamics® 310E electrical bioimpedance device was used to extract resistance, reactance, and lean mass data at a frequency of 50-kHz. The patients were asked to stay in supine position on the bed for 10 minutes before starting the exam. The distal electrodes were placed on the dorsal region of the right hand between the metacarpal and phalanges and between the metatarsus and phalanx of the right foot. The proximal electrodes were placed on the styloid process and malleolus of both right hand and foot [17]. The equation proposed by Gonzalez et al was used to estimate the fat-free mass (FFM)[18] and the FFM index (FFMI) was calculated as FFM (kg) divided by the body height squared. FFMI was considered reduced for values <15 kg/m² in women and <17 kg/m² in men, as proposed by the EWGSOP2 consensus [1].

Sarcopenia diagnosis

Sarcopenia was diagnosed according to EWGSOP2 [1] consensus, using HGS as a marker of muscle strength and FFMI as a marker of muscle mass quantity. No functional tests could be performed because all patients were admitted due to disease exacerbation with worsening of symptoms of dyspnea and difficulty in walking; thus, the severity of sarcopenia was not assessed. Therefore, patients with low muscle strength but normal FFMI were classified as probably sarcopenic, those with reduced strength by HGS associated with reduced muscle mass by FFMI were diagnosed as sarcopenic, and those with normal HGS were considered non-sarcopenic independent muscle mass quantity.

Since BIA is not available in all hospital nutrition services, the diagnosis of sarcopenia was also established using reduced CC as a marker of muscle mass quantity

instead of FFMI, adopting the cut-off described proposed by EWGSOP2 consensus (< 31 cm) [1].

Clinical outcomes

All electronic records were checked after discharge to collect data on the LOS and in-hospital mortality. For data analysis, LOS was considered prolonged when it was equal or higher than the median observed in the sample of the current study.

Statistical analysis

Data were analyzed in IBM SPSS Statistics for Windows, version 20.0 program and P <0.05 was considered statistically significant. Quantitative variables were described as mean and standard deviation and as median and interquartile range. Categorical variables were expressed as absolute numbers and frequencies. Kolmogorov–Smirnov tests were used to evaluate the normality of the data.

The general features of patients with and without sarcopenia were compared by Student's t or Mann–Whitney (quantitative variables) tests and chi-square or Fisher tests (categorical variables).

Logistic regression was performed to identify factors related to sarcopenia presence considering variables with P <0.20 in comparisons of patients with and without sarcopenia (bivariate analyses) and these with clinical relevance in AECOPD patients, including age, sex, and inflammation (C-reactive protein [CRP] values). Crude analysis was first performed to investigate the association of variables with sarcopenia; next, variables with P <0.20 were included in the construction of a multivariate model.

Aiming to simplify the diagnosis of sarcopenia, the concordance of sarcopenia diagnosis using FFMI and CC to define reduced muscle mass was evaluated by kappa coefficient and construction of receiver operating characteristic (ROC) curves with calculation of sensitivity, specificity, positive predictive value, and negative predictive value.

Results

General features of the sample

Of the 244 COPD patients screened, 36 were excluded due to the impossibility of performing BIA. Thus, the sample included in the current study comprised 208 patients; 114 (54.8%) were women, 173 (83.2%) were white, and 89 (42.8%) were married, with an average age of 67.6±10.1 years and with an education level comprising 5 (3.0-5.8) years of study.

Most of the sample had moderate or severe pulmonary obstruction (GOLD stages 2 and 3) and severe dyspnea (mMRC >3 points). In addition, more than half had been hospitalized in the last year due to disease exacerbation. The median LOS was 10.0 (7.0-17.7) days, and the incidence of in-hospital death was 7.7%.

The clinical and nutritional characteristics of the sample are shown in **Table 1.** The frequency of low CC was 63.0%, 45.2% of the sample showed reduced HGS, and nearly 34% had reduced FFMI. Moreover, half of the subjects were malnourished at hospital admission and 16.3% were sarcopenic.

Sarcopenia and associated factors

Table 2 shows the comparisons of general, clinical, and nutritional features between sarcopenic and non-sarcopenic patients (grouped those without sarcopenia and those classified as probably sarcopenic). Subjects with sarcopenia had a higher frequency of GOLD stages 2 and 3 and a lower FEV1/FVC ratio. In addition, the group diagnosed with sarcopenia had significantly lower weight, BMI, FFMI, and HGS, as well as higher frequencies of weight loss and reduced CC. Moreover, 93.9% of patients in the sarcopenic group were malnourished, compared to 43.1% in the non-sarcopenic group.

Table 3 shows the factors associated with the presence of sarcopenia in AECOPD patients according to logistic regression. In the multivariate model, the presence of moderate and severe stages of COPD increased by nearly five-fold the chance of patients being sarcopenic. Likewise, the presence of malnutrition increased the risk by 16.5-fold.

Sarcopenia and clinical outcomes

Regarding the association between sarcopenia diagnosis and clinical outcomes (**Table 4)**, no differences were observed between the two groups for the median LOS, frequency of prolonged LOS, and in-hospital death. Therefore, multivariate analysis was not performed.

CC instead of FFMI in for the sarcopenia diagnosis

Considering reduced HGS plus low CC for the diagnosis of sarcopenia, the prevalence of this condition was higher than when diagnosis was based on both reduced HGS and FFMI (20.3% versus 16.3%). Reduced muscle mass for the confirmation of sarcopenia diagnosis using CC showed substantial agreement with sarcopenia diagnosed by reduced FFMI (kappa = 0.703, P<0.001), good accuracy (area under the receiver operating characteristic (ROC) curve [AUC] = 0.886; 95% confidence interval [CI] 0.811–0.961) and high sensitivity (84.8%) and specificity (92.3%).

Discussion

This study aimed to evaluate the prevalence of sarcopenia in AECOPD patients, the factors associated with this condition, and its prognostic value. In this sample, 16.3% of patients were sarcopenic, and COPD stage and malnutrition were related to increased odds for the presence of this condition. Clinical outcomes did not differ between patients with and without sarcopenia. The diagnosis of sarcopenia using CC instead of FFMI showed satisfactory accuracy and high specificity.

The prevalence of sarcopenia in the current study was almost 16%. A systematic review and metanalysis of 10 studies including subjects from the general population, nursing home residents, and clinically stable COPD patients reported a pooled prevalence of 21.6%[7]. The higher prevalence in the metanalysis could be explained by the criteria applied for the diagnosis of sarcopenia since most of the studies used the EWGSOP1 consensus, in which low muscle mass was the main criterion for diagnosis [19]. The present study applied the most recent EWGSOP consensus, which recognized reduced HGS as the main criteria defining sarcopenia [1]. The literature on sarcopenia in hospitalized COPD patients is limited: one study involving 54 AECOPD patients identified this condition in

48% of the sample. This higher prevalence may be explained by the higher frequency of GOLD stage 4 (40.7% versus 20%) compared to that in our sample [20] since the severity of COPD is associated with the presence of this musculoskeletal disease. A cross-sectional study of 622 stable COPD patients reported a sarcopenia prevalence of 14.5%, which increased according to GOLD stage [21]. In addition, another cross-sectional study of 41 COPD stable patients reported that 46.3% had sarcopenia, which was associated with worse pulmonary function, as assessed by peak inspiratory and expiratory flow [22]

Disease severity was associated with sarcopenia in the present study. Accordingly, the severity of COPD and dyspnea are the main clinical outcomes frequently associated with sarcopenia, as illustrated by studies described above [7]. Patients with reduced pulmonary function shows elevated muscle dysfunction compared to that in patients with more preserved pulmonary function [23]. The increased dyspnea caused by worse pulmonary function leads to decreased functional ability. This is often associated with worse food consumption due to fatigue, resulting in additional loss of muscle mass that enhances dyspnea [24,25]. A study of 80 stable COPD patients, reported significantly more severe symptoms of dyspnea and higher mMRC scores in patients with sarcopenia [21]. A cross-sectional study of 121 Asian COPD patients reported a 1.9-fold increased chance of sarcopenia in patients with a higher mMRC scale (OR = 1.9 95%CI 1.3–2.8)[26.] Also, a higher frequency of inability due to dyspnea, as assessed by the MRC scale, was reported in the sarcopenic group in a cohort with stable COPD patients (median score of MRC 3 in non-sarcopenic versus 4 in the sarcopenic group; $P < 0.001$ [22].

Malnutrition was also associated with sarcopenia in the current study. This condition in COPD patients is narrowly associated with reduced skeletal muscle mass and can be explained by the excessive catabolism present in these patients, due to reduced protein consumption, basal inflammation, and inactivity. Because of this metabolic response, AECOPD patients have a higher frequency of malnutrition, worse quality of life, and lower pulmonary function. This leads to a vicious cycle as sarcopenia is linked to lower skeletal muscle mass, which is associated with lower pulmonary function and, therefore, a higher risk of exacerbation [27]. In a cross-sectional study evaluating malnutrition and sarcopenia in 263 COPD patients, De Blasio and collaborators found that 24% of patients had sarcopenia, of which 14% had malnutrition, 6.8% of whom presented cachexia [28]. In

contrast, a Brazilian study of stable COPD patients did not find an association between sarcopenia and malnutrition 29. However, the authors used low BMI for malnutrition diagnosis, different from the present study, which applied SGA and De Blasio, who used the ESPEN consensus. It is important to notice that BMI is considered a less reliable marker of nutritional status. In addition, high BMI does not rule out malnutrition [30].

In this study, the presence of sarcopenia during hospital admission was not associated with intra-hospital clinical outcomes. While the frequency of death-in-hospital was three times higher in patients with sarcopenia compared to that in those without this condition, the difference was not statistically significant. To our knowledge, no other study has evaluated the association between sarcopenia and mortality or length of stay in hospitalized COPD patients. However, studies in general older hospitalized patients have reported higher length of stay and mortality rate in patients with sarcopenia than those in patients without sarcopenia [31]. A study of 432 older hospitalized patients reported a 4-day difference in length of stay in patients with and without sarcopenia. The incidence of death also differed between groups (27% in sarcopenic patients and 10% in non-sarcopenic patients) [32]. In addition, another study including 172 patients with a mean age of 82 years showed that patients diagnosed with sarcopenia had 2.23 times the risk of death within 12 months after hospitalization compared to patients without sarcopenia [33].The current study may not have sufficiently power to identify these associations and the prognostic value of sarcopenia in predicting outcomes after discharge was not evaluated. This topic warrants investigation in future studies involving AECOPD patients.

Using CC to assess the quantity of skeletal muscle mass for the diagnosis of sarcopenia, the prevalence of sarcopenia was 20.3%. This criteria for diagnosis showed substantial agreement and high sensitivity and specificity with diagnosis based on reduced FFMI. The CC is a more practical, easy, and available measure and can be obtained in different scenarios. Furthermore, studies have already demonstrated the accuracy of CC to predict loss muscle mass [18,34], nutritional risk [12], low disability [21], mortality [23.27.29], and hospital readmission [34] in non- COPD patients. A cross-sectional study with stable COPD and asthmatic patients evaluated the presence of sarcopenia adopting CC as the parameter of low muscle mass identified 11.2% of patients with this condition [35].The lower frequency of sarcopenia may be explained by the inclusion of asthmatic patients since this lung

disease is less catabolic than COPD. The authors did not report data on pulmonary function or COPD stage for comparison. However, patients with AECOPD generally have worse lung function, which is related to reduced muscle mass.

The present study has some limitations, including the non-application of the SARC-F tool for the screening of sarcopenia as recommended, by ESGWOP2 as a first step in sarcopenia investigation. However, considering that literature on sarcopenia in hospitalized COPD patients is scarce, we assessed sarcopenia diagnosis in all patients to better understand its prevalence, associated factors, and prognostic value. Additionally, we did not perform the fasting protocol for BIA. However, all patients received the same hospital diet and for all patients the BIA was performed a few hours after lunch. In contrast, the strength of this study is its originality and relevance, since it included patients with AECOPD, given the limited literature on this topic.

This study identified sarcopenia in a large sample of AECOPD patients during hospital admission. Malnourished patients and those with more advanced disease had increased chances of having this muscle disease. Although sarcopenia was not associated with worse clinical outcomes in the studied sample, its evaluation is recommended. Considering that AECOPD patients present severe dyspnea during hospital admission, which can hamper the assessment of weight and height, variables that are necessary to perform BIA, CC can be adopted as criteria to define reduced muscle mass for sarcopenia diagnosis. Future studies including a larger sample size of AECOPD patients will be able to clarify the prognostic value of sarcopenia during hospitalization and after discharge. Moreover, it is also necessary to investigate if patients with AECOPD are developing sarcopenia during hospitalization and if nutritional therapy can prevent it.

Conclusion

Sarcopenia was identified in 16.3% of AECOPD patients but was not associated with in-hospital outcomes. Malnutrition and GOLD stage were positively associated with sarcopenia. Reduced HGS combined with low CC showed satisfactory accuracy in diagnosing sarcopenia and may be an alternative for the assessment of this condition in these patients when FFMI could not be obtained.

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Declaration of Interests

The authors have no conflicts of interest to declare.

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Bruna Espíndola de Araújo: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Software; Validation; Visualization; Roles/Writing - original draft. **Paula Portal Teixeira:** Data curation; Roles/Writing - original draft; Writing - Review & Editing. **Kamila Valduga**: Data curation; Writing - Review & Editing. **Jaqueline da Silva Fink:** Writing - Review & Editing; Validation. **Flávia Moraes Silva**: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Roles/Writing - original draft; Writing - review & editing.

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Table 1. General features of hospitalized AECOPD patients.

Characteristics	**Total Sample (n= 208)**
Nutritional characteristics	
Weight (kg)	65.44 ± 20.57
BMI (kg/m²)	25.41 ± 8.26
Malnutrition (SGA B or C)	106 (51.2)
Reduced HGS	94 (45.2)
Low FFMI	59 (33.9)
Diagnosis of Sarcopenia	
No sarcopenia	114 (51.8)
Probable sarcopenia	60 (28.8)
Sarcopenia	34 (16.3)
Clinical characteristics (n = 128)	
FEV_1 (L)	1.11 ± 0.48
FEV_1 %	45.83 ± 18.61
FVC (L)	1.93 ± 0.71
FVC %	60.83 ± 17.81
FEV_1/FVC	56.32 ± 18.20
FEV_1/FVC %	71.07 ± 22.68
GOLD stage (n=128)	
1	4 (3.1)
2	45 (35.2)
3	53 (41.4)
4	26 (20.3)
mMRC > 3 points	168 (81.3)
CCI (points)	4.76 ± 2.04
Smoking time (years)	40.06 ± 13.70
C-Reative Protein (n = 169)	21.7 (6.85 – 82.55)
Hospitalization in the last year	113 (55.1)
LOS (days)	10 (7.0 – 17.7)
In-hospital death	16 (7.7)

Abbreviations: BMI, body mass index; HGS, handgrip strength; FFMI, fat-free mass index; FEV1, forced expiratory volume in 1 second; FVC, final vital capacity; mMRC, modified medical research council scale; CCI, Charles comorbidity index; LOS, length of hospital stay;

Data are presented as mean± standard deviation, median (P25-P75), or absolute frequency (relative frequency).

Table 2. Features of patients with AECOPD according to the presence of sarcopenia.

	Sarcopenic (n=34)	**Non-Sarcopenic (n=174)**	**P value**
Age (years)	68.94 ± 10.84	64.34 ± 9.90	0.398[1]
Gender (female)	15 (44.1)	98 (54)	0.338[2]
Ethnicity (white)	25 (73.5)	148 (85.1)	0.238[2]
Elderly patients	26 (76.5)	133 (76.4)	1.000[2]
CCI (points)	4.0 (3.0-6.0)	5.0 (3.0-6.0)	0.289[3]
CRP (mg/dL)	19.4 (3.3-121.8)	21.7 (7.2-81.8)	0.962[3]
Education Level (years of study)	4.0 (1.7-5.2)	5.0 (3.0-6.0)	0.104[3]
Ex-smokers	24 (70.6)	125 (71.8)	0.864[2]
Exacerbation in the last year	19 (57.6)	95 (54.7)	0.906[2]
mMRC scale	3.91 ± 1.71	3.87 ± 1.30	0.902[1]
GOLD 2 and 3	28 (83.3)	99 (56.7)	0.019[2]
FEV_1 (L)	1.06 ± 0.51	1.12 ± 0.48	0.533[1]
FVC (L)	2.07 ± 0.89	1.90 ± 0.66	0.283[1]
FEV_1 %	43.72 ± 15.05	46.34 ± 19.40	0.563[1]
FVC %	62.33 ± 18.26	60.46 ± 17.77	0.634[1]
FEV_1/FVC	50.07 ± 16.70	57.84 ± 18.31	0.055[1]
Weight (kg)	47.40 ± 10.00	68.97 ± 20.73	<0.001[1]
Weight loss	27 (79.4)	78 (44.8)	<0.001[2]
Anorexia	19 (55.9)	67 (38.5)	0.091[2]
BMI (kg/m^2)	19,16 ± 3.09	27.82 ± 8.21	<0.001[1]
FFMI (kg/m^2)	13.29 ± 2.17	17.48 ± 2.52	<0.001[1]
HGS (kg)	16.02 ± 5.68	22.10 ± 7.86	<0.001[1]
Low CC	33 (97)	98 (56.4)	<0.001[2]
Malnutrition (SGA)	32 (93.9)	75 (43.1)	<0.001[2]

Abbreviations: CCI, Charles comorbidity index; CRP, c-reactive protein; mMRC, modified medical research council scale; GOLD, Global Initiative for Chronic Obstructive Lung Disease ; FEV1, forced expiratory volume in 1 second; FVC, final vital capacity; BMI, body mass index; FFMI, fat-free mass index; HGS, handgrip strength; CC, calf circumference.

Data are presented as mean± standard deviation, median (P25-P75), or absolute frequency (relative frequency).

[1] Student T Test; [2] Chi-square test; [3] Mann-Whitney Test.

Table 3. Factors associated with sarcopenia diagnosis in AECOPD patients

Variable	Sarcopenia			
	Crude analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age (years)	1.02 (0.98-1.05)	0.396	-	-
Sex				
Female	Ref	-		
Male	0.60 (0.29-1.25)	**0.174**	1.17 (0.42-3.30)	0.761
CRP (mg/dL)	1.00 (1.00-1.01)	0.540	-	-
Educational level (years)	0.91 (0.80-1.03)	**0.128**	0.93 (0.80-1.09)	0.357
GOLD				
1-2	Ref	-	Ref	-
3-4	3.81 (1.22-11.94)	**0.022**	4.05 (1.20-13.76)	0.025
Malnutrition				
SGA A	Ref	-	Ref	-
SGA B or C	20.46 (4.75-88.19)	**<0.001**	16.50 (3.58-76.08)	<0.001

Abbreviations: CRP, c-reactive protein; GOLD, Global Initiative for Chronic Obstructive Lung Disease; SGA, Subjective Global Assessment.

Logistic regression. In multivariate analysis were included all variable with P> 0.20 in crude analysis.

Table 4. Comparison of clinical outcomes in patients with AECOPD according to the presence of sarcopenia

	Sarcopenic (n=34)	**Non-Sarcopenic (n=174)**	**P value**
LOS (days)	11.5 (8.0-18.25)	10.0 (7.0-17.25)	0.238[1]
Prolonged LOS	22 (64.7)	94 (54)	0.338[2]
In-hospital death	1 (2.9)	15 (8.6)	0.479[2]

Abbreviations: LOS, length of stay. Data are presented as median (P25-P75), or absolute frequency (relative frequency). [1] Mann-Whitney Test; [2] Chi-square test.

CONSIDERAÇÕES FINAIS

A desnutrição e a sarcopenia são duas das diversas comorbidades extrapulmonares que acometem pacientes com DPOC e que se intensificam no processo de exacerbação da doença. A prevalência de desnutrição nessa população varia entre 20 a 50% e a de sarcopenia entre 17 a 22%. Ambas comorbidades são associadas com pior função pulmonar e aumento dos sintomas de dispneia. Entretanto, a avaliação da desnutrição realizada pela maioria dos estudos disponíveis na literatura é realizada a partir do índice de massa corporal (IMC). Ainda que se saiba das limitações do IMC quanto à investigação de desnutrição, estudos que avaliem a validade diagnóstica de ferramentas integrativas em portadores de DPOC são escassos. Além disso, a maior parte dos estudos envolvendo pacientes com DPOC, e que tem como foco de investigação tanto a desnutrição como a sarcopenia, são realizados com população estável. Já se sabe que a exacerbação da doença gera um quadro inflamatório acentuado, aumento do catabolismo e redução da ingestão alimentar, sendo o paciente fenótipo exacerbador diferente daquele que mantém o quadro da doença estável.

Considerando-se o panorama exposto acima, o objetivo da presente dissertação foi avaliar o comprometimento nutricional de pacientes com exacerbação aguda da DPOC, através da investigação da desnutrição (por diferentes ferramentas integrativas propostas na última década para seu diagnóstico) e da sarcopenia (por meio de método acurado e simples de avaliação da massa muscular) e a possível associação destas alterações do estado nutricional com piores desfechos clínicos. Junto a isso, procurou-se identificar a ferramenta mais acurada para diagnóstico de desnutrição e os fatores associados à presença de sarcopenia nos pacientes que ingressam no hospital por exacerbação da doença.

Dentre os principais resultados encontrados no estudo de coorte prospectivo conduzido em um hospital público de Porto Alegre, pode-se citar a prevalência de desnutrição entre 20 e 55%, sendo essa variabilidade dependente da ferramenta de diagnóstico nutricional aplicada, sendo identificada menor frequência de desnutrição com a ferramenta da ESPEN, a qual apresentou a pior concordância com o método referência. Por outro lado, a maior frequência de desnutrição foi identificada com a ferramenta da AND-ASPEN, a qual apresentou a acurácia mais satisfatória em diagnosticar desnutrição quando

comparada à ferramenta de referência (ASG) e foi preditora de tempo de internação prolongado, sendo recomendada como ferramenta para diagnóstico de desnutrição nessa população. Ainda, 16,3% dos pacientes apresentaram sarcopenia, sendo a chance desta condição estar presente maior naqueles com estágio 3 e 4 da doença e naqueles com diagnóstico de desnutrição. A CC foi satisfatoriamente acurada para verificação de massa magra reduzida e pode ser empregada no diagnóstico de sarcopenia quando o IMLG não puder ser obtido.

Portanto, a partir desses resultados, é possível encorajar o uso da ferramenta AND-ASPEN para o diagnóstico de desnutrição no paciente com DPOC exacerbado, considerando sua menor subjetividade em comparação à ASG e seu caráter mais informativo em comparação ao IMC, além de sua capacidade em predizer tempo de internação prolongado. Ainda, em termos de aplicabilidade clínica dos resultados encontrados, pode-se recomendar o diagnóstico de sarcopenia combinando FAM reduzida com CP reduzida, o que é mais viável, rápido e prático visto que nem todos os hospitais dispõem de BIA nos Serviços de Nutrição.

O projeto de pesquisa que gerou essa dissertação de Mestrado pode ser considerado precursor no estudo da validade preditiva e concorrente das ferramentas integrativas no diagnóstico de desnutrição no paciente com DPOC, bem como no estudo da sarcopenia em pacientes com DPOC hospitalizados; sendo recomendado que os resultados demonstrados possam ser confirmados em estudos futuros. Além disso, pesquisas futuras envolvendo pacientes hospitalizados com DPOC devem investigar a ocorrência de deterioração do estado nutricional - tanto no que diz respeito à desnutrição como no que se refere aos componentes e presença de sarcopenia - já que a mediana de tempo de internação desses pacientes é prolongada. Da mesma forma, sabendo identificar de forma acurada essas condições na admissão hospitalar desses pacientes, é imprescindível que estudos investiguem o efeito de intervenções nutricionais especializadas na associação entre o comprometimento do estado nutricional e os desfechos clínicos intrahospitalar e pós-alta.

TERMO DE CONSENTIMENTO LIVRE E ESCLARCIDO

Você está sendo convidado para participar de uma pesquisa acadêmica do Programa de Pós-Graduação Ciências da Nutrição da Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), em parceria com o Serviço de Nutrição e Dietética do Hospital Nossa Senhora da Conceição. O título da pesquisa é "Estado nutricional de pacientes com doença pulmonar obstrutiva crônica e desfechos clínicos: um estudo longitudinal prospectivo" e o objetivo principal é avaliar o estado nutricional de pacientes com doença pulmonar obstrutiva crônica (DPOC) e sua possível associação com maior tempo de internação no hospital, necessidade de internação na unidade de terapia intensiva, morte e reinternação hospitalar. O tema escolhido se justifica pela importância da avaliação do estado nutricional do paciente com DPOC, pois a desnutrição é comum nesses pacientes já que a doença contribui para a perda de peso e para a dificuldade em se alimentar por causa da falta de ar.

O trabalho está sendo realizado pela Nutricionista Bruna Espíndola de Araújo sob a supervisão e orientação da Nutricionista Jaqueline Fink (Doutora em Medicina) e da Profª Drª Flávia Moraes Silva (Professora Adjunta do Departamento de Nutrição e do Programa de Pós Graduação em Ciências da Nutrição da UFCSPA). Caso você aceite participar desse estudo, será feita uma entrevista com a Nutricionista responsável, com duração aproximada de 30 minutos, na qual você irá responder perguntas sobre seu estado de saúde e história nutricional. Serão coletadas de seu prontuário médico algumas informações clínicas e alguns resultados de exames de sangue que você fez ao chegar no hospital. Avaliaremos seu peso e sua altura, mediremos a circunferência do seu braço e da sua panturrilha (perna). Mediremos também o comprimento do seu braço. Utilizaremos um plicômetro (aparelho que se assemelha a uma "pinça") para medir a gordura do seu braço e o músculo da sua mão. Faremos uma avaliação da massa magra e massa gorda do seu corpo através de um aparelho denominado Bioimpedância elétrica. Para isso você ficará deitado e colocaremos dois eletrodos no seu braço e dois eletrodos no seu pé (como aqueles usados para fazer o eletrocardiograma – exame do coração) para que o exame possa ser realizado – o tempo para isso é de menos de dois minutos. Além disso, pediremos para você segurar e aperta com o máximo de sua força um aparelho chamado dinamômetro, através do qual avaliaremos a sua força. Você será convidado para fazer um teste de caminhada no corredor da unidade de internação – para isso você sentará em uma cadeira, levantará sem ajuda e caminhará três metros, retornando e sentando na cadeira. Esse teste dura menos de um minuto. Nós telefonaremos para você ou sua família depois que você sair do hospital, após três e seis meses, para sabermos como está a sua saúde e se você precisou voltar para o hospital. Os dados de identificação serão confidenciais e os nomes reservados. Os dados obtidos serão utilizados somente para este estudo, sendo os mesmos armazenados pela pesquisadora principal durante 5 (cinco) anos e após totalmente destruídos (conforme recomenda a Resolução 466/12).

Há riscos mínimos associados à sua participação nessa pesquisa: você pode sentir um leve desconforto com a medida da gordura do braço e do músculo da mão feitas com o plicômetro. As pesquisadoras terão todo o cuidado para que esse desconforto seja mínimo. Além disso, o teste de levantar da cadeira e caminhar por três metros poderá lhe deixar cansado. Mas você poderá interromper o teste em qualquer momento ou não realizar esse teste caso não se sinta disposto ou tenha sido classificado pela equipe de Enfermagem como tendo risco de queda.

Além disso, a retirada dos eletrodos fixados para realização da bioimpedância pode gerar um leve desconforto, ao arrancar alguns pelos da sua mão e/o pé.as, as pesquisadoras farão a retirada com o máximo de cuidado para que esse desconforto seja mínimo. Você não terá nenhum benefício em participar da pesquisa, mas contribuirá para que possamos avaliar qual a melhor maneira de identificar a desnutrição nos pacientes com a mesma doença que a sua (doença pulmonar obstrutiva crônica). Não há nenhum custo com a participação nesse estudo e lembramos que a sua participação é voluntária, ou seja, você só participará se tiver interesse. Não participar dessa pesquisa não altera em nada o seu atendimento no hospital. Da mesma forma, se você quiser retirar sua participação da pesquisa após ter concordado com a mesma, isso poderá ser feito a qualquer momento, sem nenhum prejuízo.

Eu_____, recebi as informações sobre os objetivos e a importância desta pesquisa de forma clara e concordo em participar do estudo. Declaro que também fui informado:

- Da garantia de receber resposta a qualquer pergunta ou esclarecimento acerca dos assuntos relacionados a esta pesquisa;
- De que minha participação é voluntária e terei a liberdade de retirar o meu consentimento, a qualquer momento e deixar de participar do estudo, sem que isto traga prejuízo para a minha vida pessoal e nem para o atendimento na instituição (nos casos de pesquisa com profissionais é para minha atuação profissional);
- Da garantia que não serei identificado quando da divulgação dos resultados e que as informações serão utilizadas somente para fins científicos do presente projeto de pesquisa;
- Sobre o projeto de pesquisa e a forma como será conduzido e que em caso de dúvida ou novas perguntas poderei entrar em contato com as pesquisadoras: Bruna Espíndola (telefone 51- 991248515), Flávia Moraes e Jaqueline Fink (telefone 51-3357 2259), Av. Francisco Trein, 596 – térreo, Bairro Cristo Redentor – Porto Alegre/RS.
- Também que, se houver dúvidas quanto a questões éticas, poderei entrar em contato com Daniel Demétrio Faustino da Silva, Coordenador-geral do Comitê de Ética em Pesquisa do GHC pelo telefone 3357-2407, endereço Av. Francisco Trein 596, Centro Administrativo, 1° andar – Gerência de Ensino e Pesquisa, das 08h às 12h e das 14h:30min às 15:30h.

Declaro que recebi uma via deste Termo de Consentimento Livre e Esclarecido, ficando outra via com a pesquisadora.

Porto Alegre, ___, de _____ de 20__.

Assinatura do participante:_____
Nome: _____
Assinatura da pesquisadora: _____
Nome da pesquisadora:_____

Este formulário foi lido para_____em _____/_____/_____ pelo_____ enquanto eu estava presente.
Testemunha: Assinatura:_____
Nome: _____ Data: ____/___/____