CAMILE LUDOVICO ZAMBOTI

DESEMPENHO FUNCIONAL EM DOENÇAS RESPIRATÓRIAS CRÔNICAS:

UM OLHAR APROFUNDADO NA DOENÇA PULMONAR INTERSTICIAL

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Orientador: Prof. Dr. Carlos Augusto Marçal Camillo

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Em memória de Francisco Zamboti

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"Cumpre o pequeno dever de cada momento, faz o que deves e está no que fazes".

São José Maria Escrivá

ZAMBOTI, Camile Ludovico. **Desempenho funcional em doenças respiratórias crônicas:** um olhar aprofundado na doença pulmonar intersticial. 2021. 324 f. Tese de doutorado (Programa de Pós-Graduação em Ciências da Reabilitação - Programa Associado entre UEL e UNOPAR) – Universidade Estadual de Londrina, Londrina-PR, 2021.

RESUMO

Introdução: Pacientes com doenças respiratórias crônicas (DRC) apresentam alterações pulmonares e sistemicas, com consequente limitação nas atividades de vida diária (AVDs). No entanto, existem inumeros instrumentos para avaliar o desempenho funcional de indivíduos com DRC, e portanto, difícil a compreensão dos testes mais apropriados para avaliação do desempenho funcional, em especial nas DRC que não possuam o diagnósico principal a doença pulmonar obstrutiva cronica (DPOC). Ainda, em doenças pulmonares intersticiais (DPI) são escassos os testes com propriedades métricas adequadas e que possuem relação com outros defechos clínicos, e não se sabe se a longo prazo existe piora do desempenho funcional e equilíbrio corporal, e também, se pacientes com DPI apresentam quedas. **Objetivos:** A presente tese foi elaborada no intuito de contribuir com as evidências científicas relacionadas aos instrumentos de desempenho funcional em DRC, especialmente em DPI. Bem como, aprofundar o olhar no desempenho funcional em pacientes com DPI, testes de desempenho funcional adequados para DPI, associação do desempenho funcional com atividade física da vida diária (AFVD) e diferenças no desempenho funcional, equilíbrio corporal e história de quedas em pacientes com DPI ao longo de um ano. **Metodologia:** Quatro estudos foram desenvolvidos: (1) Através de uma revisão sistemática, o primeiro estudo sumarizou as informações dos instrumentos de desempenho funcional, propriedades de medidas investigadas e associação com desfechos negativos em pacientes com DRC que não possuam como diagnóstico principal a DPOC; (2) No segundo estudo foi comparado o desempenho funcional em pacientes com DPI clínicamente estáveis e individuos saudáveis e investigado as propriedades métricas de testes de desempenho funcional em pacientes com DPI; (3) O terceiro estudo investigou a relação e um ponto de corte discriminativo do teste *timed up and go* (TUG) com a AFVD em pacientes com DPI; e por fim, (4) o quarto estudo observou o número de quedas em um ano em pacientes com DPI e comparou o desempenho funcional e equilíbrio estático em pacientes classificados como caidores e não caidores em um ano. **Resultados:** O primeiro estudo demonstrou que o desempenho funcional é avaliado primariamente por questionários em DRC não-DPOC e de acordo com os estudos publicados até o momento, a maioria dos testes com propriedades de medida satisfatórias foram em pacientes com asma e DPI e poucos intrumentos possuem associações com desfechos clínicos negativos (ex. mortalidade, hospitalização, entre outros). O segundo estudo demonstrou pior desempenho funcional em pacientes com DPI (n=40, 25 mulheres, 61±11 anos, 75±17% predito de capacidade vital forçada – CVF), comparados a indivíduos saudáveis (n=36, 22 mulheres, 61±9 anos, CVF 97±11%pred), e também mostrou que os testes TUG na velocidade usual (TUGu), rápida (TUGf) e 5 repetições de sentar e levantar (5rep-STS) possuem propriedades métricas adequadas para pacientes com DPI. O terceiro estudo encontrou uma boa relação do desempenho do TUG com as variáveis de passos e atividade moderada em pacientes com DPI (n=54, 26 mulheres,

60±11 anos, CVF 68±17%pred) e o desempenho no TUG>9,25s parece ser um bom ponto de corte discriminativo de inatividade física avaliada pelo número de passos por dia. O quarto estudo incluiu 52 pacientes com DPI (33 mulheres, 59±11 anos, CVF 69±11 %pred), 12 (22%) apresentaram queda em um ano e não houve diferença no desempenho funcional e equilíbrio estático em pacientes classificados como caidores e não caidores em um ano. **Conclusões:** Os quatro artigos científicos agregam à literatura com informações sobre instrumentos de desempenho funcional em pacientes com DRC não-DPOC, em especial em pacientes com DPI. Os instrumentos disponíveis na literatura para avaliação do desempenho funcional em DRC não-DPOC foram descritos, e considerando os estudos publicados até o momento, poucos foram os intrumentos adequados e com associações de desfechos clínicos negativos em diferentes diagnósticos com DPI. Diante das lacunas expostas, foi observado comprometimento funcional nos pacientes com DPI comparado a indivíduos saudáveis e três instrumentos (TUGu, TUGf e 5rep-STS) demonstraram ser adequados para avaliação do desempenho funcional em pacientes com DPI. Bem como, foi possível observar que existe relação do desempenho funcional (TUG) com a atividade fisica da vida diária, e apesar dos pacientes com DPI apresentarem relativamente alta proporção de quedas, não há diferença na performance funcional e equilíbrio estático entre pacientes com DPI caidores e não caidores.

Palavras-chave: doenças respiratórias; doença pulmonar intersticial; equilíbrio postural; desempenho funcional.

ZAMBOTI, Camile Ludovico. **Functional performance in chronic respiratory diseases:** a closer look into interstitial lung disease. 2021. 324 p. Thesis of doctorate degree (Post-graduation program in Rehabilitation Sciences) – State University of Londrina, Londrina-PR, 2021.

ABSTRACT

Background: Patients with chronic respiratory diseases (CRD) present systemic manifestations, with consequent restriction to activities of daily living (ADLs). However, there are numerous instruments to assess the functional performance (FP) of individuals with CRD, and therefore, it is difficult to select the most appropriat tool to assess functional performance, specially in non- chronic obstructive pulmonary disease (COPD) CRD. Specific functional performance tests to patients with interstitial lung diseases (ILD) are scarce in the literature and it is unknown the relation of functional performance with other clinical outcomes and whether patients with ILD have deterioration in functional performance and balance with a history of falls over time. **Aims:** The present thesis was elaborated in order to contribute to scientific evidences regarding to FP instruments in non-COPD CRD, specially in patients with ILD. The main aspects were the description, measurement properties of FP instruments, association with physical activity of daily living (PADL) and functional performance, balance and history of falls in patients with ILD throughout one-year. **Methods:** Four studies were developed: (1) The first study summarized information from functional performance instruments, investigated metric properties, and association with negative outcomes (e.g. mortality and hospitalisation) in patients with CRD; (2) In the second study, functional performance in ILD patients and healthy individuals was compared and the metric properties of functional performance tests in ILD patients were investigated; (3) The third study investigated the relationship and discriminative cut-off point of the timed up and go (TUG) test with PADL in patients with ILD; and finally (4) the fourth study compared functional performance and static balance in patients with ILD according to a one-year history of falls. **Results:** The first study demonstrated that functional performance is primarily assessed by questionnaires in CRD, most tests with adequate metric properties were in patients with asthma and ILD, and few instruments have associations with negative clinical outcomes. Study 2 demonstrated worse functional performance in patients with ILD (25 women, 61±11 years, 75±17%predict of forced vital capacity – FVC), compared to healthy individuals (22 women, 61±9 years, FVC 97±11%pred), and showed that the TUG test in usual pace (TUGu), fast pace (TUGf) and 5-repetition sit-to-stand test (5rep-STS) have adequate metric properties for patients with ILD. The third study found a good relationship of TUG performance with step variables and moderate activity in patients with ILD (26 women, 60±11 years, FVC 68±17%pred), and performance on TUG>9.25s seem to be good discriminative cutoff point for physical inactivity (number of steps per day). The fourth study included 52 patients with ILD (33 women, 59±11 years FVC 69±11 %pred), 12 (22%) fall in one-year and there was no difference in static balance and functional performance in patients with ILD fallers and non-fallers in one year. **Conclusions:** The four scientific articles add to the literature with information about functional performance instruments in patients with CRD, especially in patients with ILD. Instruments available in the literature for assessment of functional performance in non-COPD CRD was describes, also considering the current

literature, few instruments were adequate and have associations with negative outcomes in different diagnoses of ILD. In this context, functional impairment was observed in patients with ILD compared to healthy individuals and three instruments were adequate for ILD patients (TUGu, TUGf, 5rep-STS). As well, there was relationship in functional performance (TUG) and activity of daily lviing. Although, patients with ILD have a realtively high proportion of falls, there was no difference in functional performance and static balance between fallers and non-fallers.

Key words: respiration disorders; interstitial lung disease; physical functional performance; postural balance.

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LISTA DE ABREVIATURAS E SIGLAS EM PORTUGUÊS

AFVD	Atividade física de vida diária
AVDs	Atividades de vida diária
CIF	Classificação internacional de funcionalidade, incapacidade e saúde
COP	Centro oscilatório de pressão
CVF	Capacidade vital forçada
D_{LCO}	Capacidade de difusão de monóxido de carbono
DRC	Doenças respiratórias crônicas
DPI	Doença pulmonar intersticial
DPOC	Doença pulmonar obstrutiva crônica
DTC	Doenças do tecido conjuntivo
FC	Fibrose cística
FP	Fibrose pulmonar
FPI	Fibrose pulmonar idiopática
IMC	Índice de massa corporal
MDCI	Mínima diferença clínica importante
MDD	Mínima diferença detectável
OMS	Organização mundial de saúde
SEM	Erro padrão de medida
TC6min	Teste de caminhada de 6 minutos
TCAR	Tomografia computadorizada de alta resolução
Vel-AP	Velocidade de deslocamento na direção anteroposterior
Vel-ML	Velocidade de deslocamento na direção mediolateral

LISTA DE ABREVIATURAS E SIGLAS EM INGLÊS

1min-STS	One-minute sit-to-stand test
4MGS	Four-metre gait speed
5rep-STS	Five repetition sit-to-stand test
6MWT	Six-minute walk test
30sec-STS	Thirty seconds sit-to-stand test
AUC	Area under the curve
BMI	Body-mass index
CI	Confidence interval
COP	Center of pressure
COPD	Chronic obstructive pulmonary disease
CTD	Connective pulmonary disease
D_{LCO}	Diffusion capacity of the lung for carbon monoxide
FEV_1	Forced expiratory volume in the first second
FVC	Forced vital capacity
HG	Handgrip force
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
MVICq	Maximal voluntary isometric contraction of quadriceps
MVPA	Moderate to vigorous physical activity
OLS – EO	One-legged stance with eyes open
REP	Repetition
SEC	Seconds
SF-36	Medical Outcomes Short Form 36 item of Health Survey
SPPB	Short physical performance battery
QS	Quadriceps strength
TLS – EO	Two-legged stance with eyes open
TLS – EC	Two-legged stance with eyes closed
TUGu	Timed up and go in usual pace
TUGf	Timed up and go in fast pace
Vel-AP	Velocity sway of COP in antero-posterior direction
Vel-ML	Velocity sway of COP in medio-lateral direction

SUMÁRIO

APRESENTAÇÃO DA TESE

Esta tese aborda o tema de desempenho funcional em indivíduos com doenças crônicas respiratórias, especialmente nas doenças pulmonares intersticiais. É composto pela contextualização do conteúdo, artigos científicos e conclusão geral. A tese de doutorado apresenta quatro artigos científicos realizados no Laboratório de Análise do Movimento Humano do Centro Especializado do Programa de Pós-Graduação do Centro de Ciências da Saúde, da Universidade Estadual de Londrina. Esta tese foi desenvolvida em consonância com as regras do Programa de Pós-Graduação em Ciências da Reabilitação da Universidade Estadual de Londrina (UEL) com a Universidade do Norte do Paraná (UNOPAR).

CAPÍTULO 1

INTRODUÇÃO GERAL

1. INTRODUÇÃO GERAL DA TESE

Doenças respiratórias crônicas (DRC) são doenças que acometem as vias aéreas e outras estruturas pulmonares (1), possuem destaque na literatura internacional devido a sua alta prevalência e aumento da incidência na atualidade (2), mesmo com a diminuição do uso do tabaco a nível mundial. Em 2017, foi estimado que ao menos 544.9 milhões de pessoas no mundo possuem alguma doença crônica respiratória (2), e continuam como uma das principais causas de morte e incapacidade em todo o mundo (2). Segundo a organização mundial de saúde, a doença pulmonar obstrutiva crônica (DPOC), asma, doenças pulmonares intersticiais (DPI), fibrose cística e hipertensão arterial pulmonar são algumas das doenças consideradas como DRC (3).

Apesar das diferenças na fisiopatologia de cada diagnostico das DRC, alguns sintomas pulmonares (4, 5) e também sintomas extrapulmonares, são comuns, como intolerância ao exercício físico, fadiga, diminuição da força muscular periférica, ansiedade e depressão (6-9). Devido a sua característica crônica, e dependendo do diagnóstico da doença e o caráter progressivo, os pacientes apresentam tendência a ser menos ativos com consequente limitação nas suas atividades de vida diária (AVDs) e atividades sociais (10, 11) e prejuízo na qualidade de vida (8).

A asma, seguida pela DPOC, é a DRC mais prevalente, no entanto, entre homens e mulheres a maioria das mortes relacionada a DRC é por DPOC (2), e também, a DPOC é considerada a quarta causa mundial de mortalidade e uma das principais causas de incapacidade (12). Neste sentido, devido a maior severidade e taxa de mortalidade, a DPOC é a DRC mais estudada, com características clínicas, resposta à reabilitação e prognóstico melhor definido comparados a outras DRC (13, 14). Devido as manifestações extrapulmonares, em especial a restrição das atividades de vida diária, a avaliação do desempenho funcional é necessária na avaliação dos pacientes com DRC para melhor compreensão do quadro clínico, direcionar a reabilitação de forma mais adequada

ao caso, além disso alguns instrumentos de desempenho funcional está relacionados com o prognóstico da doença (15, 16). Desempenho funcional é definido como as atividades que pessoas fazem no curso normal de suas vidas para alcançar as necessidades básicas. Nesse sentido, vários instrumentos foram propostos na literatura para avaliação do desempenho funcional e, ao menos quatro revisões sistemáticas, direcionam a adequação dos instrumentos propostos para avaliação de desempenho funcional de pacientes com DPOC (15, 17-19).

No entanto, estudos que sumarizem as informações dos instrumentos de desempenho funcional foram encontrados apenas em DPOC, e diante da variedade de instrumentos disponíveis na literatura para avaliação do desempenho funcional, difícil é a seleção do instrumento mais adequado para avaliação do desempenho funcional na população estudada, especialmente em DRC não-DPOC. Assim, na prática clínica, a seleção do instrumento pode ser influenciada pelas informações referentes aos instrumentos de desempenho funcional da literatura sumarizados em revisões sistemáticas existentes em DPOC (17, 19). Apesar das manifestações extrapulmonares comuns, a fisiopatologia e o prognóstico são diferentes entre as DRC (20-22). Portanto, estudos que sumarizem as informações da literatura sobre a avaliação do desempenho funcional na DRC não-DPOC são necessários para direcionar a avaliação do desempenho funcional de maneira adequada a diferentes diagnósticos de DRC.

Dentre as diferentes DRC, as doenças pulmonares intersticiais (DPI) são consideradas com menor incidência quando comparado a outras DRC (2), e portanto, mais escassos são os estudos que avaliam o desempenho funcional de pacientes com DPI. Apesar de imprevisível o curso clínico da doença, a DPI é caracterizada como progressiva e com ruim prognóstico (23), com declínio do quadro geral ao longo do tempo, e consequentemente, restrição das AVDs e prejuízo na qualidade de vida. No entanto, poucos são os testes de desempenho funcional considerados válidos para a DPI, e em sua maioria realizada com

estudos que envolvem apenas a fibrose pulmonar idiopática (FPI) que é considerada a DPI mais prevalente e de caráter mais agressivo (24, 25).

Na literatura atual, apenas os testes *four-metre gait speed* (4MGS)(26, 27) e *1-minute sit-to-stand* (1min-STS)(28, 29) que consistem na avaliação da velocidade de caminhada em 4 metros e do número de repetições para se sentar e se levantar em um minuto, respectivamente, possuem propriedades métricas adequadas investigadas em pacientes com DPI em países da europa e asia. No entanto, vários outros testes de desempenho funcional que são observados na literatura ainda não possuem propriedades métricas investigadas em DPI (18). Portanto, são necessários estudos que avaliem o desempenho funcional de pacientes com DPI comparado a um grupo de indivíduos saudáveis, bem como a verificação da adequação dos instrumentos especificamente para pacientes com DPI por meio de investigação das propriedades de medida.

Os instrumentos de avaliação do desempenho funcional vêm ganhando destaque na literatura pela sua fácil aplicabilidade (15), valor prognóstico (24) e relação com outros desfechos clínicos, como as atividades de vida diária (30). Estudo com diferentes DRC relata que existe relação da atividade física da vida diária (AFVD) com o desempenho do 4MGS, e resultados inferiores a 1,07 m/s discriminam pacientes inativos (31). Nesse sentido, devido ao baixo custo para aplicação dos testes de desempenho funcional e facilidade de aplicação (15), a relação do desempenho funcional com outros desfechos clínicos, como a AFVD, podem possibilitar uma estimativa de inatividade física quando a mensuração de AFVD não estiver disponível na prática clínica, e assim estimular a prática da atividade física de acordo com a condição clínica do indivíduo ativo ou inativo.

Considerando o quadro clínico comum do paciente com DPI, a dispneia, diminuição da força muscular periférica e intolerância ao exercício tendem a piorar conforme a progressão da doença e com maior tempo de diagnóstico (32, 33), e portanto, o desempenho funcional também possa ter prejuízo no decorrer do tempo. Apesar do comprometimento do desempenho funcional estar associada a

mortalidade e hospitalização em pacientes com FPI (24, 25), a literatura atual necessita de estudos que avaliem o desempenho funcional ao longo do tempo.

Além disso, as manifestações extrapulmonares, em especial a fraqueza muscular periférica, podem impactar na manutenção do equilíbrio corporal (34), e portanto, pacientes com DPI podem apresentar alterações no equilíbrio corporal, e consequentemente, influenciar no acontecimento de quedas. A queda é definida como um evento inesperado e não intencional em que leva o indivíduo ao nível do chão ou a um nível inferior à posição inicial (35) e está associada a desfechos clínicos negativos como a mortalidade e incapacidades em outras DRC (36). No entanto, também não se sabe, se assim como pacientes com DPOC (37), os pacientes com DPI apresentam prejuízo no equilíbrio corporal e apresentam elevado número de quedas no decorrer do tempo.

Na presente tese, questões específicas sobre os instrumentos disponíveis e propriedades de medida para avaliação do desempenho funcional em DRC, e em especial na DPI, assim como a relação do desempenho funcional com a atividade física da vida diária, mudanças no desempenho funcional e no equilíbrio estático ao longo do tempo e comparação entre indivíduos classificados como caidores e não caidores foram abordadas. Quatro estudos desenvolvidos para responder estas questões foram apresentados em forma de capítulos nesta tese e uma breve contextualização com a justificativa de cada estudo foram descritos na sequência.

1.1 Introdução aos capítulos e hipóteses dos estudos

1.1.1 Artigo 1 – *Functional measures in non-COPD chronic respiratory diseases: a systematic review*

Diante da repercussão das manifestações extrapulmonares no desempenho funcional de pacientes com DRC, muitos instrumentos foram propostos para a avaliação do desempenho funcional (17). Recentes revisões

sistemáticas sumarizam informações e propriedades métricas investigadas na literatura em pacientes com DPOC (15, 17-19). Uma destas revisões sistemáticas abordam apenas instrumentos objetivos para avaliação do desempenho funcional (15), e os demais incluíram instrumentos subjetivos e objetivos da avaliação funcional (17-19), já que questionários também possuem vantagens em relação à mensuração por instrumentos objetivos, como a possibilidade de investigação de diferentes desfechos clínicos em um único instrumento subdividido em domínios, como o questionário *Medical Outcomes Study 36-item Short Form of Health Survey* (SF-36), e são frequentemente utilizados na literatura (17).

Neste sentido, até o presente momento é dificil sintetizar os instrumentos existentes confiáveis para investigar o desempenho funcional em pacientes com DRC não-DPOC. O primeiro estudo desta tese, contempla uma revisão sistemática da literatura (Capítulo 3) que busca elucidar os tipos de instrumentos mais utilizados para avaliação do desempenho funcional, bem como suas características, propriedades de medida e associações com desfechos negativos como hospitalizações e mortalidade para DRC não-DPOC.

Hipotetizou-se que existem poucos instrumentos descritos na literatura com propriedades métricas adequadas para diagnósticos específicos de DRC, e também que poucos instrumentos possuem relação com desfechos clínicos negativos. Esta revisão sistemática foi realizada por meio de uma busca em quatro bases de dados e trinta e um instrumentos subjetivos e objetivos foram encontrados em 184 estudos incluídos. Os questionários e testes de desempenho funcional mais comuns por doença, os instrumentos com propriedades métricas investigadas e a relação com desfechos clínicos negativos foram sumarizados em tabelas por doença respiratória crônica.

1.1.2. Artigo 2 – *Impairment and measurement properties of functional desempenho tests in interstitial lung disease patients*

A avaliação do desempenho funcional em pacientes com DRC cresceu nos últimos anos e vêm ganhando relevância clínica (15). Recentes estudos publicados avaliaram o desempenho funcional de pacientes com DPI por meio do *four-metre gait speed* e investigaram a relação com severidade da doença, mortalidade, hospitalização (25, 26, 38). No entanto, vários instrumentos estão disponíveis na literatura e poucos são os testes funcionais com propriedades métricas em pacientes com DPI, a maioria em amostras que incluem apenas a FPI (27-29).

Portanto, o segundo artigo desta tese (Capítulo 4), é do tipo transversal que teve como objetivo comparar o desempenho funcional em pacientes com DPI e amostra saudável, bem como avaliar a validade e reprodutibilidade de testes de desempenho funcional em pacientes com DPI. A hipótese deste estudo foi que os pacientes com DPI possuiam pior desempenho funcional comparado a indivíduos saudáveis, e também que os testes de desempenho funcional podem possuir propriedades métricas adequadas em pacientes com DPI. Foram incluídos 40 pacientes com DPI e 36 pacientes saudáveis, que realizaram três baterias de testes de desempenho funcional, de forma aleatorizada, com dois avaliadores em dois momentos diferentes. Neste capítulo é possível observar que houve diferença no desempenho funcional entre pacientes com DPI comparado a indivíduos saudáveis e quais os testes de desempenho funcional são válidos e reprodutíveis para pacientes com DPI.

1.1.3. Artigo 3 – *Timed up and go stratifies daily physical activity in patients with interstitial lung disease*

O desempenho funcional vem se mostrando associado a desfechos clínicos, como atividade física da vida diária e capacidade de exercício (31, 39) e

também com prognóstico das doenças (24) na DPOC (16, 40). No entanto, o teste de caminhada de 6 minutos (TC6min), principal teste utilizado na prática clínica para avaliar a capacidade de exercício, demanda espaço e pode ser difícil de realizar dependendo do quadro clínico do paciente. Já o teste *timed up and go*, que é um teste de capacidade física e se associa aos desfechos do TC6min possui a vantagem de ser simples, fácil e rápido de ser aplicado (15). Nesse sentido, talvez o desempenho funcional, por se tratar de uma mensuração intimamente relacionada com as atividades da vida diária, atividades estas que são realizadas frequentemente no dia-a-dia, possam também apresentar relação com a AFVD.

Em um estudo com diferentes DRC foi observado que velocidade lenta de caminhada mensurada pelo 4MGS está associado a inatividade física (31). Em pacientes com DPOC, o segundo teste que teve mais forte associação com as variáveis da AFVD foi o TUG, com bom poder discriminativo para identificar pacientes inativos (41). No entanto, ainda não está estabelecido qual a relação dos testes de desempenho funcional com as variáveis da AFVD em pacientes com DPI. Considerando que o TUG é um teste que envolve diferentes atividades da vida diária (caminhada em curta distancia, mudança de direção e o movimento de se sentar e se levantar), a hipótese do presente estudo foi que o teste TUG está associado as variáveis da AFVD, bem como que o TUG possui poder discriminativo em pacientes inativos ou inativos extremos.

O terceiro estudo desta tese (Capítulo 5) foi do tipo transversal que observou a relação do teste TUG com as variáveis da AFVD e o valor discriminativo do teste TUG para predizer inatividade e inatividade extrema em pacientes com DPI. Foram incluídos 54 pacientes com DPI, avaliados por meio do monitor de atividade física durante 6 dias por 24h, e realizaram os dois protocolos do teste TUG, em velocidade usual e rápida. Após a leitura deste artigo, é possível compreender a relação e o poder discriminativo do TUG com as variáveis da AFVD.

1.1.4 Artigo 4 – *Functional performance, balance and falls in interstitial lung disease: a preliminary one-year prospective cohort study*

As manifestações extrapulmonares da DPI envolvem a fraqueza muscular de membros inferiores, maior intolerância ao exercício, limitação as atividades da vida diária nos pacientes com DPI e tendem a piorar com a evolução da DPI (42, 43). Além disso, sabe-se que o desempenho funcional de pacientes com DPI está relacionado a piora de desfechos clínicos, envolvendo mortalidade e hospitalizações (24, 25), especialmente na FPI. Neste contexto, o equilíbrio corporal pode ser impactado pelas manifestações extrapulmonares comuns dos pacientes com DPI, assim como em outras DRC como a DPOC (44), que por sua vez está associado ao risco aumentado de quedas (45).

Neste sentido, o quarto artigo desta tese (Capítulo 6) contempla a avaliação do equilíbrio estático em pacientes com DPI, bem como a avaliação da história de quedas e o seu impacto no equilíbrio corporal e desempenho funcional em pacientes com DPI durante um ano. A hipótese deste estudo foi que pacientes com DPI com história de queda também apresentam pior desempenho funcional e equilíbrio estático no decorrer de um ano.

Para realização deste estudo foram incluídos 52 pacientes com DPI, e foram avaliados com relação ao desempenho funcional e equilíbrio estático. A história de queda em pacientes com DPI foi coletada por meio de ligações mensais e os pacientes com DPI retornaram ao laboratório para avaliação do desempenho funcional e equilíbrio estático em duas visitas a cada 6 meses. Do nosso conhecimento, trata-se do primeiro estudo na literatura que foi avaliado o equilíbrio estático de pacientes com DPI e avaliado o desempenho funcional e o equilíbrio em acompanhamento longitudinal de um ano.

1.2 Objetivos gerais da tese

- Determinar os instrumentos subjetivos e objetivos para avaliação do desempenho funcional descritos na literatura e com propriedades de medida adequadas para as diferentes doenças respiratórias crônicas não-DPOC.

- Comparar o desempenho funcional entre pacientes com DPI e individuos saudáveis, e conhecer as propriedades métricas dos testes de desempenho funcional em pacientes com DPI.

- Descrever a relação do desempenho funcional do teste *timed up and go* com a atividade física da vida diária em pacientes com DPI.

- Entender o perfil do equilíbrio e ocorrência de quedas em pacientes com DPI e observar as alterações no desempenho funcional e equilíbrio estático em pacientes com DPI caidores e não caidores em um ano.

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CAPÍTULO 2

CONTEXTUALIZAÇÃO DA TESE

2. CONTEXTUALIZAÇÃO DA TESE

2.1 As Doenças pulmonares intersticiais (DPI)

A doença pulmonar intersticial (DPI) também descrita como, doença parenquimatosa difusa nos pulmões, consiste em um grupo de mais de 300 doenças pulmonares com características clínicas similares relacionadas a inflamação e fibrose intersticial (1, 2). De acordo com a Sociedade Brasileira de Pneumologia e Tisiologia (SBPT), as doenças diagnosticadas como DPI são classificadas em cinco categorias, baseadas nos critérios clínicos, radiológicos e histológicos, são elas: causas conhecidas, pneumonias intersticiais idiopáticas, linfoides, granulomatosas e miscelânia (**Figura 1**). As patologias mais comuns são: sarcoidose, fibrose pulmonar idiopática, pneumoconioses, indução a DPI por drogas e fibrose pulmonar associada a doenças do tecido conjuntivo (DTC) (3, 4). A DPI possui menor incidência em comparação a outras doenças respiratórias crônicas, mas segundo a *European Respiratory Society* a fibrose pulmonar idiopática e a sarcoidose são as doenças mais comuns e compõem cerca de 50% das doenças intersticiais (4).

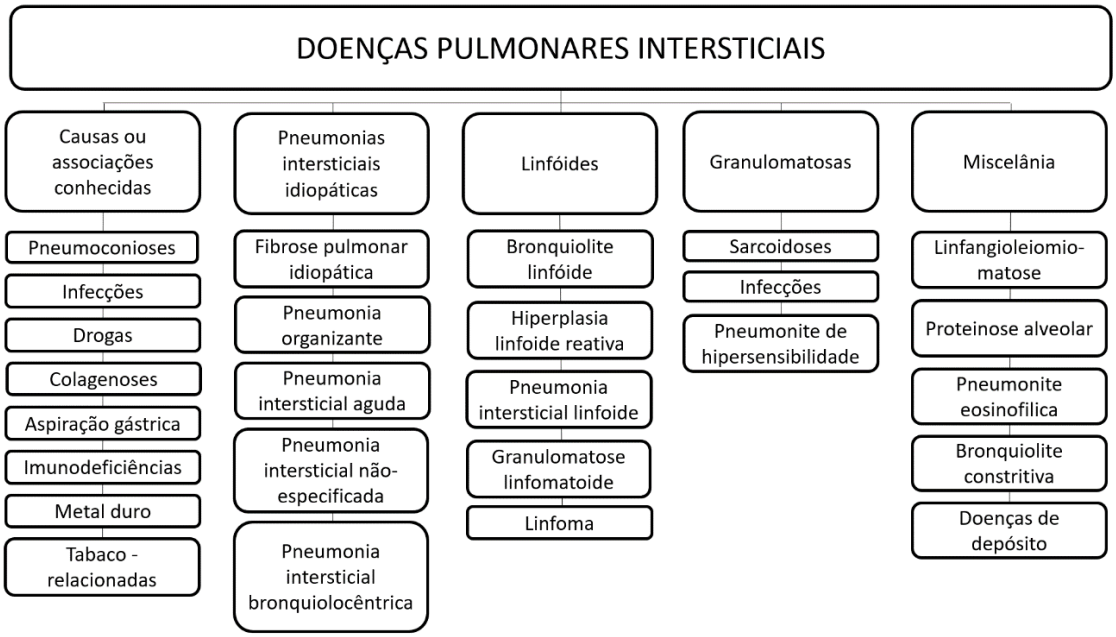

Figura 1. Classificação das doenças pulmonares intersticiais.

Fonte: Adaptado das Diretrizes de Doenças Pulmonares Intersticiais da Sociedade Brasileira de Pneumologia e Tisiologia descrita por Baldi e colaboradores (2012) (3).

O diagnóstico vai além da avaliação clínica e anamnese detalhada, são solicitados radiografia de tórax, tomografia computadorizada de alta resolução (TCAR) de tórax, testes de função pulmonar e testes de exercício para definição do diagnóstico (3). A radiografia de tórax é realizada afim de avaliar visualmente os volumes pulmonares, o padrão e a distribuição do acometimento pulmonar (3). O exame de TCAR permite caracterizar padrões que variam de acordo com a patologia, considerado fundamental para diagnostico diferencial das DPIs (3, 5). Dentre os padrões encontrados estão: padrão de vidro fosco e faveolamento (fibrose pulmonar idiopática [FPI]), padrão nodular (sarcoidose) e padrão reticular (bronquiectasias) (**Figura 2**) (5, 6). Quando o resultado da TCAR é insuficiente para diagnosticar a doença de base da DPI, técnicas invasivas como broncoscopia e biópsia pulmonar podem ser indicadas para permitir tratamento mais específico ao diagnóstico (2).

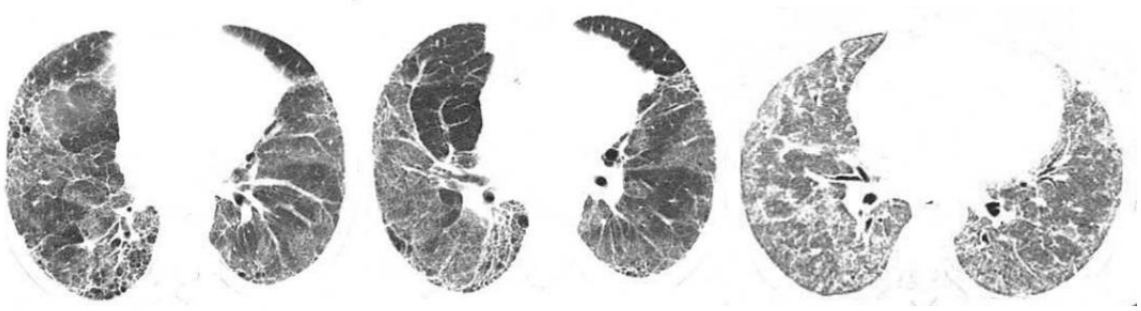

Figura 2. Imagem ilustrativa de achados patológicos característicos de fibrose pulmonar idiopática, padrões de vidro fosco e faveolamento alveolar em uma tomografia computadorizada de tórax em paciente com DPI (corte axial). Fonte: acervo da autora.

As manifestações pulmonares dos pacientes com DPI estão relacionadas as alterações na mecânica pulmonar e na troca gasosa pulmonar. Em decorrência da destruição do leito capilar pulmonar, ocasionada pela inflamação generalizada

e áreas de fibrose nas paredes alveolares resulta em incompatibilidade da ventilação-perfusão e limitações de difusão de oxigênio (7). E portanto, os pacientes com DPI tendem a apresentar redução do volume pulmonar respiratório (padrão restritivo), redução da distensibilidade alveolar e/ou do tamanho alveolar e lesão inflamatórias intersticiais prejudicando a troca gasosa pulmonar, com consequente comprometimento na função cardiovascular (8, 9). Devido a isto, os pacientes ambulatoriais com DPI, podem apresentar na gasometria arterial uma hipoxemia em repouso e, especialmente, no exercício (3).

Neste sentido, os testes de função pulmonar, mensurações objetivas dos volumes e capacidades pulmonares, podem auxiliar no diagnóstico de DPI. Por meio dos testes de função pulmonar, confirma-se o padrão restritivo pulmonar, caracterizado principalmente pela diminuição da capacidade vital forçada (CVF) e diminuição da difusão de monóxido de carbono (D_{LCO}) (3). A capacidade de difusão (D_{LCO}) é o teste mais sensível da função pulmonar por estar diretamente relacionado com a capacidade de troca gasosa (10). E por isso, tanto a capacidade vital forcada quanto o D_{LCO} são considerados indicadores da gravidade da doença em DPI (11, 12).

O curso clinico da doença é heterogêneo e, portanto, variável o prognóstico do paciente com DPI. Os pacientes podem sofrer complicações por meio de uma deterioração respiratória aguda definida como exacerbação aguda, caracterizadas por piora dos sintomas respiratórios com aumento acentuado da dispneia e hipoxemia, como também, tosse, febre, aumento da expectoração e em geral, com duração menor ou igual a 1 mês (13). A exacerbação aguda é clinicamente significativa, geralmente associada ao prejuízo nas atividades de vida diária e a qualidade de vida, além de estar associada a alta carga econômica devido à alta taxas de hospitalização, mau prognóstico e alta taxa de mortalidade (14).

As DPIs com caráter fibrosante progressivo, são caracterizadas pelo declínio da função pulmonar, piora da dispneia, deterioração da qualidade de vida, portanto, com progressiva morbidade geralmente associados a episódios agudos

de exacerbação da doença (2, 15, 16). O prognóstico é variado de acordo com a doença diagnosticada, no entanto estima-se que o prognóstico de pacientes com FPI é de 3 a 5 anos, apenas 20% dos pacientes com FPI sobrevivem após 5 anos do diagnóstico. A fibrose pulmonar associada a doença do tecido conjuntivo (DTC) também possui ruim prognóstico, porém melhor quando comparados a FPI e são variadas em função do diagnostico especifico da DTC (3, 17).

2.1.1 Intolerância ao exercício e a limitação no desempenho funcional em pacientes com DPI

Apesar do acometimento das DPIs inicialmente afetar os pulmões, os mecanismos da limitação do exercício estão relacionados com a combinação de fatores que incluem a alteração de troca gasosa pulmonar e anormalidades na mecânica ventilatória (18), associadas à manifestações sistêmicas (19). Pacientes com DPI apresentam manifestações musculares, como fraqueza muscular e fadiga, manifestações hemodinâmicas relacionadas ao prejuízo da circulação sanguínea pulmonar, que comprometem o estado geral de saúde (18). E portanto, a limitação ao exercício pode estar associada a causas pulmonares, hemodinâmicas ou musculares (20, 21).

Dentre as possíveis alterações pulmonares, os pacientes com DPI apresentam destruição do leito vascular por fibrose parenquimatosa progressiva, vasoconstrição hipóxica e volumes pulmonares reduzidos que contribuem para o aumento da resistência vascular pulmonar na DPI (7, 20, 22, 23). Com consequente limitação circulatória, o paciente com DPI está mais suscetível ao aparecimento de hipertensão arterial pulmonar, o que contribui para a disfunção cardíaca, e assim impacta na realização do exercício (alterações hemodinâmicas) (20, 22, 24).

Ao mesmo tempo, os pacientes com DPI apresentam menor força e resistência da musculatura periférica (22, 25), relacionada a hipoxemia crônica,

estresse inflamatório e oxidativo, uso de corticosteroides, inatividade física e desnutrição (22). Desta forma a hipoxemia de repouso e/ou ao esforço associado com o aumento do trabalho respiratório torna os músculos respiratórios e periféricos mais propensos à fadiga (complicações musculares) (19, 21, 25-27), contribuindo para a intolerância do exercício.

A intolerância ao exercício, pode ser observada em testes submáximos e máximos, como o teste de caminhada de 6 minutos (TC6min) e teste cardiopulmonar de esforço (TCPE) (28). Pacientes com DPI apresentam pior desempenho na capacidade de exercício comparado a indivíduos saudáveis (19). Pico de VO_2, dessaturação ao exercício e baixo desempenho na capacidade de exercício parecem estar associados à sobrevivência de pacientes com FPI (29, 30). Apesar de primariamente apresentarem alterações pulmonares, são as variáveis relacionadas ao exercício consideradas melhores preditores de prognóstico comparado aos exames de função pulmonar ao repouso (31).

Além do baixo desempenho, a fadiga é presente após ou durante a realização do exercício, contribuindo a intolerância ao exercício. Apesar da fadiga estar associada a fisiopatologia da DPI, estima-se que apenas 11% da variação da fadiga pode ser explicada pelo diagnóstico específico (32), e portanto, outros fatores podem estar relacionados com a fadiga (33). Fatores físicos, psicológicos e comportamentais como a deterioração física aguda, stress social e psicológico parecem precipitar a fadiga, enquanto que desordens do sono, inflamações, dispneia, ansiedade, depressão e efeitos colaterais medicamentosos são aspectos que contribuem na persistência da fadiga, fatores presentes nos pacientes com DPI (33).

Além do comprometimento muscular e hemodinâmico, os pacientes com DPI apresentam como queixa principal a dispneia, que piora com a realização de atividades físicas. A etiologia da dispneia é complexa e multifatorial, pode estar relacionada as lesões pulmonares, alterações da biomecânica respiratória que envolve por exemplo o aumento da frequência respiratória e também, pode estar

relacionado a hipoxemia (34). A dispneia pode estar presente em repouso nos pacientes mais graves, no entanto é intensificada na maioria dos pacientes com DPI durante o esforço físico, o que favorece os indivíduos a evitar as atividades relacionadas ao aumento da dispneia (19). A dispneia é inversamente proporcional a capacidade vital forçada (35), e demonstra estar associada ao pior prognóstico em pacientes com FPI (34, 36).

Assim, a presença de dispneia relaciona-se com a diminuição de atividade física, o que favorece a disfunção muscular e cardiovascular e contribui para manutenção em atividades mais sedentárias e, consequentemente, o descondicionamento físico (18, 19). O descondicionamento físico, por sua vez, acarreta em piora da capacidade de exercício e aumento da dispneia a pequenos esforços, o que pode caracterizar um ciclo vicioso da doença (18, 37), assim como em outras doenças respiratórias crônicas (38).

Pacientes com DPI possuem redução na capacidade de exercício e atividade física da vida diária (18, 19, 39). A redução da capacidade de exercício e a dessaturação ao exercício parecem ser bons preditores de mortalidade na DPI (31, 40). Pacientes com DPI possuem maior chance de serem dependentes nas AVD's, menor chance de possuir bons scores autorrelatados de saúde e participar de atividade física comparado a indivíduos saudáveis (41). Assim, a fisiopatologia da DPI parece possuir impacto negativo para a limitação ao exercício, e consequentemente na capacidade e independência funcional.

2.2 Conceito de funcionalidade e desempenho funcional

A funcionalidade é um termo abrangente que envolve as funções e estruturas do corpo, atividades e participação na sociedade, com diferentes definições existentes na literatura (42-44). Nesse sentido, Nagi (43) propôs a definição de saúde englobando as alterações no contexto da função física do indivíduo, e não se restringe as estruturas e funções corporais, considera-se

também as limitações de atividades, participação social, fatores ambientais e pessoais.

Baseado na definição proposta por Nagi (43), a OMS desenvolveu a classificação internacional de funcionalidade, incapacidade e saúde (CIF) para fornecer parâmetros de definições e estruturas abrangentes voltados a reabilitação. A CIF classifica a funcionalidade em domínios da função física de acordo com as atividades e participação (45). Desta forma, o contexto individual do paciente é considerado, ao invés de ter foco apenas nos aspectos fisiopatológicos das doenças (45).

A avaliação da funcionalidade vai além da observação de um único domínio ou componente corporal, porque a função física envolve diferentes componentes para realização de uma única tarefa. Por exemplo, o movimento de se sentar e se levantar exige força muscular de membros inferiores, músculos do tronco são recrutados para estabilização dos segmentos durante o movimento, e equilíbrio corporal (46, 47). Portanto, o *status* funcional envolve conceitos de força muscular periférica, condicionamento físico, coordenação e entre outros. De acordo com a atividade, movimentos e esforço físico exigido, faz-se necessário a subdivisão de diferentes domínios de funcionalidade (44).

Além destes domínios específicos para concretização da função, sabe-se que a função física é influenciada por fatores pessoais relacionados aos aspectos psicológicos. No entanto, esta tese teve enfoque na funcionalidade englobando apenas as dimensões da função física, assim como proposta por Leidy em 1994 (44). A definição de *status* funcional proposta por Leidy (44) considera diferentes aspectos físicos e divide o *status* funcional em quatro principais domínios: capacidade funcional, reserva funcional, desempenho funcional e capacidade funcional de utilização (**Figura 3**), relacionada ao esforço físico necessário para realização das atividades.

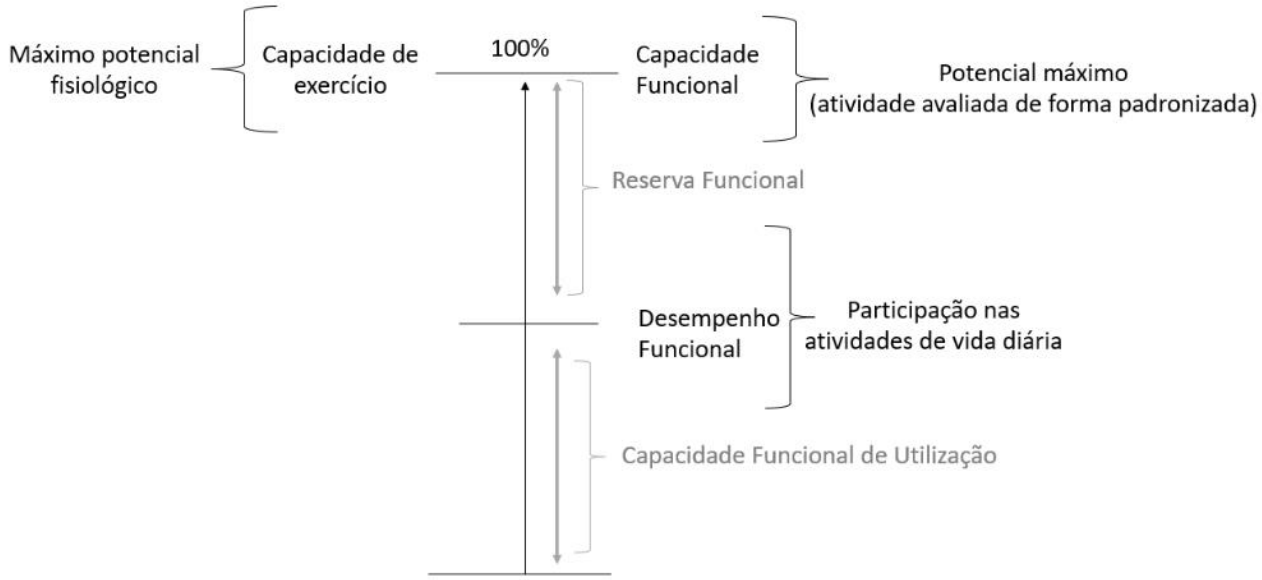

Figura 3. Classificação da funcionalidade descrita por Leidy (1994) e adaptada por Bui e colaboradores (2017). Fonte: Bui e colaboradores (2017) (45).

Capacidade funcional é definida como o potencial máximo para realizar as atividades necessárias no dia a dia (44). Dentro da fisiologia, a capacidade funcional se refere como o máximo esforço, compreendido como a maior taxa metabólica que um indivíduo consegue atingir em condições de esforço máximo (48). Testes de caminhada ou com bicicleta ergométrica, geralmente são descritos como capacidade de exercício, um aspecto da funcionalidade intimamente relacionado ao domínio de capacidade funcional (45).

O desempenho funcional é definido como a atividade que pessoas fazem no curso normal de suas vidas para alcançar as necessidades básicas, realizar as atividades usuais e necessárias para manter a sua saúde e bem-estar. Envolve a integração dos movimentos para promover de forma eficiente os movimentos necessários para se atingir as atividades de vida diária, e que geralmente não requer e nem chegue próximo ao esforço desprendido para a capacidade de exercício. Ou seja, está intimamente relacionadas às atividades de vida diária como se vestir, comer, tomar banho e atividades intermediarias para alcançar essas atividades (44, 45).

O desempenho funcional pode ser avaliado utilizando a estratégia de mensuração direta das atividades de vida diária ou avaliado por meio de questionários como o domínio de função física do *Medical Outcomes Short Form 36 item of Health Survey* (SF-36) (45). A quantificação da atividade física da vida diária (definida como a totalidade de movimentos musculoesqueléticos produzidos de forma voluntária nas tarefas do dia-a-dia) está intimamente relacionado com as AVDs e portanto, possui relação com a avaliação do desempenho funcional, principalmente quando comparados com grupo saudável (49, 50).

A reserva funcional é a diferença entre a capacidade funcional e o desempenho funcional (**Figura 3**), que é descrita como as habilidades que podem ser necessárias para execução de algumas atividades. É importante destacar que a dimensão da reserva funcional pode variar de pessoa para pessoa, de acordo com sua habilidade para desenvolver a capacidade funcional (44). E a capacidade funcional de utilização é inversamente proporcional à reserva funcional, que se refere a movimentos e habilidades básicas que compõem as atividades básicas da vida diária (44), sem elas não é possível realizar o desempenho funcional. Ou seja, para uma pessoa que possui dificuldade em realizar atividades básicas da vida diária, a capacidade funcional, estará mais próxima do desempenho funcional, e assim menor a reserva funcional (**Figura 3**).

Neste sentido, os diferentes domínios do status funcional são entrelaçados, porém cada domínio do status funcional auxilia o conhecimento sobre o impacto funcional de maneira diferente, de acordo com o esforço físico e atividade exigida (45). Em indivíduos saudáveis, a capacidade de exercício e capacidade funcional estão relacionadas ao máximo esforço possível e, portanto, mais próximo das atividades de exercício, já o desempenho funcional possui menor esforço físico e, portanto, está mais relacionado as atividades de vida diária (45).

Os conceitos relacionados aos domínios de status funcional foram definidos por Leidy (44). Recente revisão proposta por Bui *et al* (45) em pacientes com DPOC, complementou as definições estabelecidas por Leidy (44) e classificou as formas de mensuração de funcionalidade relacionando os domínios propostos por Leidy com a CIF. Este estudo é de grande relevância para o tema de funcionalidade, já que aproxima os conceitos dos domínios do status funcional com as formas de avaliação mais empregadas em DPOC na prática clínica.

Dessa forma a descrição de Bui *et al* (45) foi baseada nos movimentos exigidos e na classificação da CIF, e portanto, testes com diferentes exigências foram classificados em mesmo domínio (45). Por exemplo, o teste de caminhada de seis minutos (TC6min), caracterizado como um teste submáximo, que busca avaliar máxima distância em seis minutos, que requer grande demanda ventilatória e resistência muscular e possui relação com variáveis fisiológicas do exercício físico, foi estratificado como teste de capacidade funcional (51). E também, o teste *timed up and go* (TUG) que consiste em se levantar, caminhar, dar a volta, retornar e sentar, foi classificado também como teste de capacidade funcional.

No entanto, considerando o esforço desprendido para realização das atividades de vida diária, baseados na classificação do status funcional de Leidy (1994)(44), a presente tese, assim como os seus estudos incluídos, consideraram como instrumentos para avaliação do desempenho funcional os testes e questionários relacionados às atividades de vida diária.

A avaliação do desempenho funcional é frequentemente observada na literatura e diferentes instrumentos são propostos, divididos em dois principais constructos: instrumentos subjetivos, como questionários autorrelatados e escalas, ou instrumentos objetivos, que incluem a avaliação por meio de testes de campo, ou testes funcionais (52). As duas formas de avaliação são validas e amplamente utilizadas e podem ser complementares, a primeira descreve a pontuação do ponto de vista do paciente e a segunda possibilita a mensuração real por meio de um avaliador treinado (53).

A medida subjetiva avalia a capacidade percebida através da própria percepção do indivíduo, por meio de entrevista ou por questionário autopreenchido. Na prática clínica as medidas autorrelatadas são preferidas pelo menor tempo gasto, custo e facilidade de aplicação (54). Além disso, são meios de informação da perspectiva do próprio indivíduo sobre sua própria capacidade, portanto, podem ser mais sensíveis (55), no entanto, também são influenciadas pela cognição, linguagem, viés de memória, expectativa e estado emocional do entrevistado (56).

Em contraste, as medidas objetivas, também conhecidas como medidas baseadas em desempenho físico, dependem da confiança da habilidade de um examinador, instrumentos disponíveis e ambiente adequado (52). As avaliações objetivas podem avaliar diferentes tarefas e, portanto, com exigências diferentes relacionadas a funcionalidade, e geralmente são baseadas no desempenho observado/mensurado durante a avaliação (52, 57). As mensurações objetivas da função física possuem maior precisão para detectar ganhos funcionais (54), mesmo que não percebidos pela perspectiva do indivíduo.

Usualmente, testes de desempenho funcional, são testes mais simples comparados a testes que avaliam a capacidade de exercício, desenvolvidos com movimentos necessários no cotidiano, como sentar e levantar, andar, subir e descer escadas (45), como exemplo, pode-se citar os testes de sentar e levantar (*sit-to-stand test)*, velocidade da marcha em 4 metros (*four-metre gait speed)* e o

teste cronometrado de ir e vir (*timed up and go)* (58). Testes de desempenho funcional são amplamente utilizados por envolver movimentos básicos (58). No entanto, por se tratar de uma avaliação física, a mensuração objetiva é específica referente a uma ou mais atividades englobadas em um único resultado. Portanto, para seleção do teste funcional deve ser considerado o movimento e o impacto específico da atividade avaliada na função física do indivíduo, consequentemente a sua relevância para a população estudada e as propriedades de medida.

2.3 Testes de desempenho funcional

Diferentes instrumentos são propostos na literatura, em pacientes com doenças respiratórias crônicas alguns dos instrumentos comumente utilizados são: timed up and go (TUG), Four-metre gait speed (4MGS), 5 repetições de sentar e levantar (5rep-STS), 30 segundos do teste de sentar e levantar (30sec-STS), 1 minuto do teste de sentar e levantar (1min-STS) e short physical performance battery (SPPB) (45,58). Estes testes específicos, utilizados nos estudos incluídos nesta tese, foram descritos de forma mais aprofundada.

2.3.1 *Timed up and go*

O teste *timed up and go* (TUG), foi desenvolvido por Podsiadlo e Richardson em 1991 como um instrumento para avaliar a mobilidade física, e inicialmente, voltado a averiguação da fragilidade em pessoas idosas (59). A mobilidade física pode ser avaliada de diferentes maneiras, porém, para a elaboração do TUG foram considerados as atividades básicas de mobilidade que envolvem o equilíbrio e manobras da marcha utilizadas diariamente (59).

A versão atual do TUG de Podsiadlo, que envolve se levantar, ir, dar volta, retornar e sentar, foi o resultado da adaptação do teste proposto por Mathias e colaboradores em 1986 (60), que envolve a observação da execução e, de acordo com a avaliação visual do avaliador era atribuído uma pontuação de 0 a 5, e portanto, impreciso e não confiável. Afim de melhorar a precisão do teste descrito

por Mathias e colaboradores (60), Podsiadlo & Richarson propuseram a avaliação objetiva e direta do TUG (59), o desfecho do teste passou a ser a duração do tempo de teste (segundos), e assim, o teste cronometrado minimizou a parcialidade do avaliador.

O TUG (**Figura 4**) é um instrumento frequentemente aplicado na prática clínica para avaliação funcional de mobilidade, velocidade e capacidade para caminhar, também possibilita avaliação do equilíbrio dinâmico e risco de queda (59). Além disso, na literatura o TUG é aplicado para pacientes com diferentes condições clínicas, incluindo diferentes doenças respiratórias crônicas como asma (61) e DPOC (62). É reconhecido por ser um teste simples, barato e confiável (59) e de fácil execução, o que facilita sua aplicação na prática clínica.

Para execução do TUG o participante é instruído a se levantar, caminhar por 3 metros, dar a volta, retornar e sentar (**Figura 4**), o tempo de teste é cronometrado pelo avaliador. O participante inicia o teste com a coluna encostada na cadeira e nenhuma assistência é fornecida para realização do teste. O participante pode realizar o teste com o seu calçado usual, que não o atrapalhe para desempenho e caso necessário pode utilizar seu equipamento acessório a marcha (62). No protocolo instruído por Podsiadlo & Richardson (59), o participante é orientado a caminhar na sua velocidade usual (TUGu), porém outra versão do teste encontrada na literatura propõe também a sua execução na velocidade rápida (TUGf), na qual o sujeito é instruído a andar o mais rápido que puder, sem correr (58).

Figura 4. Imagem ilustrativa da execução do teste *timed up and go*. Fonte: acervo da autora.

O desfecho do TUG é tempo de execução do teste e quanto maior o tempo para execução do teste maior a dificuldade para a realização das atividades funcionais, pior o resultado. Sugere-se que seja realizado ao menos duas execuções e o melhor desempenho seja utilizado (63). Apesar da sua simplicidade para execução, resultados prolongados no TUG estão relacionado com desfechos clínicos negativos, como a queda (64). Idosos que possuem desempenho maior do que 10 segundos são idosos com maior fragilidade (65) e desempenho superior a 20 segundos está associado a mortalidade (66). Como os estudos incluídos nesta tese é composto de mulheres e homens com idade próxima a 60 anos, foi considerado o valor de normalidade do TUG descrito na literatura para população brasileira de 60 a 69 anos: ≤12,47 e ≤10,06 segundos para velocidade usual, ≤10,60 e ≤8,26 segundos na velocidade rápida, respectivamente (67).

2.3.2 *Four-metre gait speed*

Four-metre gait speed (4MGS) é um teste de desempenho funcional para avaliação da velocidade da marcha (68). A avaliação da velocidade da marcha pelo 4MGS é considerada um importante item na avaliação de pacientes com diferentes patologias: cardíacas (69), respiratórias (68), musculoesqueléticas (70)

e neurológicas (71). E em doenças respiratórias crônicas, o 4MGS é um dos testes de desempenho funcional mais utilizados (58, 61, 68, 72, 73).

O 4MGS é considerado um teste simples, rápido e fácil de ser aplicado, necessitando apenas do avaliador, cronometro e um corredor (74). Diferentes protocolos são encontrados com relação ao espaço para ser realizado o teste (i.e 8m e 4m), no protocolo mais encontrado na revisão sistemática o participante é instruído a caminhar na sua velocidade usual por 8 metros, os 2 metros iniciais e finais são considerados para a aceleração e desaceleração do movimento (**Figura 5**), apenas o tempo gasto para caminhar os quatro metros é cronometrado e o desfecho do teste é metros por segundos (68, 74).

O desempenho do teste é a velocidade da marcha descrita em metros por segundos. Devem ser realizadas ao menos duas execuções e a melhor execução, ou seja, o menor tempo gasto durante o teste é utilizado. É permitido ao participante, caso seja necessário, utilizar seu dispositivo auxiliar para marcha (68). Na literatura outros protocolos para avaliação da marcha já foram descritos, com velocidade rápida e com caminhada em 10 metros, no entanto o protocolo do 4MGS em velocidade usual é o mais utilizado (72).

O desempenho do 4MGS em velocidade usual, e quando avaliada em metros por segundos, é considerada como normal quando acima de 0.80m/s e lenta quando abaixo de 0,80m/s (72, 75). Idosos que apresentam marcha lentificada (<0,80m/s) possuem maior risco de apresentar sarcopenia e apresentar quedas (72) e desempenho abaixo de 1,0 m/s está associado a maior risco de hospitalizações e mortalidade em idosos (72). Neste sentido, a avaliação da velocidade da marcha, especialmente por meio do 4MGS, demonstra cada vez mais relevância clínica e valor prognostico em diferentes populações. O valor de normalidade descrito na literatura, para mulheres e homens saudáveis brasileiros de 60 a 69 anos no desempenho em velocidade usual foi de ≥0,67m/s e ≥0,84 m/s, respectivamente (67).

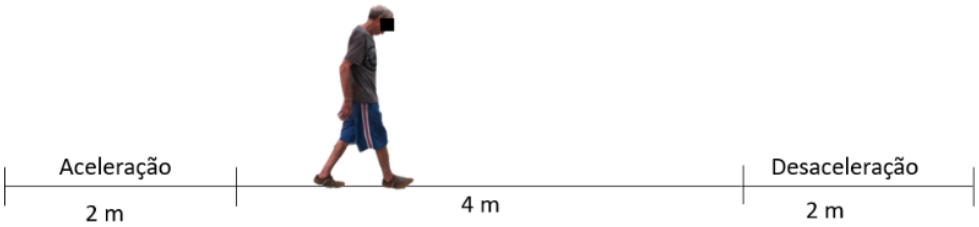

Figura 5. Imagem ilustrativa da execução do teste *four-metre gait speed*. Fonte: acervo da autora.

2.3.3 *Sit-to-Stand Test*

Os protocolos de sentar e levantar, descritos nesta tese como *sit-to-stand test* avaliam a desempenho funcional por meio do movimento de levantar-se e se sentar (**Figura 6**), que é considerado um movimento de transição de posturas (76) mais realizados pelos seres humanos (46, 47). Existem diferentes protocolos descritos na literatura: 5 repetições (5rep-STS), 30 segundos (30sec-STS), 1 minuto (1min-STS), 2 e 3 minutos de sentar e levantar (77, 78). No entanto, a maioria dos estudos na literatura utilizam os três primeiros protocolos descritos (79).

O teste de 5 repetições de sentar e levantar (5rep-STS) consiste em executar cinco movimentos completos de se levantar e se sentar o mais rápido possível, e o desfecho é tempo de duração do teste (segundos) (80). Os demais protocolos possuem tempo estabelecido e solicitam o maior número de execuções do movimento de se levantar e se sentar dentro do tempo estipulado, seja 30 segundos, 1, 2 ou 3 minutos, de acordo com o protocolo selecionado, e o desfecho do teste é número de execuções (58, 79).

Para realização do teste, é necessário cadeira sem apoio para braço e um cronometro, seja para marcar o tempo do desempenho no teste de 5 repetições, ou delimitar o tempo de teste nos protocolos com tempo definido (**Figura 6**). O indivíduo pode realizar o teste com o seu sapato e é orientado a permanecer durante as execuções com o membro superior cruzado no tronco para evitar o

apoio na execução do teste. A reprodutibilidade do teste foi previamente estabelecida, com necessidade de duas execuções do teste, e como resultado é considerado a melhor execução, ou seja, maior número de repetições para os protocolos com tempo estabelecido e menor tempo de desempenho para realização das 5 repetições (5rep-STS) (81, 82).

A posição ideal para realização do teste é com a cadeira encostada na parede, para promover segurança durante as execuções, e idealmente, a posição sentada com flexão de quadril, joelho e tornozelo em 90 graus (81). No entanto, cadeiras ajustáveis podem refletir insegurança ao paciente para realização do teste e, portanto, na literatura é encontrado variação da altura de cadeiras com 40 a 48cm para realização do teste (82). Apesar de não ser possível o ajuste adequado das articulações em posição ideal para todos os pacientes, no cotidiano os pacientes encontram cadeiras com a mesma variação de altura, o que sugere que não há comprometimento da validade externa dos resultados encontrados (82-84).

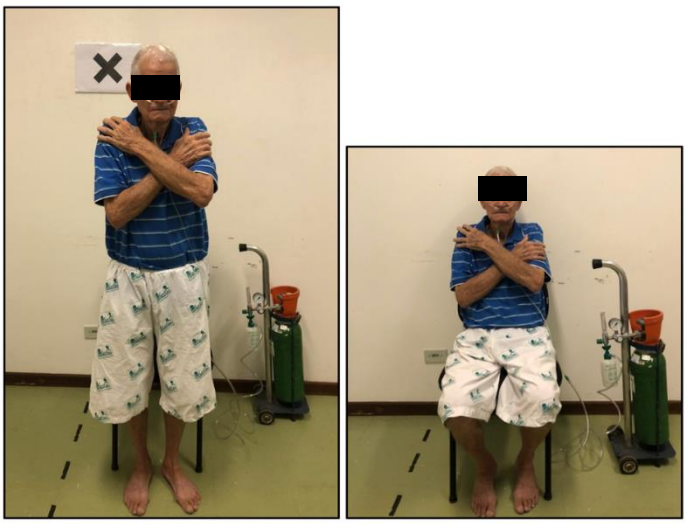

Figura 6. Imagem ilustrativa da realização do teste de sentar e levantar (*sit-to-stand test)*. Fonte: acervo da autora.

Os protocos do *sit-to-stand test* são utilizados e validados em diferentes populações, como em idosos (81) e pacientes com patologias ortopédicas (85), neurológicas (86) e cardiorespiratórias (58). Apesar de ser necessário equilíbrio, controle de tronco e capacidade cognitiva para realização do movimento de sentar e levantar, este movimento é primariamente realizado pelos membros inferiores (87), e portanto, o *sit-to-stand* é descrito também na literatura como avaliação funcional de membros inferiores (58). Neste sentido, diferentes protocolos do s*it-to-stand* possuem relação com avaliação de força de quadríceps em pacientes com doenças respiratórias crônicas não-DPOC (39, 58, 61, 88). O valor de normalidade dos testes 5rep-STS, 30sec-STS e 1min-STS para indivíduos saudáveis de 60 a 69 anos foi ≤13,72 e ≤14,93 segundos, ≥11 e ≥13 repetições, ≥22 e ≥23 repetições, para mulheres e homens, respectivamente (67).

2.3.4 Short physical performance battery

Short Physical Performance Battery (SPPB) avalia o desempenho funcional por meio de três componentes da função dos membros inferiores: equilíbrio estático em pé, velocidade de marcha em passo habitual e força indireta de membros inferiores (89). O SPPB foi criado nos Estados Unidos, e tem como principal autor Jack M. Guralnik, a adaptação cultural para o Brasil e avaliação da reprodutibilidade da SPPB foi feita por Nakano e colaboradores (90). Em cada componente, um teste é avaliado com pontuação de 0 a 4, a somatória do resultado de cada componente é o escore total do SPPB, com variação de 0 a 12 pontos (75) (**Figura 7**). Pontuação de 0 a 6 é considerada uma baixa performance, 7 a 9 performance moderada e acima de 10 performance adequada, ou seja, quanto maior a pontuação do SPPB melhor o desempenho funcional do indivíduo (89, 91).

Figura 7. Imagem ilustrativa dos três componentes avaliados no *Short Physical Performance Battery*. Fonte: acervo da autora.

O componente de equilíbrio se refere a avaliação do equilíbrio estático, pelo posicionamento em pé em três diferentes posições: romberg, semi-tandem e tandem (**Figura 7**). O componente de velocidade de marcha é realizado por meio do teste 4MGS (descrito no item 2.3.2). O participante é instruído a caminhar na velocidade usual, e o tempo gasto para percorrer 4 metros é cronometrado. O desfecho do teste é o tempo e de acordo com o resultado é dada a pontuação deste componente, quanto menor o tempo de teste melhor o resultado. Para a pontuação utiliza-se a execução mais rápida de duas tentativas (91). O componente de força indireta de membros inferiores é avaliado pelo teste 5rep-STS (descrito no item 2.3.3) devido a correlação do número de execuções do teste com a força muscular de quadríceps femoral (92). As classificações das pontuações de cada componente do SPPB foram descritas na **Tabela 1**.

Tabela 1. Pontuação de cada componente do score total do SPPB.

Pontuação	Equilíbrio	Velocidade de marcha	Força indireta de MMII
1	Romberg: 10s ou Semi-Tandem: 10s ou Tandem: até 3s	>8,7s	>16,7s
2	Romberg: 10s e Semi-Tandem:10s ou Tandem:10s	6,21 a 8,7s	13,7 a 16,6s

3	Romberg: 10s Semi-Tandem: 10s Tandem: 3 a 9,9s	4,82 a 6,20s	11,2 a 13,6s
4	Romberg: 10s Semi-Tandem: 10s Tandem: 10s	<4,81s	<11,1s

Legenda: MMII: membros inferiores. Fonte: Tabela elaborada pela autora.

O SPPB é amplamente utilizado para avaliação funcional de idosos (91, 93). Idosos com comprometimento funcional, avaliado pelo desempenho no SPPB, possuem maior risco de apresentar quedas (75, 93) e sarcopenia, e o desempenho no SPPB é preditor de hospitalizações (94) e mortalidade (95). Apesar de o SPPB ser amplamente utilizado em idosos, este teste também é utilizado em diferentes doenças, inclusive doenças respiratórias crônicas, como asma, DPOC e DPI (61, 96, 97), e em DPOC possui valor preditivo com desfechos negativos como sarcopenia e mortalidade (97, 98).

2. 4 Equilíbrio corporal

Equilíbrio é um termo comum, frequentemente usado por profissionais de saúde em diferentes especialidades, e geralmente, está associado a estabilidade e controle postural (99). Apesar do uso difundido deste termo, diferentes definições de equilíbrio corporal foram descritas (100), as duas principais definições aceitas são: “um conceito multidimensional, que se refere a habilidade de uma pessoa não cair” (100, 101), ou “habilidade de manter o centro de massa corporal no interior da base de suporte ou sustentação” (102).

O equilíbrio envolve um processo complexo de ações coordenadas dos componentes biomecânicos, sensoriais e neuromotores. Os sistemas sensoriais detectam as oscilações posturais do corpo e geram respostas compensatórias no sistema muscular para as correções e ajustes necessários para manutenção do equilíbrio postural (101), e assim permitir o desempenho das atividades de vida

diária (103). O equilíbrio pode ser dividido em estático e dinâmico, ambos investigados para avaliar a independência nas atividades de vida diária (104).

O equilíbrio estático, também descrito como controle postural, envolve função, anatomia e limites mecânicos para manter a estabilidade sem mudar a base de suporte, ou seja, quando as estratégias de manutenção corporal estão relacionadas a base de suporte (105). Refere-se a distância ou ângulo voluntário máximo que o indivíduo pode deslocar seu centro de gravidade em uma determinada direção, sem retirar sua base de suporte de lugar, e sem perder o equilíbrio (106), em outras palavras relacionado especificamente com a manutenção da posição corporal (104). O equilíbrio dinâmico é essencial para o controle motor e é dependente do centro de gravidade, se refere ao deslocamento do peso e atividade muscular (107), ou seja, ao ajuste postural durante atividade motora.

Assim como o desempenho funcional (descrita no item 2.2.1), a avaliação do equilíbrio pode ser realizada de forma subjetiva, com uso de escalas ou questionários e de forma objetiva por meio da plataforma de força ou testes funcionais que requisitam controle postural (103). A avaliação por meio de escalas, depende da percepção do indivíduo e das escalas disponíveis na literatura, geralmente relacionado a informações do complexo motor, não exclusivamente ao equilíbrio corporal. Neste sentido, a avaliação subjetiva oferece maior viés, em comparação as formas objetivas de avaliação postural e, portanto, as formas objetivas devem ser priorizadas na avaliação postural (103).

A avaliação do equilíbrio dinâmico pode ser realizada por meio de testes de desempenho funcional, nos quais, geralmente são solicitadas atividades motoras e a pontuação também é dada com base no desempenho motor, no entanto, sem influência da percepção individual. São alguns testes reconhecidos que avaliam o equilíbrio postural, os testes TUG (descrito no item 2.3.1), *BESTest (108)*, *Mini-BESTest (109)*, *Berg-balance scale* (103) e SPPB (110) (descrito no item 2.3.4). A avaliação do equilíbrio estático também pode ser realizada por meio de testes

funcionais como o teste de apoio unipodal, nesse caso o desfecho é o tempo (103). No entanto, a avaliação do equilíbrio estático por meio da plataforma de força é mais sensível as alterações e amplamente utilizada na literatura.

2.4.1 Avaliação do equilíbrio estático pela plataforma de força

A avaliação do equilíbrio estático na literatura é realizada principalmente por meio da plataforma de força, constituída por sensores (células de carga) que quantificam a magnitude da força de reação dos pés na posição vertical. A avaliação da plataforma de força possibilita a mensuração das oscilações corporais durante a postura ereta, já que o corpo nunca está em uma condição de total equilíbrio, pois as forças que atuam sobre ele são nulas apenas momentaneamente. Apesar do alto custo, o deslocamento corporal sobre a plataforma de força é descrito em diferentes parâmetros, que expressam objetivamente o controle postural de forma mais acurada (111).

Os sinais elétricos de força são transformados por meio de uma análise estabilográfica para extrair os principais parâmetros de equilíbrio associados aos movimentos do centro oscilatório de pressão (COP). Dentre as possíveis mensurações da plataforma de força, além do centro oscilatório de pressão, são avaliados a amplitude do deslocamento, frequência das oscilações e a velocidade das oscilações nos sentidos antero-posterior e mediolateral (112). Em geral, os parâmetros mais sensíveis para detectar as diferenças no equilíbrio postural entre diferentes grupos de indivíduos, assim como os mais fidedignos, são a área elipse de deslocamento do COP e a velocidade de oscilação do COP em ambas as direções do movimento (111, 113).

Diferentes posições ortostáticas são solicitadas na avaliação da plataforma de força, entre elas a posição bipodal e unipodal são frequentemente empregadas (**Figura 8**) (114). As posições romberg e semi-tandem também podem ser avaliadas na plataforma de força, e alguns estudos avaliam o equilíbrio sobre superfícies mais instáveis, posicionando espuma (ou outro material) sobre a plataforma de força (114, 115). Apesar da posição unipodal ser frequentemente

estudada por estar associada com o risco de quedas em idosos (116), é uma posição mais difícil de ser executada e não é possível de ser mantida por todos os indivíduos (114), o que limita as informações obtidas na avaliação postural.

Figura 8. Imagem ilustrativa da avaliação do equilíbrio estático pela plataforma de força em posição bipodal e unipodal. Fonte: acervo da autora.

2.5 Risco e avaliação de quedas

O comprometimento do equilíbrio corporal associado a alterações sistêmicas como a fraqueza muscular favorecem a ocorrência de quedas em idosos e em pacientes com DPOC (117, 118). A queda é um evento não intencional, multifatorial, acidental, involuntário, repentino ou não planejado onde o indivíduo se desloca a um nível inferior da posição inicial, relacionado a perigos ambientais ou maior suscetibilidade pelas características individuais (119, 120).

Estima-se que um terço dos idosos acima de 65 anos experienciam ao menos uma queda por ano, e ocorre aumento dessa proporção conforme o aumento da idade (121-123). A maioria das quedas ocorrem durante o dia, durante atividades de vida diária (123, 124). As repercussões negativas relacionadas a quedas são conhecidas mundialmente (125), estão associadas a piora da

qualidade de vida, dependência para as AVDs, necessidade de hospitalização e por sua vez aumento dos gastos hospitalares, com altos índices de mortalidade em idosos internados por queda (126).

Diante das consequências físicas associadas a queda, a sua avaliação é extremamente relevante e frequentemente observada em especial nos estudos com população idosa (120), mas também em pacientes com outras doenças crônicas, como a DPOC e a asma (117, 127). A avaliação de quedas é realizada e descrita de diferentes maneiras na literatura (119), a forma descrita mais frequente encontrada em uma revisão sistemática foi o número de pessoas com história de queda, porém a queda também pode ser avaliada pelo o número de quedas no decorrer de um tempo, taxas de quedas, localização e características associadas a queda e o tempo para o evento da queda, dependendo do design de cada estudo (119, 120).

Ainda, pessoas com quedas recorrentes (≥2 quedas) possuem maior morbidade e mortalidade comparadas a pessoas que apresentam apenas uma história de queda (120). Assim, a discriminação de pacientes baseado no número e história de quedas pode contribuir para a compreensão das alterações presentes nos pacientes com história de queda. Já com relação a avaliação do risco de quedas, sugere-se que sejam realizados estudos prospectivos com um ano de acompanhamento para permitir avaliação dos fatores associados a queda (119, 128).

2.6 Propriedades de medida

Propriedades de medida são definidas como critérios estatísticos que direcionam os avaliadores da área de saúde a selecionar um instrumento apropriado para população estudada (129). As propriedades de medida se referem a três principais conceitos: validade, reprodutibilidade e responsividade (129). A validade e reprodutibilidade são os domínios mais tradicionais avaliados e se

aplicam tanto a medidas derivadas de um teste, instrumento de coleta de dados, técnicas de aferição, quanto ao delineamento da investigação – a pesquisa propriamente dita. Já a responsividade, investiga a mudança no desfecho ao longo do tempo ou após uma intervenção (129). Diante da variedade de aspectos que englobam as propriedades de medida, as classificações de validade, reprodutibilidade e responsividade foram sumarizados na **Tabela 1**.

Quadro 1. Definições de propriedades de medida descritas por Bui *et al* (130), Polit *et al* (129) e COSMIN (131).

Propriedades de medida	**Definição**
Validade	
Validade de conteúdo	Adequação da relevância do conteúdo para instrumentos que possuem vários itens de um constructo
Validade concorrente	Nível de associação dos resultados obtidos no instrumento com outro instrumento de referência.
Validade de constructo	Nível de associação de resultados obtidos entre dois instrumentos que mensuram o mesmo aspecto
Validade convergente	Capacidade de fornecer resultados altamente correlacionados com outro teste, instrumento ou questionário que medem o mesmo constructo, na falta de um instrumento padrão ouro,
Validade de critério	Se refere ao quão bem relacionadas uma medida está com a medida de referência (padrão ouro)
Validade discriminativa	Habilidade de distinguir os resultados obtidos por dois grupos com características diferentes
Reprodutibilidade	
Consistência interna	Correlação entre elementos que deveriam medir o mesmo conceito no mesmo teste ou questionário
Intra-avaliadores	Capacidade de um avaliador repetir o mesmo resultado com os mesmos participantes, no mesmo contexto.
Inter-avaliadores	Capacidade de mais de um avaliador repetir a mesma medida com os mesmos participantes em mesmo contexto, e em diferentes ocasiões, e para obter resultados semelhantes.
Teste-reteste	Capacidade de dar os mesmos resultados com repetidas avaliações, nas mesmas condições em momentos diferentes.
Erro padrão de medida (SEM)	Quantificação de reprodutibilidade que representa o padrão desvio de desvio de erros de medição.
Responsividade	

Mudanças longitudinais	Capacidade de detectar mudanças clinicamente relevantes no decorrer do tempo
Interpretabilidade	
Mínima diferença clínica importante (MDCI)	Mínima mudança necessária para mostrar uma mudança significativa para o paciente
Mínima diferença detectável (MDD)	Mínima mudança estatisticamente perceptível superior ao erro padrão de medida

Fonte: Tabela elaborada pela autora.

A validade é definida pelo COSMIN como o grau que um instrumento (questionário ou teste) realmente mede o constructo/aspecto que foi proposto e desenvolvido para medir (131). Em outras palavras, um instrumento é válido na extensão em que mede aquilo que se propõe medir e pode ser comparado com o padrão de referência (129). É comum apresentar-se a validade de um instrumento como o seu primeiro requisito, mas, para ser válida uma medida deve também ser confiável (132).

A reprodutibilidade se refere à capacidade de se obter o mesmo resultado medido por instrumentos similares ou paralelos, com diferentes avaliadores e em momentos diferentes. Uma medida fidedigna é constante e precisa, porque fornece uma medida estável de variação, ou seja, possui elevado coeficiente de segurança, ou baixa margem de erro do aparelho de medição (133). Em outras palavras, a reprodutibilidade de uma medida é a confiança que a mesma inspira. Os dois aspectos da reprodutibilidade mais frequentemente avaliados são a reprodutibilidade interavaliadores, quando o instrumento é avaliado por diferentes avaliadores, e a reprodutibilidade teste-reteste, quando o instrumento é avaliado em momentos diferentes (131, 133).

Quando se deseja avaliar as mudanças ao longo do tempo – decorrentes de um procedimento ou um tratamento - uma terceira propriedade que pode ser investigada, a responsividade (134), também chamada de sensibilidade para mudanças. E a interpretabilidade, é a habilidade do instrumento medir mudanças pequenas, mas clinicamente importantes que o sujeito desenvolve em resposta a uma intervenção terapêutica efetiva (129, 130, 131). Ou seja, mudanças clínicas importantes, geralmente associadas a mudanças nas pontuações de outros instrumentos e domínios (131). A interepretabilitadade não é considerada uma

propriedade de medida, mas uma característica importante de um instrumento de medida (131).

Os aspectos das propriedades de medida não são traços estáticos de instrumentos, mas variam em função de contextos, propósitos e populações. E assim, não é incomum a utilização de instrumentos na prática clínica sem propriedades de medidas adequadas, ou instrumentos descritos como válidos e confiáveis mensurados de maneira inadequada, e portanto não deveriam ser recomendados para o uso na prática clínica (135, 136). Neste sentido, a avaliação das propriedades de medidas é necessária para verificar adequação do instrumento em diferentes populações.

2.7 Referências

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CAPÍTULO 3

Functional measures in non-COPD chronic respiratory diseases: a systematic review.

Zamboti CL, Garcia T, Krinski GG, Bertin LD, Almeida HDS, Pimpão HA, Tavares BL, Cavalheri V, Ribeiro M, Pitta F, Camillo CA.

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Functional measures in non-COPD chronic respiratory diseases: a systematic review

Running title: Functional performance in chronic respiratory diseases

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Take-home message:

Although functional performance is vastly studied in non-COPD chronic respiratory diseases, few instruments have acceptable measurement properties, mostly in ILD and asthma and association with negative outcomes remains to be elucidated.

Abstract

Introduction: Functional performance (FP) is widely investigated in non-COPD chronic respiratory diseases (CRD). The vast number of available tools to assess FP makes the decision to select the which one is most appropriate difficult and know the information of measurement properties could facilitate this decision. **Objectives:** To identify FP instruments, their measurement properties, and the association with negative outcomes in non-COPD chronic respiratory diseases. **Search methodology:** Studies were systematically identified from a literature search using PubMed, PEDro, EMBASE and CENTRAL databases, the reference lists of the included articles and via hand searching. **Study Selection**: Studies including at least one instrument to assess functional performance as an outcome in any non-COPD chronic respiratory diseases. No limits were applied for year and language. **Data Extraction:** Two researchers independently performed study selection. Sample characteristics, instruments and available data, their measurement properties and the association with negative outcomes (e.g. mortality and hospitalization) were selected for extraction. The quality of studies was assessed by COSMIN risk of bias, PEDro and Downs & Black, according to studies designs. **Data Synthesis:** One hundred and eighty-four studies were included with thirty-one different instruments, in seven subgroups of diseases: asthma, bronchiectasis, cystic fibrosis (CF), interstitial lung disease (ILD), pulmonary arterial hypertension (PAH) and subjects with CRD in the waiting list for or who underwent lung transplantation (LTx). Interstitial lung disease was the subgroup with most studies investigating FP. The assessment of FP was more frequent with questionnaires. The most common tool was the domain of physical function or physical component summary in the “Medical Outcomes Study 36-item Short Form of Health Survey”, followed by the domain activities of the “Saint´s George Respiratory Questionnaire”. The one-minute sit-to-stand (1min-STS) and the four-metre gait speed (4MGS) were the most common FP tests used. Measurement properties of instruments (i.e. subjective or objective) were investigated mostly in FP tests, although in included studies few present

acceptable measurement properties, mainly in patients with asthma and ILD. Associations with negative outcomes included: mortality and hospitalisation in ILD (using 4MGS and 8-Foot-up-and-go test), mortality in PAH (using the NYHA and WHO functional class, and the physical score in the Minessota living with heart failure questionnaire) and exacerbation frequency (using physical function score of the Seattle Obstructive Lung Disease Questionnaire) in bronchiectasis. **Conclusion:** Functional performance is vastly studied in non-COPD chronic respiratory diseases, thirty-one instruments were found in seven subgroups of diseases. The SF-36 was the instrument most used, however, in the current literature, in included studies only a few instruments have acceptable measurement properties in non-COPD chronic respiratory diseases, mostly in ILD and asthma. Association with mortality and hospitalisations are scarcely reported and exist with 4MGS and 8-FUGT in ILD and NYHA, WHOfc and MLHFQ in PAH.

Key Words: Systematic review; lung disease; Functional capacity; Functional status; metric properties.

Background

Chronic respiratory diseases (CRDs) are among the most common diseases worldwide, including chronic obstructive pulmonary disease (COPD), asthma, interstitial lung diseases, bronchiectasis and cystic fibrosis (1, 2). In 2017, it was estimated that 545 million people in the world had a CRD and this number has been increasing over time (1). With the disease progression, patients experience similar symptoms, such as dyspnoea, compromised ventilatory mechanics and lower O_2 diffusion capacity which corroborates to a complex and often unpredictable disease course (3). Additionally, reduced muscle strength, exertional dyspnoea and exercise intolerance are common extrapulmonary manifestations in CRDs leading to a reduced participation in daily physical activities and poor health-related quality of life (4). Thus, the assessment of patients' ability to carry out daily tasks and fulfil their social roles (i.e. assessing their functional performance) has become an important piece within the management of CRDs (5).

Functional performance (FP) tools are instruments used to evaluate the impact of a clinical condition on their ability to perform activities and are classified according to their purpose and what is required in the instrument (6). Functional performance is widely investigated in CRDs, especially in patients with chronic obstructive pulmonary disease (COPD) (7, 8). There is a large number of studies assessing FP in COPD and recent systematic reviews (7-12) summarize FP tools, clinical setting needs and measurement properties. Recent findings suggest that FP instruments are related with mortality and hospitalisation in COPD (12). Such level of knowledge, however, is surprisingly unknown in other CRDs. Albeit the extrapulmonary manifestations of CRDs might be similar, one cannot use interchangeably FP tools amongst CRDs unless there is data supporting its use.

Functional status can be measured by several methods with varying constructs, usually divided into two types: patient-reported tools (e.g. questionnaires, scales) and performance-based tests (e.g. functional performance tests). Performance-based tests require everyday tasks involving basic movements, related with physical performance and changing body positions (8,

10). In contrast, patient-reported tools consider individual's opinion about their own capacity and difficulties (13). Questionnaires or scales assess specifically functional performance, or comprise a subset of a total score that reflects overall health status (6). The ease of application and availability of such tools may explain why questionnaires and scales are more often used in clinical practice. Finally, the selection of a FP tool relies on the presence of adequate measurement properties for a specific disease group (6). Measurement properties encompass many statistical tests studies tend to report only few aspects of measurement properties for each time, according to design of study. This is particularly troublesome to the clinician who needs to select a FP tool as a complete overview of its measurement properties might only be available after a long literature search.

Selecting the most appropriate FP instrument to a specific CRD might be challenging due to the vast number of available tools, instrument's reliability, and conflicting information (9). Thus, there is a need for studies that can comprehensively summarise available FP instruments, their clinical relevance, their measurement properties and associations with negative outcomes to facilitate the selection of the most appropriated tool to clinical practice. In this systematic review of the literature, we aimed to identify FP instruments, functional performance tests or patient-reported outcome measure, previously used in non-COPD CRD, provide their characteristics, measurement properties and associations with negative outcomes in non-COPD chronic respiratory diseases.

Methods

Protocol

The protocol of this study was registered in PROSPERO (CRD42018102771). No protocol had been previously published for this review. There was no restriction of language and year of publication. Any study that used a functional performance test (i.e. objective measure) or patient-reported outcome measures (i.e. subjective measure), such as questionnaires to assess functional performance in people with any non-COPD chronic respiratory diseases was

included. This review rather explores and report the functional performance tests and questionnaires available for patients with non-COPD chronic respiratory diseases, and it is not a systematic review that investigates effectiveness of a specific intervention. This study reports functional performance tests and questionnaires available for any non-COPD chronic respiratory disease. This study aims to include only instruments (functional performance tests or questionnaires or scales) which investigates activities motivated by personal bodily needs as activities of daily living (ADL) such as intermediate activities to enable these needs (5). Exercise capacity tests such as 6-minute walk test (6MWT) or cardiopulmonary exercise test (CPET), questionnaires which do not provide specific measurement related with functional performance or other domains of functional measures were not investigated in this study. Also, case report, case series and studies with only qualitative results were excluded.

Information sources, search and study selection

We used the four following electronic bibliographic databases for the search: EMBASE, Cochrane Cochrane Library, PEDro and MEDLINE. The search strategy included only terms relating to or describing functional tests in chronic respiratory diseases. The search terms used were a combination of: (lung or pulmonary or respiratory or cystic fibrosis) AND (walk/gait speed or sit-to-stand or chair-stand or 4MGS or muscle dysfunction or physical function or physical performance or functional capacity or physical fitness). The search terms were adapted for use with other bibliographic databases. Full manuscripts published in any language in a peer reviewed journal were eligible. Also, for subjective measures composed by domains to assess different variables, only domain associated with functional performance was considered. Studies with mixed population of people with COPD, lung cancer and other chronic lung diseases in statistical analysis, as well as groups with children, where subgroup reporting/analysis have not been presented/undertaken were excluded. The searches were re-run just before the final analyses in august of 2021 and further studies retrieved for inclusion.

A standardized eligibility assessment was performed by two independent reviewers (CZ, TG). All studies identified by the search strategy were assessed based on title/abstract for eligibility. If there was insufficient information to include/exclude a study. Consensus was required by both reviewers. Disagreements were settled by a third independent reviewer (CAC). Full text of all relevant studies was obtained and read to ensure the inclusion criteria were met. If there was insufficient information to include/exclude an article, the authors were contacted where possible. If functional performance was assessed by an instrument design to assess another outcome, the study was excluded if functional performance domain were not described. All references were stored in a specific software (Mendeley©, Elsevier, v1.19.8.).

Data collection process and analysis

A data collection form was specifically developed and used to extract data from studies by the reviewer (CZ). Collected data were stored in Microsoft Office Excel©, 2016. Disease, characteristics of included participants, information of functional performance instruments and their measurement properties were collected. Also, information regarding association of performance with negative outcomes including mortality, hospitalisations, respiratory exacerbations, dyspnoea and depression were collected. To analyse risk of bias and quality assessment different instruments were used according to the design of the studies included. The instruments used were: (i) the COSMIN Risk of Bias Checklist (supplemental material – Table S2) for studies with assessment of measurement properties; (ii) the PEDro scale for randomized clinical trials; and (ii) the Downs & Black checklist for all other study types. Negligible to weak correlations were defined as <0.4 weak, moderate 0.4 to 0.69 and strong 0.7 to 1.0 (14). An instrument was considered validated, regarding concurrent validity, when correlation values were at least moderate and above 0.5. Reliability was deemed moderate if ICC values were between 0.50 and 0.75, good if between 0.76 and 0.90, and excellent if above 0.90 (15).

Results

From 16.588 records identified in the database search, one hundred and eighty-four studies met eligibility criteria and were included in the review (**Figure 1**). Information of included studies were described in supplemental material (Table S1). Seven subgroups of diseases were identified and the subgroup of diseases with most studies were: pulmonary arterial hypertension (PAH) with fifty-seven studies (**Figure 2**), followed by interstitial lung disease (ILD), asthma, cystic fibrosis (CF), bronchiectasis, patients with chronic respiratory disease waiting for or who underwent lung transplantation (LTx) and non-specified chronic respiratory diseases (NS-CRD). Characteristics of participants per disease were described in **table 1**. The designs of included studies were clinical trials (n=87), cross-sectional studies (n=77) and longitudinal cohorts (n=20).

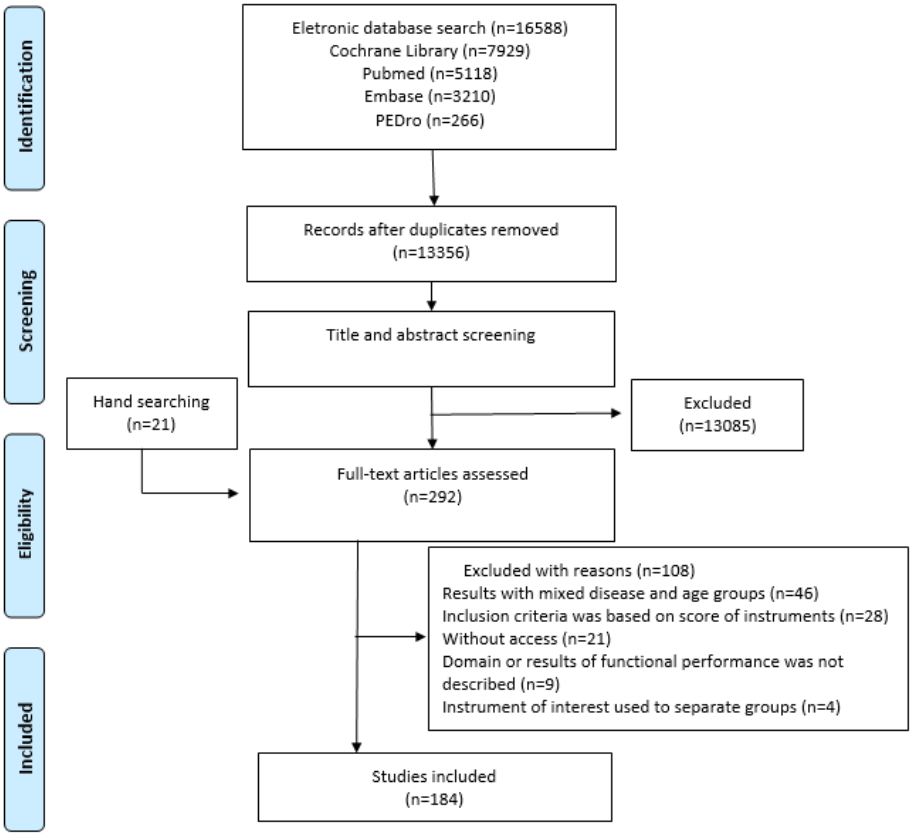


Figure 1. Study flow diagram.

Table 1. Characteristics of the participants in each disease.

Disease	n	Age Mean (SD)/[CI95]	Sex (F/M) (%)	VEF1 (%pred)	FVC (% pred)	FEV_1/FVC
Asthma	3823	45.9 [39-52]	57/43	73	80	68
Bronchiectasis	428	54.6 [48-60]	56/44	63	77	70
Cystic Fibrosis	850	28.6 [25-32]	51/49	64	81	61
ILD	4026	62.3 [57-69]	38/62	74	68	71
PAH	3952	50.5 [48-53]	73/27	ϴ	ϴ	ϴ
LTx	61	42.5 [31-54]	49/51	54	61	ϴ
NS-CRD	17	72.9 (7.9)	29/71	ϴ	ϴ	ϴ

Captions: ILD – Interstitial lung disease, PAH – Pulmonary arterial hypertension, LTx – patients with chronic respiratory disease waiting/submitted to lung transplantation, NS-CRD – Non-specific chronic respiratory disease, SD – Standard deviation, CI – confidence interval, FEV1 – forced expiratory volume in first second; % of predicted, FVC – forced vital capacity; % of predicted, ϴ – Missing information.

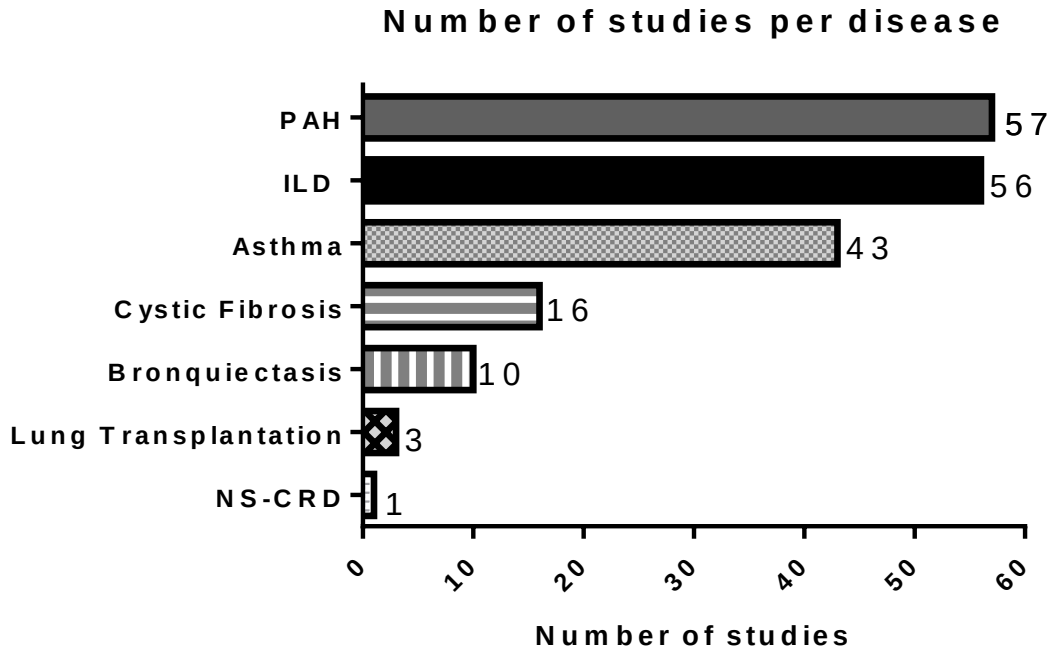


Figure 2. Number of studies per chronic respiratory disease.

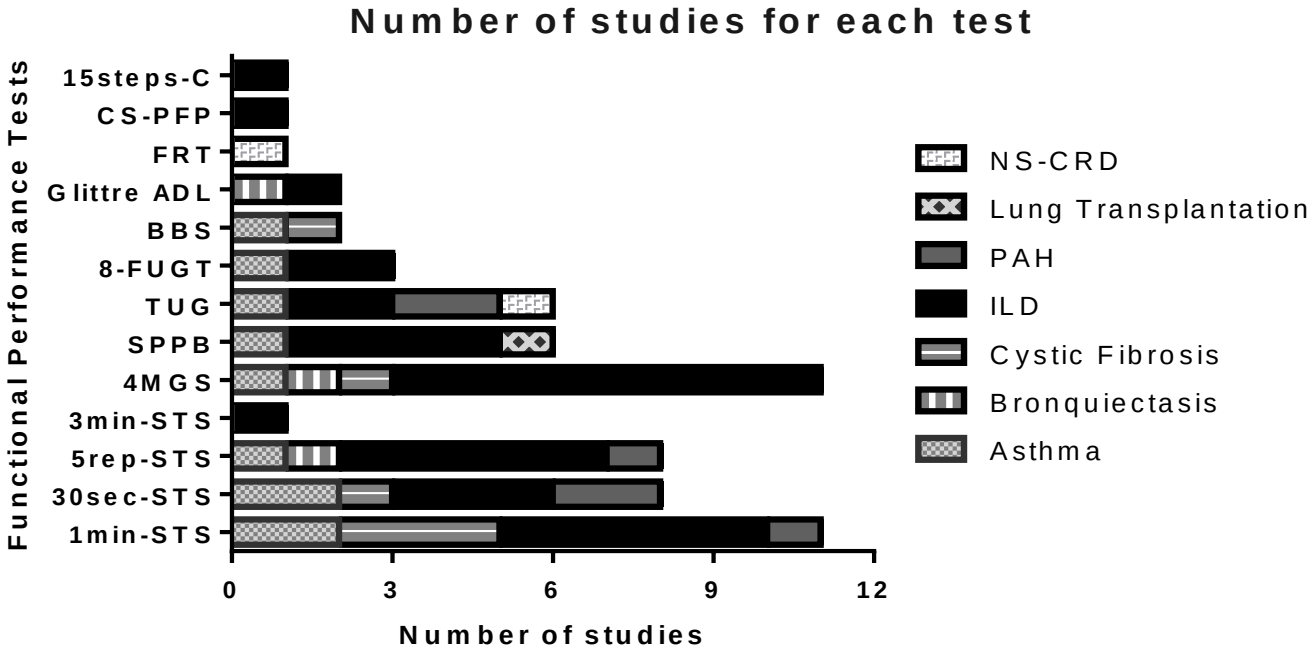
In total, thirty-one instruments were identified (thirteen performance-based tests and eighteen patient-reported tools). The most investigated performed-based tests in non-COPD chronic respiratory diseases were the one-minute sit-to-stand

(1min-STS) and four-metre gait speed (4MGS), followed by 30 seconds sit-to-stand (30sec-STS), five-repetitions sit-to-stand (5rep-STS), Short Physical Performance Battery (SPPB), timed up and go (TUG), 8 foot up and go (8-FUGT), Berg balance scale (BBS), Glittre activities of daily living (Glittre ADL), functional reach test (FRT), continuous scale – physical function performance (CS-PFP), three-minutes sit-to-stand (3min-STS) and 15-steps climbing test (15-stepsC). All functional performance tests found was focused on assess lower limb functional limitations. The full overview of performed-based tests assessing functional performance according to disease is depicted in **figure 3** and in ths supplementsal material were described each functional performance tests (Table S5). The most common patient-reported tool to assess functional performance were the physical function domain (PFd) and physical component score (PCS) of the Medical Outcomes Study 36-item Short Form of Health Survey (SF-36) followed by the activities domain of Saint´s George Respiratory Questionnaire (SGRQ), World Health Organization functional class (WHOfc), New York Heart Association functional class (NYHA), activity domain of Asthma Quality of Life Questionnaire (AQLQ), PFd of Cystic fibrosis quality of Life questionnaire (CFQoL), PFd and PCS in Medical Outcomes Study 12-item Short Form of Health Survey (SF-12), PFd of Patient-Reported Outcomes Measurement Information System (PROMIS-29), physical health construct of Living with Asthma Questionnaire (LWAQ), activity domain of Mini AQLQ (M-AQLQ), activity limitation domain of Cambridge pulmonary hypertension outcome review (CAMPHOR), physical limitation domain of quality of life from *Escola Paulista de Medicina* (QoL-EPM), physical sub-score of Minessota Quality of Life (Minessota QoL), physical domain of Quality of life – Bronchiectasis (QoL- B), physical activity score of London Chest Activities of Daily Living scale (London ADL), Functional performance inventory (FPI), PFd of Multi-dimensional health assessment questionnaire (MDHAQ) and physical function score of Seattle Obstructive Lung Questionnaire (SOLQ). The full overview of the patient-reported tools assessing functional performance according to disease is depicted in **figure 4**. Details of included studies and protocols of instruments

included (functional performance tests or patient-reported outcomes) are summarized in the supplemental material (Table S1).

Summary of metric and psychometric properties of functional performance instruments were reported on **Table 2** and **Table 3,** respectively. Thirty-three from one-hundred and eighty-four studies included investigated measurement properties, most in functional performance tests. Statistical values of measurement properties per instrument included were described in the supplemental material (Tables S3 and S4). According to the objectives and analysis carried out in each study, all studies with measurement properties investigated were evaluated by the Cosmin risk of bias (supplemental material). Most of them investigated validity and reliability. Interstitial lung diseases and asthma were subgroups of diseases that presented the highest number of functional performance tests with investigation of measurement properties. Furthermore, some instruments have no measurement properties described in any non-COPD chronic respiratory disease (i.e. BBS, FRT, WHOfc, NYHA, SF-12, LWAQ, M-AQLQ, QoL-EPM, FPI). Description of the risk of bias assessment by Cosmin checklist was provided in the supplemental material (Table S2).

In the current literature, few instruments have association with negative outcomes in asthma, bronchiectasis, ILD and patients with CRD waiting or submitted to lung transplantation. Association of instruments were found with disease severity, dyspnoea, depression, frequency exacerbation, hospitalization and mortality. The description of functional performance tests and patient-reported outcomes association with negative outcomes are provided in **Table 2** and **Table 3**, respectively.



Captions: NS-CRD – non-specified chronic respiratory diseases, Lung transplantation – patients with chronic respiratory disease waiting/submitted to lung transplantation, 1min-STS – 1minute sit-to-stand, 4MGS – four-metre gait speed, 30sec-STS – 30 seconds sit-to-stand, 5rep-STS – 5 repetitions sit-to-stand, SPPB – short physical performance battery, TUG – timed-up-and-go, 8-FUGT – 8-foot-up-and-go, BBS – berg balance scale, Glitre ADL – Glittre Activities of daily living, FRT – function reach test, CS-PFP – continuous scale physical function performance test, 3min-STS – 3-minute sit-to-stand, 15-steps climbing.

Figure 3. Number of studies per disease and number of use each instrument per disease.

Performance-based tests

Sit-to-stand Test

Four different protocols of sit-to-stand test used in non-COPD chronic respiratory diseases were reported: one-minute sit-to-stand (1min-STS), 30 seconds sit-to-stand (30sec-STS), 5 repetitions sit-to-stand (5rep-STS) and 3 minutes sit-to-stand (3min-STS). The protocols of 1min-STS, 30sec-STS and

3min-STS use the number of repetitions in the test as main outcome (16, 17), whilst the 5rep-STS uses the duration taken to complete the 5 repetitions as main outcome (10, 18). The test evaluates a common activity in daily life and is addressed to disabled patients providing useful information on their independence/disability in daily life (19). Its execution depends on only limited space, time, equipment or training, making the test attractive to assess functional performance in clinical routine (20). Also, protocols of sit-to-stand are used to assess lower limb muscle strength, or used as a surrogate to physiological variables (i.e. peak of heart rate and oxygen desaturation) of sub maximum and maximum exercise capacity (21-24).

The most used protocol of the sit-to-stand in non-COPD CRDs was the 1min-STS. Eleven studies used this protocol in asthma (25, 26), cystic fibrosis (24, 27, 28), ILD (17, 21, 22, 29, 30) and PAH (31). The validity, through correlation values ranges from weak to strong ($0.33<r<0.93$) with exercise capacity (i.e. CPET and the 6-minute walk test, 6MWT) and peripheral muscle strength ($0.41<r<0.60$) (i.e. quadriceps strength, handgrip force and 6MWT) in three investigated diseases (i.e. asthma, CF and ILD) (17, 22, 25, 28-30). Validity and reliability were reached only in cystic fibrosis against CPET (i.e. Watts maximum and maximal oxygen uptake, Vo_2 peak) (28) and ILD with quadriceps strength ($r=0.60$; $p<0.05$)(29) and 6MWT ($0.5<r<0.82$; $p<0.001$) (21, 22). Good to excellent reliability in intra-rater analysis ($0.87<ICC<0.98$) and good to excellent reliability in inter-rater analysis ($0.80<ICC<0.91$) was observed in the three investigated diseases (25, 28-30). The minimal important difference (MID) of the test was only described for CF in the 1min-STS (i.e. MID=5 repetitions)(28).

The 30sec-STS were assessed in eight studies in asthma (25, 32), CF (33), ILD (30, 34, 35) and PAH (36, 37). Although measurement properties were investigated in asthma, cystic fibrosis, ILD and PAH, validity was reached only in cystic fibrosis and PAH (i.e. correlations with quadriceps strength; $r>0.5$). Good to excellent intra-rater and inter-rater reliability were achieved in asthma, ILD and PAH patients ($0.85<ICC<0.95$). The 5rep-STS were used in eight studies in asthma (25), bronchiectasis (38), ILD (30, 39-42) and PAH (18). Validity was reached in

asthma with 6MWD (r=-0.56; p<0.001), in ILD with quadriceps strength (r=-0.50; p<0.05), good intra-rater (0.84<ICC<0.87) and good to excellent in inter-rater (0.86<ICC<0.90) analysis for asthma and ILD (25, 30, 40). The 3min-STS was assessed in only one study (17) with ILD, validity was reached with pulmonary function (i.e. TCLO % of predict, r=0.55; p<0.001) and excellent test-retest reliability was found (ICC:0.96). No association with hospitalisations or mortality was reported in any subgroups of diseases with the four protocols of the sit-to-stand. Further details of protocols of sit-to-stand are described in **Table 2**.

Four-metre gait speed (4MGS)

Eleven studies used 4MGS, in ILD (30, 39, 40, 43-47), asthma (25), bronchiectasis (38) and cystic fibrosis (48). The 4MGS has been recommended as a potentially useful marker of multisystemic wellbeing and it is reliable and quick to perform (49). The standardised protocol requires an 8m course (i.e. a 2m acceleration zone, a 4m timing area, a 2m deceleration zone), little time and equipment or training, making it easy to perform (50). Although, the 8-m course is the most investigated protocol, variations of the test exist. Some studies used only 4-m course and the acceleration and deceleration needed during the performance are considered in the timed measured (50). Further details of protocols of 4MGS in included studies are described in supplemental material (**Table S1**)**.**

In ILD, the 4MGS was deemed valid via correlations with exercise capacity, peripheral muscle strength, dyspnoea and disease severity (-0.56<r<0.77) and presented excellent intra-rater (0.92<ICC<0.95) and moderate to excellent inter-rater (0.56<ICC<0.98) reliability. The 4MGS was the functional performance test with most number of studies investigating its measurement properties in ILD (22, 30, 40, 46, 47). In asthma, the 4MGS appears to have validity via correlations with handgrip strength and 6MWT (-0.64<r<-0.52; p<0.001) and has good intra-rater (ICC:0.86) and moderate inter-rater (ICC:0.58) reliability (25). Performance in the 4MGS associates with worse dyspnoea, health status, ILD severity and prognosis ($0.58<r^2<0.67$) in ILD (43, 46). Also, slow gait speed (4MGS<0.8 m/s) is an

independent predictor of all-cause mortality and non-elective hospitalisation and appears to be responsive to pulmonary rehabilitation (mean - 95% CI) change: 0.16 (0.12–0.20) m/s) in idiopathic pulmonary fibrosis (45).

Short physical performance battery (SPPB)

The SPPB evaluates balance, gait and strength by examining an individual's static balance in three positions, time to walk in four-metre (i.e. 4MGS) and time to rise from a chair and return to the seated position five times (i.e. 5rep-STS) (51). It is easy and quick to perform, and requires little infrastructure. Six studies applied SPPB to assess functional performance: one in asthma (25), four in patients with ILD (30, 39, 42, 52) and one with patients with CF submitted to LTx (53). Measurement properties were investigated in asthma and ILD (25, 30), weak to moderate correlations with exercise capacity and handgrip force in asthma and ILD, although, validity was reached only in asthma patients ($0.50<r<0.61$; $p<0.05$) (25, 30). Moderate to good reliability in the intra-rater ($0.75<ICC<0.83$) and inter-rater (ICC:0.75) analysis was observed in asthma and ILD (25, 30). The MID in the SPPB was reported for patients with CF submitted to LTx (i.e. 1 point improvement in the total score) (53). No study reported associations with hospitalisation, mortality or other negative clinical outcome.

Timed up and go (TUG)

The TUG is a test of general mobility where the patient is observed and timed while he rises from a chair, walks 3 meters, turns, walks back, and sits down again (54). In this review, TUG was used as a functional performance test in six studies (two in ILD (30, 42) and in PAH (36, 37), one study in patients with asthma (25) and one in non-specified chronic respiratory disease(55)). Two protocols of TUG were reported, with usual and fast pace. The TUG using usual pace was the protocol most frequently reported. Measurement properties were investigated in asthma, ILD and PAH and TUG associated (validity) moderately with 6MWT (r=-

0.62; p<0.0001) in asthma (25) and with 6MWT and handgrip force (-0.69<r<0.56; p<0.05) in ILD (30). A weak correlation of the TUG with quadriceps strength was observed in patients with PAH (36). Also, good to excellent intra-rater (0.88<ICC<0.90) and inter-rater (0.76<ICC<0.89) reliability was observed in asthma and ILD patients. Excellent intra-rater (ICC:0.96) reliability was reached in patients with PAH. No association of the TUG with hospitalisation, mortality or other negative clinical outcome were reported in any non-COPD chronic respiratory diseases.

8-foot up and Go (8-FUGT)

8-FUGT is a functional test designed to provide objective assessments of functional mobility, strength, balance, and agility. The patient is instructed to get up from the chair, walked around a cone that was placed 8-feet (2.40m) from the chair, and return to a seated position on the chair as fast as possible. Except for the distance to walk, this test is similar to TUG with the performance quantified in seconds (56). The 8-FUGT was reported in three studies: two studies in ILD (42, 52) and one study in asthma (32). Validity was reached via correlations with exercise capacity (6MWT and CPET (-0.72<r-0.61; p<0.05) and with functional performance tests via 30sec-STS (r=-0.65; p<0.001) in ILD. Also, performance above 6.9 seconds is associated with hospitalisation and mortality in ILD patients (52). No association of the 8-FUGT with hospitalisation or mortality were reported in any non-COPD chronic respiratory diseases.

Berg balance scale (BBS)

The BBS examines balance using different standardized positions and actions related to daily life. Consists of 14 tasks including sitting to standing, standing unsupported, and picking up object from the floor from a standing position. Each task is scored on a scale of 0 (unable to perform a task) to 4 (able to perform

the task independently), and total score range from 0 to 56 with higher score is indicative of better performance on the measure. In older healthy adults, BBS 45 to 51 points is associated with high risk to fall, although the evidence to support the use to predict falls is insufficient (57). In this review, BBS was used in two studies: one with asthma (58) and other in cystic fibrosis patients (59). No measurement properties and associations with hospitalisations or mortality were reported in any non-COPD chronic respiratory diseases.

Glittre Activities of Daily Living test (Glittre ADL)

The Glittre ADL consists of a 10-meter circuit in which the individual starts from a sitting position, walks, goes up and down two interposed steps and walks again until reaching a shelf, individually adjusted according to the height of the shoulder and waist (60). The patients are instructed to complete five laps in the shortest time, using a backpack with 2.5 kg (for women) or 5 kg (for men), the shortest time is used as an outcome. Two studies used Glittre ADL test to assess functional performance in bronchiectasis (61) and ILD (60). In both studies, measurement properties were assessed, validity was investigated via correlations with 6MWT in bronchiectasis and ILD ($r=-0.41$; $r=-0.70$ respectively; $p<0.05$), but only reached in ILD. Also, excellent reliability was observed in test-retest analysis (ICC:0.90) for ILD patients (60). No association of the Glittre ADL with hospitalisation or mortality were reported in any non-COPD chronic respiratory diseases.

Functional reach test (FRT)

The FRT is suggested to be a clinical measure of the stability limits. The FRT displaces the participant's centre of gravity and gives a measure of margin of stability and postural control, asking to the participant achieve the maximum distance able to reach forward from an initial upright posture to maximal leaning posture is recorded, without moving feet (62). It is fast and easy test to do, and to

perform is necessary a tape-measure to reach distance achieve of the finger between initial position and end position, three executions are recommended and average of three execution is used to analysis. One study applied FRT in chronic respiratory failure (55). No metric properties of the test or association with hospitalisation or mortality were reported.

Continuous scale physical function performance (CS-PFP)

The CS-PFP is a test of physical functional capacity that directly assesses activities of daily living. It consists of a series of 10 tasks covering everyday life activities required to maintain independence. Subjects are asked to complete the tasks at maximal effort, but with safety. This instrument was created to resemble daily activities, such as cooking, making the bed, and transferring laundry. In comparison with other tests, it is more time consuming (i.e. 30-40 minutes) and request larger environments to occur (63). In this review, one study with CS-PFP was found in ILD (64). CS-PFP showed validity with domain activities of SGRQ ($r=-0.80$; $p=0.002$), 6MWT ($r=0.66$; $p=0.008$), pulmonary function (FVC% and D_{LCO}%; $0.63<r<0.67$, $p<0.05$) and with PFd of SF-36 ($r=0.64$; $p=0.007$), also excellent reliability in intra-rater analysis (ICC=0.84) was demonstrated. No association with hospitalisation or mortality were reported in included studies.

15-steps climbing (15-stepsC)

In the 15-steps climbing test (15-stepsC), patients were asked to climb up and down the step 15 times as fast as they could, without any fixed pacing using a step measuring 25 cm length by 50 cm width by 20 cm height. The test is performed twice with total time of the test (from the start to complete recovery) recorded. In ILD (65), validity was done via correlations with physiological variables and performance of the CPET and 6MWT, moderate to strong correlations were found with physiological variables of CPET (maximum volume of oxygen utilization – Vo_2, respiratory rate, total ventilation ratio and saturation in the end of CPET) and

oxygen saturation (-0.80<r<0.85; p>0.05) and performance of 15-stepsC have moderate correlation with distance in 6MWT (r=-0.49; p=0.0003) (65), although convergent validity was not reached (i.e. r<0.5). Reliability was not investigated and no association with hospitalisation or mortality were reported in included studies.

Table 2. Metric properties and associations with negative outcomes of functional performance tests in non-COPD chronic respiratory diseases.

		Asthma	Bronchiectasis	Cystic Fibrosis	ILD	PAH	LTx	NS-CRD
Objective measures								
1min-STS	Validity	Weak correlation (6MWD and QS) (25)		Strong correlation (watts in CPET) and moderate correlation (peak VO_2) (27, 28)	Weak correlation (HGS) Moderate correlation (QS, FVC %pred, TLC %pred) (17, 22, 29, 30) Strong correlation (6MWT)			
	Reliability	Very good intra and inter-rater analysis (25)		Very good intra-rater reliability (28)	Very good intra-rater and excellent inter-rater analysis (30)			
	Interpretability			MID: 5.4 repetitions (28)				
	Negative outcomes							
30sec-STS	Validity	Moderate correlation (6MWD and HGS) (25)		Moderate correlation (QS peak torque) (33)	Moderate correlation (6MWD and QS) (30)	Moderate correlation (QS) (36)		
	Reliability	Excellent intra-rater and very good inter-rater analysis (25)			Excellent intra-rater and very good inter-rater analysis (30)	Excellent intra-rater analysis (36)		
	Interpretability							
	Negative outcomes							

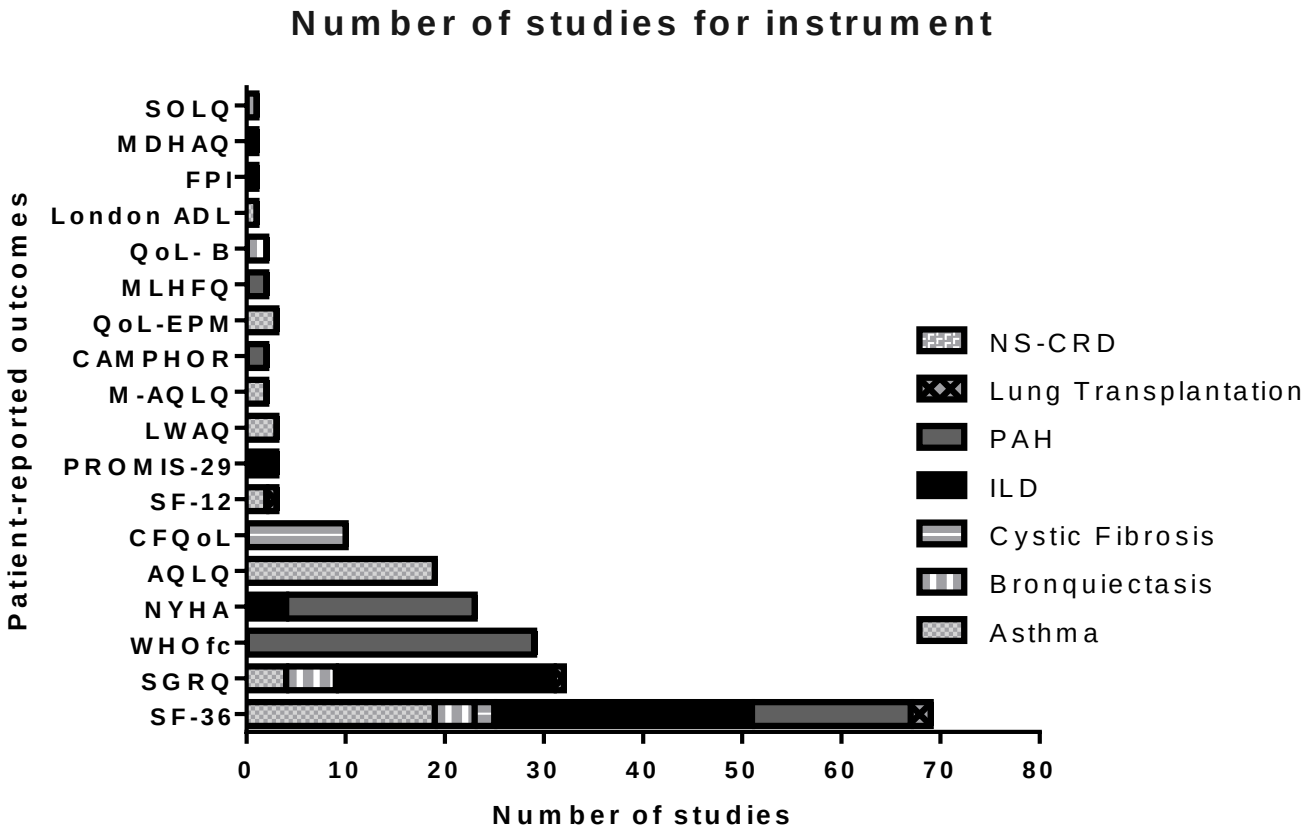
5rep-STS	Validity	Moderate correlation (6MWD and HGS) (25)		Moderate correlation (QS peak torque) (33)	Moderate correlation (6MWD and QS) (30)	Moderate correlation (QS) (36)	
	Reliability	Very good intra and inter-rater analysis (25)			Excellent intra-rater and very good inter-rater analysis (30)	Excellent intra-rater analysis (36)	
	Interpretability						
	Negative outcomes						
3min-STS	Validity				Moderate correlation (FVC% pred and TCLO% pred) (17)		
	Reliability				Excellent test-retest reliability (17)		
	Interpretability						
	Negative outcomes						
4MGS	Validity	Moderate correlation (QS) (25)			Strong correlation and moderate correlation (KBILD, mMRC, GAP index, dyspnoea and HGS) (22, 30, 40, 43, 46, 47)		
	Reliability	Very good intra-rater and moderate inter-rater analysis(25)			Excellent intra-rater and moderate to excellent intra-rater (22, 30, 40, 46)		
	Interpretability						
	Negative outcomes				Dyspnoea and prognosis (46) ILD severity (43)		

					4MGS<0.8 m/s and mortality/hospitalisation (45)		
SPPB	Validity	Moderate correlation (6MWD and HGS)(25)			Weak correlation (6MWD) (30)		
	Reliability	Moderate intra and inter-rater analysis(25)			Very good intra-rater and moderate inter-rater analysis (30)		
	Interpretability						MID:1 point (53)
	Negative outcomes						
TUG	Validity	Moderate correlation (6MWD, QS and HGS)(25)			Moderate correlation (6MWD, QS and HGS) (30)	Weak correlation (QS) (36)	
	Reliability	Excellent intra-rater and very good inter-rater analysis.(25)			Excellent intra-rater and inter-rater analysis (30)	Excellent intra-rater analysis (36)	
	Interpretability						
	Negative outcomes						
8-FUGT	Validity				Moderate correlation (6MWD, CPET, 30sec-STS) (52)		
	Reliability						
	Interpretability						
	Negative outcomes				8-FUGT>6.9s and mortality		
BBS	Validity						
	Reliability						
	Interpretability						

	Negative outcomes					
Glittre ADL	Validity		Moderate correlation (6MWD)(61)		Moderate correlation (6MWD, Total EE) (17)	
	Reliability				Excellent test-retest reliability (17)	
	Interpretability					
	Negative associations					
FRT	Validity					
	Reliability					
	Interpretability					
	Negative outcomes					
CS-PFP	Validity				Strong correlation (SF-36 – pain scale; activities of SGRQ) moderate correlation (6MWD, SF-36 - PF, D_{LCO}, FEV_1 and FVC%) (64)	
	Reliability				Excellent test-retest and internal consistency (64)	
	Interpretability					
	Negative outcomes					
15-steps climbing	Validity				Strong correlation (Vo_2, oxygen desaturation) Moderate correlation (6MWD)	

		Weak correlation (D_{LCO}%) (65)	
Reliability Interpretability Negative outcomes			

Captions: Interpretability refers to the Minimal important difference (MID); ILD – Interstitial lung disease. PAH – Pulmonary arterial hypertension. LT – patients with chronic respiratory diseases waiting/ submitted to lung transplantation. NS-CRD – non-specified chronic respiratory diseases. ND – no description. 1min-STS – 1minute sit-to-stand, 4MGS – four-metre gait speed, 30sec-STS – 30 seconds sit-to-stand, 5rep-STS – 5 repetitions sit-to-stand, SPPB – short physical performance battery, TUG – timed-up-and-go, 8-FUGT – 8-foot-up-and-go, BBS – berg balance scale, Glittre ADL – Glittre Activities of daily living, FRT– function reach test, CS-PFP – continuous scale physical function performance test, 3min-STS – 3-minute sit-to-stand, 15-steps climbing; Vo_2 - maximum volume of oxygen utilization; 6MWT – six-minute walt test; 6MWD – distance in six-minute walk test, QS – Quadriceps strength; HGS – Handgrip strength; QS – Quadriceps strength; Total EE – Total energy expenditure in daily physical activities, in kilocalories; MIVC – Maximal isometric voluntary contraction; FEV1 – Forced expiratory volume in 1 s; FVC – Forced vital capacity; mMRC – Modified medical respiratory council dyspnoea score; TLC – Total lung capacity.



Captions: NS-CRD – non-specified chronic respiratory diseases, Lung transplantation – patients with chronic respiratory disease waiting/submitted to lung transplantation SF-36 – Medical Outcomes Study 36-item Short Form of Health Survey, SGRQ – Saint´s George Respiratory Questionnaire, WHOfc – World Health Organization functional class, NYHA – New York heart association, AQLQ – Asthma Quality of Life Questionnaire, CFQoL – Cystic fibrosis quality of life, SF-12 – Medical Outcomes Study 12-item Short Form of Health Survey, Promis-29 – Patient-Reported Outcomes Measurement Information System, LWAQ – Living with Asthma Questionnaire, M-AQLQ – Mini Asthma Quality of Life Questionnaire, CAMPHOR – Cambridge pulmonary hypertension outcome review, QoL-EPM – Asthma Quality of Life from Escola Paulista de Medicina, MLHFQ – Minessota living with heart failure questionnaire, QoL-B – Quality of Life in Bronchiectasis, London ADL – London Activities of Daily Living, FPI – Functional performance inventory, MDHAQ – Multi dimensional health assessment questionnaire, SOLQ – Seattle Obstructive Lung Questionnaire.

Figure 4. Number of studies per disease and number of use each subjective measure.

Patient-reported tools

Medical Outcomes Study 36-item Short Form of Health Survey (SF-36)

The Medical Outcomes Study 36-item Short Form of Health Survey (SF-36) is a generic instrument, developed by Rand Corporation in 1992 and has been used ever since to assess health related quality of life. It is a multi-purpose QoL questionnaire with a broad range of applications, containing 36-items categorized into 8 dimensions, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health, and a physical and mental composite score (66). The physical function domain (PFd) of the SF-36 assess impact of functional performance on daily living activities and physical composite score (PCS) considers other aspects that influence on body function. Both outcomes were deemed measures of functional performance in this review. SF-36 is the most frequently questionnaire used in the included studies, sixty-nine studies used PFd or PCS in six out of seven subgroups of diseases investigated: asthma, bronchiectasis, cystic fibrosis, ILD, PAH and patients waiting for or who underwent LTx. Six studies (67-72) observed psychometric properties of SF-36, including PFd or PCS domains, validity was investigated in asthma and ILD, reliability was analysed only for ILD patients and the MID of the tool was stablished for ILD (i.e. 4 points in PCS) (68) and PAH (i.e. 5 points in the PFd and 13 points for the PCS) (69). Validity of PFd was reached via correlation with symptoms score ($r=0.50$; $p<0.001$) in asthma (70), also validity was achieved with 6MWT ($0.53<r<0.69$; $p>0.001$), mMRC ($r=-0.61$; $p>0.0001$), pulmonary function (i.e. total lung capacity – TLC, forced expired volume in the first second – FEV_1 and vital capacity – VC, $0.50<r<0.61$; $p>0.05$) and baseline dyspnoea index ($r=0.73$; $p>0.001$) in ILD patients (67, 68). The PCS of the SF-36 was validated in bronchiectasis correlating it with 6MWT ($r=-0.71$; $p>0.0001$), also with and with the Scleroderma Health Assessment Questionnaire Disability Index (HAQ-DI) ($r=-0.50$; $p>0.001$) in ILD. Additionally, in ILD the PCS was correlated, but not validated, with the 6MWT ($r=0.44$; $p>0.0001$), dyspnoea sensation (modified Medical Research Council scale, mMRC) ($r=0.48$; $p>0.0001$) and the forced vital capacity ($r=0.35$; $p<0.001$) (67, 68). Reliability was analysed in one study with ILD patients

(68) via the comparation between two measures and no differences in test-retest were observed. No other measures of reliability were reported in any non-COPD CRDs. Worse scores in PFd was associated with worse functional class (WHOfc), lower education level, need of oxygen therapy and more years since diagnosis in PAH. In contrast, better exercise capacity (6MWT) and functional class (assessed via the WHOfc) were associated with a better result in PFd also in PAH (73). No further clinical associations were found in non-COPD CRDs. One study investigated the impact of changes in the PCS composite score on mortality in patients waiting for or who underwent LTx (74). An increase of at least 50% in PCS over 6 months was associated with higher survival rates. Of note, this result belongs to a study excluded from the present study as it was not possible to guarantee the absence of COPD patients in the cohort.

Medical Outcomes Study 12-item Short Form of Health Survey (SF-12)

The SF-12 is a multipurpose, generic 12-item questionnaire developed from the Short Form-36. It provides a shorter but yet valid and reliable alternative to the SF-36 for use in large samples. The SF-12 includes eight domains, and the final score of the scale ranges from 0 to 100. Similar to the SF-36, higher score indicate better QOL (75). Three studies used SF-12: two in asthma (76, 77) and one in patients waiting for or who underwent LTx (53).There were no studies investigating SF-12 psychometric properties or its associations with mortality and hospitalisations.

Saint's George Respiratory Questionnaire (SGRQ)

The Saint's George Respiratory Questionnaire (SGRQ) is a respiratory-specific HRQL instrument developed for patients with chronic obstructive pulmonary disease (78). The questionnaire has three components: symptoms, activities and impact. Higher scores correspond to worse health-related quality of life. The SGRQ was developed for COPD patients, but it is used in asthma patients (79) and is possible to find adapted versions for other chronic respiratory diseases, such as ILD (SGRQ-I)

(80). From the questionnaire, the activities domain can be used to describe functional performance. Thirty-two studies used the activities domain of the SGRQ as functional performance measure in asthma, bronchiectasis, ILD, patients waiting for or who underwent LTx and NS-CRD. Its validity, reproducibility, and response to change over time have been demonstrated in patients with asthma, bronchiectasis and IPF (79, 81, 82). Psychometric properties of the SGRQ were reported in ILD (67, 81) and in bronchiectasis (72). In ILD, the activities domain showed validity with strong correlation with PFd of SF-36 ($r=-0.71$; $p<0.05$) and baseline dyspnoea index (BDI) ($r=0.75$; $p<0.05$), moderate correlation with 6MWT ($r=-0.66$; $p<0.001$), and lung function (Total lung capacity, forced expired volume in the first second, and vital capacity; $0.54<r<0.65$; $p<0.05$). In bronchiectasis, the activity domain presented strong correlation with the 6MWT ($r=-0.76$; $p>0,001$) (72). Good to excellent reliability was achieved in intra-rater (ICC:0.93) and inter-rater (ICC:0.88) analysis in ILD patients (81). Reliability was not investigated in other diseases. The activity domain in the SGRQ is an independent factor associated with depression and dyspnoea in patients with asthma (83), although no association with mortality or hospitalisation were reported.

World Health Organization functional class (WHOfc)

The World Health Organization functional class (WHOfc) classifies the severity of pulmonary arterial hypertension (PAH). The World Health Organization (WHO) classification of functional status of patients with PAH is an adaptation of the NYHA functional classes, and can be applied using a standardized questionnaire (84). WHO functional class is based on patient's functional performance, defined as symptoms and limitation in routine activities, and has a powerful prediction value of survival. There are four different classes where class I is the mildest and class IV is the most severe form of PAH. Assessors classify the level of the patients and based on the classification, interventions and patient prognosis are defined. Assigning a functional class helps the PAH healthcare team to understand how the patient is affected by

their condition. The WHOfc was reported only in PAH patients, in twenty-nine studies. None of the included studies reported psychometric properties of the instrument. The WHOfc has been used to assess exercise training effectiveness in PAH (85, 86) and medication efficacy (87-89). The WHOfc was associated with clinical failure in PAH (90) and PAH patients in classes III and IV appear to have higher risk of mortality than the other two classes (91).

New York Heart Association functional class (NYHA)

The New York Heart Association (NYHA) classification provides a simple way of classifying the severity of heart failure (92). It classifies patients in four categories based on the presence of symptoms and limitations of daily physical activity (84, 92). NYHA was reported in twenty-two studies (eighteen in PAH and four in ILD), but none reported psychometric properties. In ILD patients, NYHA appears to be a helpful tool for early diagnosis, but in studies with PAH patients, the difficulty to diagnose PAH collaborates to delay the diagnosis and consequently NYHA is more frequently used when patients are in advanced stages (93). Mortality rates were more prevalent in PAH patients classified as NYHA III or IV (94).

Asthma Quality of Life Questionnaires (AQLQ) and Mini-AQLQ

The Asthma Quality of Life Questionnaire (AQLQ) (95) consists of 32 questions designed to evaluate daily symptoms that are typically found in asthmatic adults. Each question has seven response options, one-point represents totally/severely limited, most activities not done, whilst 7 indicates none or never, and 2–6 are intermediate degrees. Higher scores represent a better quality of life. The questionnaire has four domains: symptoms, emotional function, environmental stimulus and activity limitation. From the questionnaire, the activity limitation domain can be used to describe functional performance (95, 96). The AQLQ was used in eighteen studies, as expected, all in patients with asthma. A shorter version of AQLQ (the Mini-AQLQ, M-AQLQ) was reported in two studies (97, 98). The AQLQ was validated using the

questionnaire of asthma control, and questionnaires of general health or quality of life ($0.50<r<0.57$; $p<0.05$). The AQLQ has excellent intra-rater reliability (ICC=0.93) (95) and the MID of the tool has been described as 0.51 points in activities domain (96). There were no studies reporting association of the AQLQ and mortality and hospitalisation. As Mini-AQLQ has the same construct of AQLQ, this instrument was described with AQLQ. No measurement properties or association with mortality of hospitalisation were observed in Mini-AQLQ.

Cystic Fibrosis Quality of Life (CFQoL)

The CFQoL was the first disease specific patient reported outcome developed for CF patients and then was slightly revised. CFQoL is a profile measure of both CF-specific and general domains of functioning. The questionnaire consists of 50 questions, generating standardized scores from 0 to 100 in the following domains: body image, digestive symptoms, eating, emotional functioning, health perceptions, physical functioning, respiratory symptoms, role functioning, social functioning, treatment burden, vitality, and weight. Higher scores in each domain indicate better HRQoL (99). Physical functioning domain (PFd) can be used to describe functional performance. CFQoL was used in ten studies (100-108), as expected all with CF patients. Validity was reached with PFd of SF-36 ($r=0.73$; $p<0.001$) and excellent intra-rater reliability was demonstrated (ICC=0.93)(108). There were no studies reporting association of the CFQoL and mortality and hospitalisation.

Patient-Reported Outcomes Measurement Information System (PROMIS-29)

The Patient-Reported Outcomes Measurement Information System (PROMIS) aims to measure patient-reported symptoms, such as pain and fatigue, and aspects of HRQOL across a wide variety of chronic diseases and conditions. The questionnaire has seven domains: depression, anxiety, pain interference, physical function, fatigue, satisfaction with social role participation, and sleep disturbance, as well one 11-point rating scale is included for pain intensity. Physical function was considered as functional performance domain. Three studies (71, 109, 110) used

PROMIS-29, all in ILD and investigated psychometric properties, two studies in connective tissue disease associated with pulmonary fibrosis patients and one with IPF patients. PFd of Promis-29 strongly correlate with PFd (r=0.89; p value not described) in SF-36 and activity domain of SGRQ (r=-0.84; p value not described) and moderately correlate with PCS domain (r=0.52; p<0.0001) in SF-36 and Health Assessment Questionnaire-Disability Index (HAQ-DI) (r=-0.50; p<0.001) (71, 109). Moderate reliability in intra-rater analysis (0.65<ICC<0.71) was found (109, 110) and internal consistency of physical function domain was 41% (109). Also, no domain of promis-29 appears to be responsive to changes in pulmonary function (i.e. FVC % of predicted) (109). No association with hospitalisation or mortality were reported in included studies.

Living with Asthma Questionnaire (LWAQ)

The LWAQ was developed by Hyland *et al.* to measure the QOL in asthma patients (111). The list consists of 68 items which cover 11 domains: sport, holidays, sleep, social leisure, work/other activities, colds, mobility, effects on others, medication usage, sex, dysphoric states and attitudes. For each item the score ranges from 0 to 2 (from no impairment to maximum impairment). Each domain has one to six items. The physical health construct contains statements about asthma and general health related symptoms and was used to assess FP. LWAQ was used in three studies in patients with asthma. Moderate correlations were observed through physical health construct with PCS of SF-36 (r=0.41; p value not described) and validity was reached with total symptoms score (r=0.50; p<0.001) (70). Internal consistency was investigated only for total score of LWAQ. There were no studies reporting association of the LWAQ and mortality and hospitalisation.

Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR)

The CAMPHOR questionnaire contains 65 items measuring; symptoms, activity and quality of life. Symptoms and quality of life are both scored out of 25, and activity out of 30. Scores are negatively weighted so that a higher score reflects worse quality of life and greater functional limitation. The activity domain was used as a functional

performance measure. Two studies (73, 112) used the activity domain of CAMPHOR in patients with PAH. Psychometric properties were not investigated in included studies, in exception of MID in the activity domain reported by Bunclark at al.(112) as 4 points. No studies investigated the association of CAMPHOR with hospitalisation or mortality.

Asthma Quality of Life from Escola Paulista de Medicina (QOL- EPM)

Asthma Quality of Life from Escola Paulista de Medicina (QOL- EPM) consists of four domains: physical limitation, frequency of symptoms, socioeconomic and psychosocial factors, with maximal scores of 33, 6, 11, and 7 points, respectively. The total score was calculated as the average of the four domains. Every domain was converted to percentages, and lower scores represent better QoL (113). This questionnaire was used in three studies (113-115) with asthma patients. Validity was not reached, weak to moderate correlations were reported with SF-36 domains ($-0.34<r<-0.46$; $p<0.05$)(113). Good test-retest reliability (ICC:0.87) was reported (113). There was no association with hospitalisation or mortality investigated in included studies.

Minessota Living with Heart Failure Questionnaire (MLHFQ)

Minessota Living with Heart Failure Questionnaire (MLHFQ) is a developed questionnaire with 21-item, self-administered to assess quality of life in patients with heart failure. MLHFQ is a valid tool to assess heart failure patients, consistent and responsive to changes. Patients rate their perceptions of how much their disease impacts the physical, socio-economic, and psychological aspects of daily life from 0 (not at all) to 5 (very much). To be applied in patients with PAH, the term “heart failure” need to be replaced by “pulmonary hypertension”. Scores on the total instrument range from 0 to 105, with higher scores reflecting a worse perceived quality of life and the first eight questions consider primarily physical functioning (physical sub score) used to assess functional performance (116). Two studies (116, 117) used physical sub score of MLHFQ in PAH patients. Moderate correlation was found with functional class by NYHA and 6MWD ($0.40<r<0.59$; p value not described) (116). Strong

correlation (r=0.93; p<0.001) was found for the physical sub score in test-retest analysis and good internal consistency (α Chronbach: 0.88), although intraclass correlation coefficients was not investigated (116). Patients with MLHFQ score≥40 (overall outcome) had a significantly worse prognosis than those with a score<40 (p=0.0018) (116).

Quality of Life Bronchiectasis questionnaire (QoL-B)

Quality of Life in Bronchiectasis (QoL-B) is a disease-specific questionnaire for individuals with bronchiectasis, administered in interview format. It consists of 37 items, eight scales and takes about ten minutes to complete. Each of the 37 items is scored from 1 to 4, and each of the eight scales scores is standardized on a 0–100 points scale, with higher scores representing fewer symptoms or better functioning and health-related quality of life (118). Physical functioning is the domain considered as assessment of functional performance. Two studies (118, 119) used QoL-B in bronchiectasis. Physical functioning domain of QoL-B demonstrated validity with activities domain of SGRQ (r=-0.70; p<0.01), also PFd demonstrated convergent validity with (mMRC; r=-0.57 and incremental shuttle walk test - ISWT; r=0.59; p<0.05 for both) and discriminative validity with mMRC (i.e. mMRC≥2 compared to mMRC≤3; p<0.001)(118). Excellent reliability test-retest (ICC:0.91) was reported. No association with hospitalisation or mortality were described in included studies.

London chest activities of daily living scale (London ADL)

This 15-item questionnaire was designed to determine dyspnoea during routine daily activities. It is divided into 4 components: self-care, domestic, physical activity score and leisure. For each activity, patients score from 0 (I would not do it anyway) to 5 (someone else does this for me [or helps]). Total scores range from 0 to 75, with higher scores indicating a greater limitation in daily living activity (120). Physical activity score was used as functional performance measure in one study (120) in patients with asthma. Although, there were no studies investigating London-ADL psychometric properties or its associations with mortality and hospitalisations.

Functional performance inventory (FPI)

The Functional Performance Inventory (FPI) is a 65-item self-administered questionnaire designed to evaluate functional performance in patients with chronic obstructive pulmonary disease (COPD). FPI is organized according to the six domains of functional performance identified during the qualitative interviews: body care, household maintenance, physical exercise, recreation, spiritual activities, and social activities. For each activity, response options range from 1 (the activity can be performed easily, with no difficulty at all) to 4 (the activity is no longer performed for health reasons). Scores range from 0 to 3, with higher scores indicating higher levels of function (121). Only one study investigated functional performance through FPI in ILD (122), but psychometric properties were not investigated. No association with hospitalisation or mortality were reported in included studies.

Multi-Dimensional Health Assessment Questionnaire (MDHAQ)

Multi-Dimensional Health Assessment Questionnaire (MDHAQ) is a self-report questionnaire, adapted from the original Health Assessment Questionnaire (HAQ), which assess the extent of difficulty with activities of daily living. Thus, the MDHAQ yields seven scale scores (0-10, with 10 connoting greater impairment), five of which are the physical function, pain, psychological well-being, fatigue, and patient-assessed global status (123). The PFd was used as a measure of functional performance in one study with ILD (80). PFd of MDAHQ is associated with forced vital capacity (FVC % of predicted) (r^2=0.15; p=0.3)(80), although there were no studies investigating MDHAQ psychometric properties or its associations with mortality and hospitalisations.

Seattle Obstructive Lung Disease Questionnaire (SOLQ)

The SOLQ is a questionnaire composed by 29-questions developed to measure physical and emotional function, coping skills and treatment satisfaction. Individual items of the SOLQ are scored on a simple linear scale, with a response of 1

representing the lowest function. Responses to questions on the scale are summed into a raw score and then transformed to a normalized score ranging from 0 to 100. Each of the 4 scales is scored separately, with a score of 100 representing the highest possible function. The physical function domain was used as functional performance measure. One study (124) used the PFd of SOLQ in patients with bronchiectasis. The PFd of SOLQ was validated using the PCS domain of SF-36 ($r=0.53$; $p<0.001$). The SOLQ demonstrated good reliability in intra-rater analysis (ICC:0.83) and good internal consistency (α Chronbach:0.72). Also, PFd of SOLQ is related with exacerbation frequency ($r=-0.20$; $p<0.01$), but no association with hospitalisation and mortality in included studies were described.

Table 3. Psychometric properties and associations with negative outcomes of patient-reported outcome measures of functional performance in non-COPD chronic respiratory diseases.

		Asthma	Bronchiectasis	Cystic Fibrosis	ILD	PAH	LT	NS-CRD
SF-36 (PFd or PCS)	Validity	Moderate correlation with symptoms score (70)	Moderate correlation with 6MWT (72)		Strong correlation with BDI Moderate correlation with HAQ-DI, 6MWD, mMRC, D_{LCO}, TLC, FEV, VC and NYHA (67, 68)			
	Reliability				No differences in test-retest (68)			
	Interpretability				MID: 4 points in PCS (68)	MID:13 points in PF and 5 points in PCS (112)		
	Negative outcomes							
SGRQ (activities)	Validity		Strong correlation with 6MWT (72)		SGRQ-I Strong correlation with PFd in SF-36 Moderate correlation with 6MWT, FEV_1, TLC and VC (47, 67, 81)			
	Reliability				Excellent intra-rater and good inter-rater analysis (81)			
	Interpretability							
	Negative outcomes	Depression and dyspnoea (83)						

WHOfc	Validity Reliability Interpretability Negative outcomes				WHOfc≥III increase the risk of death (91) WHOfc is related to clinical failure (90)	
NYHAfc	Validity Reliability Interpretability Negative outcomes				Mortality is associated with NYHA III or IV (94)	
AQLQ (activities)	Validity Reliability Interpretabilitys Negative outcomes	Moderate correlation with Asthma Control and Health Survey (95) Excellent reliability test-retest (95) 0.51 points (96)				
CFQoL (PFd)	Validity Reliability Interpretability Negative outcomes			Moderate correlation PFd of SF36 (108) Excellent intra-rater reliability(108)		

Promis-29 (PFd)	Validity					Moderate correlation PCS in SF-36 and HAQ-DI (71, 109)			
	Reliability					Moderate intra-rater reliability			
	Interpretability								
	Negative outcomes								
SF-12 (PFd or PCS)	Validity								
	Reliability								
	Interpretability								
	Negative outcomes								
LWAQ (PHC)	Validity	Moderate correlation with PCS SF-36 and Symptoms score (70)							
	Reliability								
	Interpretability								
	Negative outcomes								
M-AQLQ (AL)	Validity								
	Reliability								
	Interpretability								
	Negative outcomes								
CAMPHOR (AL)	Validity								
	Reliability								
	Interpretability						MID: -4 points(112)		

	Negative outcomes					
QoL-EPM (PL)	Validity	Weak to moderate correlations with SF-36 domains (113)				
	Reliability	Good test-retest reliability (113)				
	Interpretability					
	Negative outcomes					
MLHFQ (PSS)	Validity				Moderate correlation with NYHA and 6MWD(116)	
	Reliability				Strong test-retest correlation(116)	
	Interpretability					
	Negative outcomes				Mortality (total score≤40) (116)	
QoL-B (PFd)	Validity		Moderate correlation with SGRQ (activities), ISWT and mMRC (118)			
	Reliability		Excellent test-retest reliability (118)			
	Interpretability					
	Negative outcomes		Dyspnoea severity (mMRC) (118)			
London ADL (PAS)	Validity					
	Reliability					
	Interpretability					
	Negative outcomes					

FPI	Validity Reliability Interpretability Negative outcomes				
MDHAQ (PF)	Validity			Significant correlation (FVC%) (80)	
	Reliability Interpretability Negative outcomes				
SOLQ	Validity		Moderate correlation with PCS of SF-36 (124)		
(PFS)	Reliability		Good test-retest reliability (124)		
	Interpretability				
	Negative outcomes		Exacerbation frequency (124)		

Captions: Interpretability refers to the Minimal important difference (MID); ILD – Interstitial lung disease, PAH – Pulmonary arterial hypertension, LT – patients with chronic respiratory disease waiting/submitted to lung transplantation, NS-CRD – Non-specified chronic respiratory diseases, MID – Minimal important difference, SF-36 – Medical Outcomes Study 36-item Short Form of Health Survey, SGRQ – Saint´s George Respiratory Questionnaire, WHOfc – World Health Organization functional class, NYHA – New York heart association, AQLQ – Asthma Quality of Life Questionnaire, CFQoL – Cystic fibrosis quality of life, SF-12 – Medical Outcomes Study 12-item Short Form of Health Survey, Promis-29 – Patient-Reported Outcomes Measurement Information System, LWAQ – Living with Asthma Questionnaire, M-AQLQ – Mini Asthma Quality of Life Questionnaire, CAMPHOR – Cambridge pulmonary hypertension outcome review, QoL-EPM – Asthma Quality of Life from Escola Paulista de Medicina, MLHFQ – Minessota living with heart failure questionnaire, QoL-B – Quality of Life in Bronchiectasis, London ADL – London Activities of Daily Living, , FPI – Functional performance inventory, MDHAQ – Multi dimensional health assessment questionnaire, SOLQ – Seattle Obstructive Lung Questionnaire, 6MWD – 6 minute walk distance, mMRC – modified Medical Respiratory Council dyspnoea score, D_{LCO} – Diffusion capacity of carbon monoxide, FEV1 – Forced expiratory volume in 1 s, FVC – Forced vital capacity, BDI – Baseline dyspnoea index, TLC – Total lung capacity, VC – Vital capacity, PF – Physical functioning, HAQ-DI – Scleroderma Health Assessment Questionnaire Disability Index, PF – Physical functioning, PCS – Physical component score, AL – Activity limitation, PHC – Physical health construct, PL – Physical limitation, PFS – Physical functional score, PSS – Physical sub score, PAS – physical activity score; ISWT – Incremental shuttle walk test; ł: p value not described.

Implications to practice: selection of instruments by disease

The results of this systematic review demonstrate the large number of available tools to assess functional performance in non-COPD chronic respiratory diseases. Surprisingly, few tools have their measurement properties thoroughly investigated. Evidence for the association of functional performance with negative outcomes is scarce, with hospitalisations and mortality only reported in ILD and PAH patients.

The results in the present review were not able to find a tool that have all "boxes ticked". For instance, there is no such tool for each non-COPD CRDs that assess functional performance and have a comprehensive set of measurement properties, reported MIDs and has its association with negative outcomes investigated. The selection of the most appropriate tool to assess functional performance, thus, should be based on one's needs. If the intention is to assess functional performance but also investigate its responsiveness to an intervention, then tools with reported MIDs are those of preference. Instead, if one's need is to identify prognosis or risk of hospitalisations, maybe a different tool should be used. A summary of recommendation considering measurement properties and association with mortality or hospitalisation is provided below.

For asthma patients, 1min-STS, SF-36 and AQLQ were the objective and subjective instruments most used. Functional performance tests validated to asthma patients were: 4MGS, 5rep-STS, SPPB and TUG (25). At least good reliability was reached in 1min-STS, 30sec-STS, 5rep-STS, SPPB and TUG. Patient-reported outcomes valid were PCS of SF-36, AQLQ and LWAQ. Excellent reliability was observed in patient-report tools only for AQLQ (95). The MID of activities domain of AQLQ was established in 0.51 points (96) and activities domain of SGRQ present association with dyspnoea and depression (83). No association with hospitalisation or mortality was reported in any FP tests and patient-reported tools for asthma patients.

For patients with bronchiectasis, the FP tests used were 4MGS, 5rep-STS, Glittre-ADL and the most common questionnaire used was the activities domain of SGRQ. None FP tests were valid for bronchiectasis ($r>0.50$), only moderate

correlation in Glittre-ADL with 6MWT was observed (61). Reliability of FP tests was not investigated in bronchiectasis. Patient-report tool valid were the PCS of SF-36, activities domain of SGRQ, PFd of QoL-B and PFS of SOLQ. Good reliability was observed in QoL-B, SOLQ (118, 124). QoL-B is associated with dyspnoea severity (118) and PFd of SOLQ with exacerbation frequency (124). No association with hospitalisation or mortality was reported in any FP tests or patient-report tools in bronchiectasis.

For adult patients with cystic fibrosis, the 1min-STS was the FP test most used and the PFd of CFQoL was the most questionnaire used. Validity was reached in 1min-STS and 30sec-STS, but only 1min-STS is reliable for CF patients (28). The MID of 1min-STS was 5.4 repetitions (28). CFQoL is the only patient-report tool valid for CF, have strong correlation in test-retest analysis (i.e. ICC was not investigated) and excellent internal consistency (108). No association of FP tests or patient-report tools with hospitalisation or mortality was reported.

Interstitial lung disease was the disease with most different instruments used to assess FP. The most used FP test was the 4MGS (i.e. used in eight studies) and PFd of the SF-36 was the questionnaire most used. FP tests valid for ILD were: 1min-STS, 4MGS, 5rep-STS, TUG, 8-FUGT, Glittre-ADL, CS-PFP and 3min-STS. At least good reliability was reported in 1min-STS, 30sec-STS, 5rep-STS, SPPB, TUG, Glittre ADL, CS-PFP and 3min-STS. Lower velocity in 4MGS (4MGS<0.8 m/s) and performance higher than 6.9s in 8-FUGT were associated with hospitalisation and mortality in ILD (45, 52). PFd of SF-36, activities domain of SGRQ-I, PFd of Promis-29 were valid in ILD. Only activities domain of the SGRQ-I is deemed reliable (i.e. ICC≥0.75) (81). The MID of PCS of SF-36 is 4 points (68). No association of patient-report tools with hospitalisation or mortality was reported in ILD patients.

For PAH patients, FP tests most used was the 30sec-STS and the most used questionnaire/scale was the WHOfc. Only the 30sec-STS is valid for PAH patients. TUG and 30sec-STS have good reliability. PSS in MLHFQ have moderate correlation with NYHA and 6MWD, good internal consistency and strong correlation in test-retest analysis, although values of correlation in PSS domain and the ICC was not reported. (116). No other study investigated measurement properties in

other instruments for PAH patients. The MID of activity limitation domain of CAMPHOR is the reduction of 4 points (112), improvement of 13 and 5 points are the MID for PFd and PCS of SF-36, respectively (69). WHOfc is associated with clinical failure, score equal or greater than three are associated with a higher risk of death. Also, score in NYHA≥3 is associated with mortality (94) and total score of MLHFQ≥40 is associated with worse prognosis (116).

For patients with CRD waiting for or who underwent LTx, the SPPB was the only functional performance test used and the most used questionnaire was the PFd of SF-36. No measurement properties were reported of SPPB and improvement of 1 point in total score of SPPB was described as the MID (53). Also, no metric properties of patient-report tools were reported in the included studies. No association of hospitalisation or mortality were reported with FP tests or patient-report tools in patients waiting for or who underwent LTx. Although, as this systematic review is related with different diseases including a large number of instruments, the information of patients waiting for or who underwent LTX is restricted to studies which analysed different diagnosis of CRD separately. Studies which investigated with functional performance instruments considering mixed chronic respiratory diseases were excluded, which may restrict the information of functional performance in patients waiting for or who underwent LTx. Also, only one study (55) assessed functional performance in other chronic respiratory disease (i.e. chronic respiratory failure) and used only objective functional performance assessment through TUG and FRT. No measurement properties or association with hospitalisation and mortality were reported.

Strengths, limitations and future directions

The large array of available tools to assess functional performance in respiratory diseases makes difficult to select the most appropriate tool. A strength of this study is the ease for clinicians to check whether a specific tool suffices one's needs. Recommendations of patient-centred outcomes selection in other non-COPD exist (125). This is, however, the first study that provided a compilation of

both performed-based and patient-reported tools to assess functional performance in non-COPD CRD patients. The provision of details regarding construct, measurement properties, and clinical implications of the tools (i.e. negative impact of worse functional performance) offers a guide to tool selection.

The large number of included instruments, the heterogeneous constructs of the tools used to assess functional performance and different methodologies of included studies difficult comparisons between them. Thus, making a strong recommendation for the selection of a tool would inevitably be flawed and based on subjective opinion only. Additionally, the heterogeneous array of interventions and limited opportunity for meta-analysis meant that recommendation of a specific tool was difficult. Also, as it was not the purpose of this study investigate effectiveness of an intervention and due to heterogeneity of included studies only MID was investigated regarding responsiveness.

Despite the large number of instruments used in non-COPD CRDs reported in this review, the limited information of their measurement properties is worrisome. Future studies focusing on the measurement properties of the tools to specific diseases, mainly in bronchiectasis, cystic fibrosis, pulmonary arterial hypertension and patients waiting/submitted to lung transplantation are needed. Also, studies investigating other properties such as responsiveness to interventions, interpretability and associations with negative outcomes of functional performance instruments in different chronic respiratory are necessary.

Conclusion

The findings of the present systematic review confirm that functional performance is vastly studied in non-COPD chronic respiratory disease. Thirty-one instruments were found in seven subgroups of diseases: asthma, bronchiectasis, cystic fibrosis, ILD, PAH, patients waiting for or who underwent LTx and non-specified CRDs. Patient-reported tools (i.e. questionnaires and scales) were more frequently used, compared to performance-based tests. The most common FP tool used was the physical function domain of the SF-36, followed by activity domain in

the SGRQ. All functional performance tests focused on assess lower limb functional impairment and the most common were the 1min-STS and 4MGS followed by 30sec-STS and 5rep-STS. Albeit FP instruments are widely used in non-COPD CRDs, in the current literature only a few studies have reported measurement properties to support their use in clinical practice. Association with mortality and hospitalisations are scarcely reported and were found only with 4MGS and 8-FUGT in ILD and NYHA, WHOfc and MLHFQ in PAH.

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Supplemental Material

Table S1. Description of studies included in the final screening.

First Author (ref)	Disease	Age	Sex (F/M)	Complete n (% of initial)	Protocol
One-minute sit-to-stand					
JM Oliveira et al. 2020 (25)	Asthma	47 [38-58]	32/20	52(100%)	"…the participants should stand up and sit down as many times as possible for 1min with results in number of repetitions."
FC Freitas et al. 2012 (26)	Asthma	49.8 (8.1)	9/3	12 (100%)	"Sit-to-stand as fast as possible in one minute"
T Radtke et al. 2017 (27)	Cystic Fibrosis	31 [25-33]	7/8	15 (100%)	"Sit-to-stand as fast as possible in one minute with 3-min rest"
T Radtke et al. 2016 (28)	Cystic Fibrosis	29 [25-36]	8/6	14 (100%)	ND
M Gruet et al. 2016 (24)	Cystic Fibrosis	30 (9)	8/17	25	"Subjects were instructed to complete as many Sit-to-Stand cycles as possible within 1 min at a self-paced speed"
CL Zamboti et al. 2021 (30)	ILD	60.8 (11)	25/16	46(86%)	"…participants were requested to perform the highest number of sit-to-stand movements during 1minute…"
A Fedi et al. 2021 (17)	ILD	60(6)	5/28	33(89%)	"…patients were asked to perform as many repetitions as possible in 1 minute."
T Labrecque et al. 2020 (22)	ILD	69 (7)	5/10	15(88%)	"The participant was instructed to stand-up completely and to sit back down as many times possible within one minute…"
B Wallaert et al. 2020 (29)	ILD	57 (14)	45/62	107(100%)	"…as many times as possible at a self-paced speed (safe and comfortable) for 1 minute, …"
J Briand et al. 2018 (21)	ILD	57 (14)	45/62	107	"…standing upright and then sitting down at a self-paced speed as many times as possible for 1 min"
L Nakazato et al. 2020 (31)	PAH	44.3(13.2)	16/4	20(100%)	"…involves the performance of as many sit-to-stand actions as possible in one minute without using the upper limbs"
30 second sit-to-stand					

First Author (ref)	Disease	Age	Sex (F/M)	Complete n (% of initial)	Protocol
JM Oliveira et al. 2020 (25)	Asthma	47 [38-58]	32/20	52(100%)	"…the participants should stand up and sit down as many times as possible for 30s with results in number of repetitions."
M Majewski et al. 2015 (32)	Asthma	70.8	10/0	10 (91%)	ND
E Sheppard et al. 2019 (33)	Cystic Fibrosis	32(13)	6/9	15(100%)	"The participant was instructed to stand from a seated position as many times as possible in 30 s."
CL Zamboti et al. 2021 (30)	ILD	60.8 (11)	25/16	46(86%)	"…participants were requested to perform the highest number of sit-to-stand movements during 30seconds…"
B Vainshelboim et al. 2015 (35)	ILD	68.8 (6)	5/10	15 (100%)	"…as many full stands as possible from the sitting position on the chair within the 30 s"
B Vainshelboim et al. 2014 (34)	ILD	68.8 (6)	5/10	15 (100%)	"…as many full stands as possible from the sitting position on the chair within the 30 s"
B Kahraman et al. 2020 (37)	PAH	50.2(18.0)	7/31	38(100%)	"…were asked to rise from a seated position and sit as quickly and safely as possible in 30seconds."
B Kahraman et al. 2020 (36)	PAH	52.5(25-62)	3/9	11(73%)	ND
5 seconds sit-to-stand					
JM Oliveira et al. 2020 (25)	Asthma	47 [38-58]	32/20	52(100%)	"…stopwatch started on the command "go" and stopped at the end of the completed fifth stand, with results in seconds."
Z McKeough et al. 2020 (38)	Bronchiectasis	74(8)	16/17	33(100%)	"…measures the time taken to stand five times as quickly as possible..."
CL Zamboti et al. 2021 (30)	ILD	60.8 (11)	25/16	46(86%)	"…the time necessary to perform 5 movements was recorded..."
AR Koczulla et al. 2020 (41)	ILD	62(49-74)	5/6	11(78%)	"Subjects were asked to stand up and sit down 5 times as quickly as possible with their arms folded across their chest."
JN Justice et al. 2019 (39)	ILD	70.8(55-84)	2/12	14(100%)	"To evaluate time to complete 5-repition chair-stands, participants were asked to stand up and sit down on a straight-backed chair five times, as quickly as possible without using their arms."

First Author (ref)	Disease	Age	Sex (F/M)	Complete n (% of initial)	Protocol
AEM Bloen et al. 2018[c] (40)	ILD	68 [63-74]	14/37	42 (82%)	"…to stand up and sit down 5 times, as quickly as they could without any form of assistance"
P Mendes et al. 2015 (42)	ILD	61 (8)	7/19	26 (100%)	ND
L González-Saiz et al. 2017 (18)	PAH	46 (11)	12/8	20 (100%)	ND
3-minute sit-to-stand					
A Fedi et al. 2021 (17)	ILD	60(6)	5/28	33(89%)	"...the number of chair rises was imposed during the first minute (12 or 20, depending on the investigator's appreciation of the patient's fitness), and patients were asked to repeat the movement as many times as possible in the next 2 minutes."
Four-metre gait speed					
JM Oliveira et al. 2020 (25)	Asthma	47 [38-58]	32/20	52(100%)	"…the participants walk in a 4 m corridor… and were instructed to walk in a usual pace, …and also in a fast-pace walking mode, … fast as possible without run."
Z McKeough et al. 2020 (38)	Bronchiectasis	74(8)	16/17	33(100%)	"…over a 4m flat straight walking track with participants instructed to walk at their usual speed."
MDM Martinez-Garcia et al. 2020 (48)	Cystic Fibrosis	32.4(12.4)	17/21	38(92%)	"Subjects were instructed to walk at their normal comfortable pace. Two meters were provided prior to and following the timed portion to allow for acceleration and deceleration phases."
CL Zamboti et al. 2021 (30)	ILD	60.8 (11)	25/16	46(86%)	"…participants were required to walk in a usual gait speed measured over 4 m."
R Hirabayashi et al. 2020 (47)	ILD	74.2 (7.5)	35/16	51(100%)	"Patients walked 4m…"
JN Justice et al. 2019 (39)	ILD	70.8(55-84)	2/12	14(100%)	"…asking the participants to walk at their usual pace over a 4 m course, with the faster of two walks used to compute walking speed."
SA Guler et al. 2019[a] (43)	ILD	65.5 (9.5)	44/71	115 (70%)	"…to walk at their usual pace along a 4-m course…"

First Author (ref)	Disease	Age	Sex (F/M)	Complete n (% of initial)	Protocol
CM Nolan et al. 2018 (46)	ILD	75 (7.6)	13/33	46 (100%)	"…4-m course … with participants walking at their usual speed…"
AEM Bloem et al. 2018[c] (40)	ILD	68 [63-74]	14/37	42 (82%)	"...to walk as quickly as possible 4 meters (moving start) …"
CM Nolan et al. 2018 (45)	ILD	72 (7)	22/108	130(98%)	"to walk… your usual speed, just as if you were walking down the street to go to the shops."
CJ Ryerson et al. 2014 (44)	ILD	69.4(10.8)	28/26	54 (100%)	"… to walk 4m at their normal pace."
Short Physical Performance Battery					
JM Oliveira et al. 2020 (25)	Asthma	47 [38-58]	32/20	52(100%)	"…balance assessment, walking speed at usual pace, and sitting and rising in the chair 5 times."
CL Zamboti et al. 2021 (30)	ILD	60.8 (11)	25/16	46(86%)	"…composite of 3 balance tests, a gait speed test and sit-to-stand test."
JN Justice et al. 2019 (39)	ILD	70.8(55-84)	2/12	14(100%)	"…performance on 4 m gait speed and chair-stands tests and a balance test were scored and combined to derive the summary SPPB Score."
B Vainshelboim et al. 2019 (52)	ILD	68(8)	12/22	34(100%)	"Patients were encouraged to complete as many full stands as possible from a sitting position on a chair during 30s."
P Mendes et al. 2015 (42)	ILD	61 (8)	7/19	26 (100%)	Includes sit-to-stand, gait speed and tandem stance for balance
AA Perez et al. 2020 (53)	LT	31(7.9)	12/15	27(90%)	"The SPPB has three timed components: chair stands, balance, and gait speed. Each component of the SPPB has a score range of 0–4 with an aggregate range of 0–12."
Timed up and go					
JM Oliveira et al. 2020 (25)	Asthma	47 [38-58]	32/20	52(100%)	"…two protocols of this test were performed, with participants walking at their usual pace and at the fastest possible pace"
CL Zamboti et al. 2021 (30)	ILD	60.8 (11)	25/16	46(86%)	"…participants performed it at usual walking pace, and as fast possible without running."

First Author (ref)	Disease	Age	Sex (F/M)	Complete n (% of initial)	Protocol
P Mendes et al. 2015 (42)	ILD	61 (8)	7/19	26 (100%)	ND
B Kahraman et al. 2020 (37)	PAH	50.2(18.0)	7/31	38(100%)	"Participants were stand up from the chair, walked 3 m at a comfortable pace, turn and walk back to the starting point, and sit down again."
B Kahraman et al. 2020 (36)	PAH	52.5(25-62)	3/9	11(73%)	ND
S Arizono et al. 2009 (55)	NS-CRD	72.9 (7.9)	5/12	17 (100%)	ND
8-Foot up and go test					
M Majewski et al. 2015 (32)	Asthma	70.8	10/0	10 (91%)	ND
B Vainshelboim et al. 2019 (52)	ILD	68(8)	12/22	34(100%)	"…the patient got up from the chair, walked around a cone that was placed 8feet (2.40m) from the chair, and returned to a seated position on the chair as fast as possible."
P Mendes et al. 2015 (42)	ILD	61 (8)	7/19	26 (100%)	ND
Berg Balance Scale					
A Lopes et al. 2014 (58)	Asthma	25.4 [22-31]	7/19	26 (100%)	"…consists of 14 tasks with scores ranging from 0 to 4… that suggests a risk of falling…"
JT Penafortes et al. 2013 (59)	Cystic Fibrosis	24.5 [22-29]	6/8	14 (42%)	"…examines balance by using different standardized positions and actions related to 14 daily life items"
Glittre ADL					
R Hena et al. 2018 (61)	Bronchiectasis	50.8(11.5)	12/3	15(100%)	"…consists of a standardized 10-meter circuit, where the individual was instructed to go through the following sequence of activities in the shortest time."
HFAlexandre et al. 2021 (60)	ILD	63.2(11.4)	ND	21(75%)	"…consists of a 10-meter circuit in which the individual starts from a sitting position, walks, goes up and down two interposed steps and walks again until reaching a shelf, individually adjusted according to the height of the shoulder and waist."

First Author (ref)	Disease	Age	Sex (F/M)	Complete n (% of initial)	Protocol
Functional Reach and Test					
S Arizono et al. 2009 (55)	NS-CRD	72.9 (7.9)	5/12	17 (100%)	ND
Continuous Scale – Physical Function Performance					
AL Olson et al. 2015 (126)	ILD	69.3 (9.2)	7/9	16 (100%)	"…is a series of 10 tasks covering everyday life activities required to maintain independence"
15-steps climbing					
V Rusanov et al. 2008 (65)	ILD	58(11)	22/29	51(100%)	"…patients were asked to climb up and down the step 15 times as fast as they could, without any fixed pacing."
Subjective measures					
SF-36 – Physical Functioning or Physical Component Summary					
CM Oliveira et al. 2016 (127)	Asthma	52 (10)	15/37	52 (88%)	ND
N Newhouse et al. 2016 (128)	Asthma	58.2 (11.7)	27/46	62 (84%)	ND
A Meyer et al. 2015 (129)	Asthma	54.0 (11.0)	5/8	13 (92%)	Self-administered
HJ Pai et al.2015 (115)	Asthma	32.5	ND	31 (100%)	Self-administered
U Ochmann et al. 2012 (130)	Asthma	64	ND	121 (100%)	ND
AM Smith et al. 2012 (131)	Asthma	68.7 (7.2)	59/18	77 (100%)	ND
S Turner et al. 2011 (132)	Asthma	65.8(10.8)	11/8	19(95%)	ND
B Kligler et al. 2011 (77)	Asthma	43.4 (11.8)	61/16	77 (100%)	ND
V Siroux et al. 2008[c] (133)	Asthma	42.4(7.3)	524/376	864(96%)	ND
Y Tohda et al. 2006 (134)	Asthma	57.9(15.3)	16/28	44(100%)	ND

First Author (ref)	Disease	Age	Sex (F/M)	Complete n (% of initial)	Protocol
DK McClish et al., 2005 (135)	Asthma	38	168/133	301(100%)	ND
MA De Oliveira et al. 2005(113)	Asthma	28.2(11.3)	19/6	35(100%)	Self-administered
M Matheson et al. 2002 (136)	Asthma	39.7 (6.4)	213/213	426	Self-administered
K Stavem et al., 2000 (137)	Asthma	47(16-88)	82/35	117(100%)	Self-administered
CA Dyer et al. 1999 (83)	Asthma	77 [70-91]	33/27	60 (100%)	Self-administered
J Ware et al. 1998 (138)	Asthma	39.5	89/57	146 (82%)	Self-administered
P Blanc et al. 1997[c] (139)	Asthma	40(8)	199/84	283(90%)	Assessor applied
T Van der Molen et al. 1997 (70)	Asthma	44(14)	56/54	110 (100%)	Self-administered
LI Okamoto et al. 1996 (140)	Asthma	50	10/22	32 (100%)	Self-administered
E Bulcun et al. 2015 (124)	Bronchiectasis	48.1 (13.5)	46/32	78 (100%)	ND
PS Jacques et al. 2012 (141)	Bronchiectasis	40.9	18/5	23 (100%)	ND
AL Lee et al. 2009 (72)	Bronchiectasis	54.4.(13.8)	16/11	27(100%)	ND
JM Guilemany et al. 2006 (142)	Bronchiectasis	52 (16)	39/21	60 (100%)	Self-administered
DK Mcclish et al. 2005[a] (135)	Cystic Fibrosis	25.0	120/103	223 (100%)	ND
L Gee et al. 2000 (108)	Cystic Fibrosis	27(16-53)	15/17	32(100%)	ND
WF Aguiar et al. 2021 (81)	ILD	59(10)	15/15	30(100%)	Assessor applied
R Zhao et al. 2020 (143)	ILD	47.3(15.1)	26/2	28(100%)	ND
S Dalichau et al. 2020 (144)	ILD	73.7(5.3)	ND	44(72%)	ND
AR Koczulla et al. 2020 (41)	ILD	62(49-74)	5/6	11(78%)	ND

First Author (ref)	Disease	Age	Sex (F/M)	Complete n (% of initial)	Protocol
R Vis et al. 2020 (145)	ILD	40.6(7.6)	4/3	7(100%)	Self-administered
E Yalniz et al. 2019 (146)	ILD	67.4(7.1)	12/38	50(100%)	ND
S Witt et al. 2019 (68)	ILD	67.3 (10.7)	69/189	258 (100%)	Assessor applied
K Pilzak et al. 2018 (147)	ILD	46.8 (8.8)	7/10	17 (100%)	Self-administered
I Naz et al. 2018 (148)	ILD	59 [52-64]	6/3	9 (100%)	ND
AEM Bloem et al. 2018[c] (40)	ILD	68 [63-74]	14/37	42 (82%)	Self-administered
CJ Fisher et al. 2017 (109)	ILD	51.9(11.8)	59/14	73(100%)	Assessor applied
H Tomioka et a. 2016 (149)	ILD	76.5 (7.1)	2/15	17 (100%)	ND
S Dalichau et al. 2010 (150)	ILD	65.7 (5.5)	0/104	104 (100%)	ND
ME Hinchcliff et al. 2015 (71)	ILD	52 [27-71]	90/10	100 (100%)	Self-administered
EH Alhamad et al. 2015 (151)	ILD	63.3 (13.3)	11/22	33 (82%)	Self-administered
AL Olson et al. 2015 (64)	ILD	69.3 (9.2)	7/9	16 (100%)	Self-administered
RM Du bois et al. 2011 (152)	ILD	65.3 (8.1)	344/812	1165 (100%)	ND
F Lumetti et al. 2015 (153)	ILD	63.3 (11.7)	47/1	48 (100%)	Self-administered
U Ochmann et al. 2012[b] (130)	ILD	64	ND	108 (100%)	ND
AC Theodore et al. 2012 (154)	ILD	ND	ND	114(100%)	Self-administered
JJ Swigris et al. 2012 (155)	ILD	69 (9)	31/149	180 (100%)	ND
JJ Swigris et al. 2011 (156)	ILD	71.5 (7.4)	3/18	21 (100%)	Self-administered
V Krishnan et al. 2008 (157)	ILD	67.7(8.7)	19/22	41(85%)	ND

First Author (ref)	Disease	Age	Sex (F/M)	Complete n (% of initial)	Protocol
C Zimmerman et al. 2007 (67)	ILD	61.4 (10.5)	8/12	20 (100%)	ND
S Ohno et al. 2005 (158)	ILD	66.6 (6.7)	12/28	40 (100%)	Self-administered
JA Chang et al. 1999 (78)	ILD	60.5 [29-81]	22/28	50 (100%)	ND
L Nakazato et al. 2020 (31)	PAH	44.3(13.2)	16/4	20(100%)	ND
H Karapolat et al. 2019 (159)	PAH	34(26-62)	3/12	12(80%)	ND
AS Babu et al. 2019 (85)	PAH	51.4(13.7)	20/22	34(80%)	ND
M Kukkonen et al. 2016 (160)	PAH	53 (16.2)	46/32	78 (100%)	ND
SC Mathai et al. 2015[c] (88)	PAH	55 (15)	317/88	405 (100%)	ND
ID Laoutaris et al. 2015 (86)	PAH	48.6(12.7)	4/1	5(100%)	ND
LA Matura et al. 2014 (161)	PAH	53.5 (15.1)	127/22	149 (100%)	Self-administered
LA Matura et al. 2012 (73)	PAH	52.2 (16.0)	76/17	93	ND
E Grunig et al. 2012 (162)	PAH	53(15)	126/57	183(94%)	Self-administered
C Gilbert et al. 2009 (69)	PAH	ND	ND	278	ND
J Pepke-Zaba et al. 2009 (163)	PAH	53(15)	59/20	71 (89%)	Self-administered
N Galie et al. 2008 (164)	PAH	52(15)	48/16	64 (100%)	ND
R Souza et al. 2007 (165)	PAH	41(11)	17/6	23 (100%)	Assessor applied
D Mereles et al. 2006 (166)	PAH	53(14)	10/5	15 (100%)	Self-administered
J White et al. 2006 (167)	PAH	48.6(11.8)	23/4	27	ND
R Souza et al. 2005 (168)	PAH	40(11)	11/4	15 (100%)	Assessor applied

First Author (ref)	Disease	Age	Sex (F/M)	Complete n (% of initial)	Protocol
D Langer et al. 2012 (169)	LTx	51(10)	15/12	27 (100%)	ND
MI Feltrim et al. 2008 (170)	LTx	54(11)	3/4	7 (100%)	Assessor applied
SGRQ – Activities					
N Duruturk et al. 2018 (120)	Asthma	46.5(13.3)	14/6	16(80%)	ND
M Majewski et al. 2015 (32)	Asthma	70.8	10/0	10 (91%)	ND
MAM Zadeh et al. 2013 (171)	Asthma	22	0/33	33 (91%)	Self-administered
CA Dyer et al. 1999 (83)	Asthma	77[70-91]	33/27	60 (100%)	Self-administered
Z McKeough et al. 2020 (38)	Bronchiectasis	74(8)	16/17	33(100%)	Self-administered
CO De Camargo et al. 2020(118)	Bronchiectasis	48(14.1)	61/57	108(125%)	Self-administered
KA Lavery et al. 2011[c] (172)	Bronchiectasis	60(9)	17/15	30(93%)	ND
AL Lee et al. 2009 (72)	Bronchiectasis	54.4(13.8)	16/11	27(100%)	ND
MA Martinez-Garcia et al. 2006 (173)	Bronchiectasis	70.9(6)	8/21	29 (93%)	ND
WF Aguiar et al. 2021 (81)	ILD	59(10)	15/15	30(100%)	Assessor applied
HF Alexandre et al. 2021 (60)	ILD	63.2(11.4)	ND	21(75%)	ND
K Ebihrara et al. 2021 (174)	ILD	76.1(5.9)	6/21	27(56%)	ND
K Janssen et al. 2020 (175)	ILD	72.7(8)	0/11	11(100%)	ND
R Hirabayashi et al. 2020 (47)	ILD	74.2(7.5)	35/16	51(100%)	Self-administered
AR Koczulla et al. 2020 (41)	ILD	62[49-74]	5/6	11(78%)	ND

First Author (ref)	Disease	Age	Sex (F/M)	Complete n (% of initial)	Protocol
JN Justice et al. 2019 (39)	ILD	70.8[55-84]	2/12	14(100%)	ND
AW Creamer et al. 2019 (176)	ILD	ND	ND	41(100%)	Self-administered
PV Santana et al. 2019 (177)	ILD	54(14)	4/5	9(100%)	ND
I Naz et al. 2018 (148)	ILD	59[52-64]	6/3	9 (100%)	ND
CJ Fisher et al. 2017 (109)	ILD	51.9(11.8)	59/14	73(100%)	Assessor applied
LM Dowman et al. 2017 (178)	ILD	70(9.6)	18/34	48 (92%)	Assessor applied
NF Braz et al. 2016 (179)	ILD	43.4(9.7)	0/23	23 (88%)	Assessor applied
MN Karadali et al. 2016 (180)	ILD	45.1(8.1)	10/5	15 (88%)	ND
AL Olson et al. 2015 (64)	ILD	69.3(9.2)	7/9	16 (100%)	Self-administered
B Vainshelboim et al. 2015 (35)	ILD	68.8(6)	5/10	15 (100%)	Self-administered
B Vainshelboim et al. 2014 (34)	ILD	68.8(6)	5/10	15 (100%)	Self-administered
WP Drake et al. 2013 (181)	ILD	54 [43-65]	11/4	8 (53%)	ND
JJ Swigris et al. 2012 (155)	ILD	69(9)	31/149	180 (100%)	ND
ZÇ Sozener et al. 2010 (93)	ILD	52.7(9.8)	28/5	33 (100%)	Self-administered
C Zimmerman et al. 2007 (67)	ILD	61.4(10.5)	8/12	20 (100%)	ND
JA Chang et al. 1999 (78)	ILD	60.5[29-81]	22/28	50 (100%)	ND
MI Feltrim et al. 2008 (170)	LTx	54(11)	3/4	7 (100%)	Assessor applied
WHO functional class					
A Arvanitaki et al. 2020 (182)	PAH	57.9(16.3)	22/12	34(100%)	ND

First Author (ref)	Disease	Age	Sex (F/M)	Complete n (% of initial)	Protocol
AS Babu et al. 2019[c] (85)	PAH	51.4(13.7)	20/22	34(80%)	ND
K Karazaum et a. 2019 (183)	PAH	54.9(10.4)	14/4	18(100%)	Obtained from clinical history
M Aldemir et al. 2018 (184)	PAH	61(10)	23/15	38 (100%)	ND
C Mihai et al. 2017 (185)	PAH	61(54-66)	14/11	25(100%)	ND
M Waligora et al. 2017 (186)	PAH	50.0(15.7)	47/19	66(100%)	ND
SA Segrera et al. 2017 (187)	PAH	58.6(9.9)	14/8	22 (73%)	ND
N Tanabe et al. 2017[c] (87)	PAH	44.5(13.3)	26/11	33 (89%)	ND
SK Saha et al. 2016 (188)	PAH	64(10)	12/13	25 (100%)	Obtained from clinical history
M Kukkonen et al. 2016 (160)	PAH	53(16.2)	46/32	78 (100%)	"…estimated based on a question on the SF-36 form (how much a moderately strenuous activity e.g. brisk walking on level ground is restricted by health issues)."
L Godinas et al. 2016 (189)	PAH	48(15)	101/52	153(100%)	ND
SC Mathai et al. 2015[c] (88)	PAH	55(15)	317/88	405 (100%)	ND
LJ Rubin et al. 2015[c] (89)	PAH	50(16)	317/79	339 (85%)	ND
AE Frost et al. 2015 (190)	PAH	50[18-27]	83/20	103(100%)	ND
DJ Webb et al. 2015 (191)	PAH	48(15)	56/15	71(100%)	ND
ID Laoutaris et al. 2015 (86)	PAH	48.6(12.7)	4/1	5(100%)	ND
Y Zhuang et al. 2014 (192)	PAH	52 (12)	46/14	54 (90%)	ND
SA Mouratoglou et al. 2014 (90)	PAH	49(15)	16/6	22(100%)	ND
LA Matura et al. 2014 (161)	PAH	53.5(15.1)	127/22	149 (100%)	"…was defined from assessment of self-reported symptom severity and activity limitations by the principal investigator."

First Author (ref)	Disease	Age	Sex (F/M)	Complete n (% of initial)	Protocol
HA Ghofrani et al. 2013 (193)	PAH	51(17)	203/34	237(93%)	ND
LA Matura et al. 2012 (73)	PAH	52.2(16.0)	76/17	93	"…was defined from assessment of self-reported symptom severity and activity limitations by the principal investigator."
RJ Oudiz et al. 2012 (194)	PAH	53(16)	48/15	52 (82)	ND
R Condliffe et al. 2018 (91)	PAH	63.9(10.5)	212/46	259(100%)	ND
N Galie et al. 2009 (195)	PAH	53(15)	59/20	79 (100%)	ND
C Gilbert et al. 2009 (69)	PAH	ND	ND	278	ND
N Galie et al. 2008 (164)	PAH	52(15)	48/16	64 (100%)	ND
J White et al. 2006 (167)	PAH	48.6(11.8)	23/4	27	ND
N Galie et al. 2005 (196)	PAH	51(16)	54/10	64 (100%)	ND
N Galie et al. 2005 (197)	PAH	48(15)	56/15	71 (100%)	ND
NYHA functional class					
K Ozen et al. 2020 (198)	ILD	52.5(10.7)	46/10	56(93%)	ND
S Witt et al. 2019 (68)	ILD	67.3 (10.7)	69/189	258 (100%)	Assessor applied
ZÇ Sozeneri et al. 2010 (93)	ILD	52.7(9.8)	28/5	33 (100%)	ND
Rusanov et al. 2008 (65)	ILD	58(11)	22/29	51(100%)	ND
K Bunclark et al. 2021 (112)	PAH	54.4(16.4)	64/65	129(70%)	ND
EV Karelkina et al. 2020[c] (199)	PAH	48(15)	16/3	14(73%)	ND
B Kahraman et al. 2020 (36)	PAH	50.2(18.0)	7/31	38(100%)	ND

First Author (ref)	Disease	Age	Sex (F/M)	Complete n (% of initial)	Protocol
T Naal et al. 2018 (200)	PAH	51.3(18.1)	203/74	277(95%)	ND
E Ozpelit et al. 2015 (201)	PAH	56 [18-77]	26/7	33 (100%)	ND
N Chueamuangphan et al. 2014 (202)	PAH	36.1(14.6)	12/4	16(100%)	ND
N Malik et al. 2012 (203)	PAH	49(11)	27/5	32(100%)	ND
RL Benza et al. 2011[c] (204)	PAH	54[18-75]	167/39	122 (59%)	ND
L Tokgozoglu et al. 2009 (94)	PAH	45.4(9.7)	32/19	51 (100%)	ND
OA Minai et al. 2007 (205)	PAH	51(12)	23/7	30(100%)	Obtained from clinical history
EM Chau et al. 2007 (206)	PAH	41(7)	5/1	6(100%)	ND
N Zafrir et al. 2007 (207)	PAH	50.8(14.7)	22/7	29 (100%)	ND
R Souza et al. 2007 (208)	PAH	37(2)	32/10	42 (100%)	ND
VV McLaughlin et al. 2006[c] (209)	PAH	51(14)	27/7	30 (88%)	ND
E Cenedese et al. 2006 (116)	PAH	50 [46-54]	31/17	48(100%)	Applied using a standardized questionnaire
J Shen et al. 2005 (210)	PAH	53(18)	20/7	27(100%)	ND
DB Badesch et al. 2000 (211)	PAH	53(13.1)	51/5	56 (100%)	ND
M Yigla et al. 1997(212)	PAH	70.5(6.7)	10/4	14(100%)	ND
AQLQ – Activity limitation					
SM Lage et al. 2021 (213)	Asthma	40.2(13.4)	14/6	20(58%)	Assessor applied
KB Evaristo et al. 2021 (214)	Asthma	50.6(9.2)	17/8	25(100%)	ND

First Author (ref)	Disease	Age	Sex (F/M)	Complete n (% of initial)	Protocol
S Majd et al. 2020 (215)	Asthma	58(11)	18/12	30(49%)	ND
PD Freitas et al. 2017 (216)	Asthma	48.5(9.6)	25/0	25(92%)	ND
A Meyer et al. 2015 (129)	Asthma	54.0(11.0)	5/8	13 (92%)	Self-administered
A Refaat et al.2015 (217)	Asthma	35.8(1.7)	21/17	38(100%)	Self-administered
S Pakhale et al. 2015 (218)	Asthma	43.3(10.3)	15/1	15(93%)	ND
TZ Rondinei et al. 2015 (219)	Asthma	57[37-51]	6/2	8(73%)	ND
S Turner et al. 2011 (132)	Asthma	65.8(10.8)	11/8	19(95%)	Self-administered
B Kligler et al. 2011 (77)	Asthma	43.4(11.8)	61/16	77 (100%)	ND
R Vempati et al. 2009 (220)	Asthma	33.5(11.4)	16/13	29(100%)	Self-administered
J-S Choi et al. 2005 (221)	Asthma	46.2(14.7)	17/23	40(100%)	Doubtful
G Riccioni et al. 2002 (222)	Asthma	26.9(12.3)	7/8	15(100%)	Assessor applied
W Busse et al. 1998 (223)	Asthma	37.2[12-80]	129/134	263(100%)	Self-administered
T Van der Molen et al. 1998 (224)	Asthma	40.8(13.2)	28/28	56 (100%)	Assessor applied
J Ware et al. 1998 (138)	Asthma	39.5	89/57	146 (82%)	Self-administered
T Van der Molen et al. 1997 (70)	Asthma	44(14)	56/54	110 (100%)	Self-administered
E Juniper et al. 1994 (96)	Asthma	42(13.7)	24/15	39(100%)	Assessor applied
E Juniper et al. 1993 (95)	Asthma	42(13.7)	24/15	37(95%)	Assessor applied
CFQoL – Physical Functioning					
KB Knudsen et al. 2017 (107)	Cystic Fibrosis	23.6[18-30]	12/6	18(90%)	Self-administered

First Author (ref)	Disease	Age	Sex (F/M)	Complete n (% of initial)	Protocol
KCA Aguiar et al. 2017 (104)	Cystic Fibrosis	ND	ND	52(100%)	Self-administered
VJ Ribeiro-Moço et al. 2017 (100)	Cystic Fibrosis	25.5(6)	9/12	21(70%)	ND
T Radtke et al. 2016 (28)	Cystic Fibrosis	29[25-36]	8/6	14 (100%)	ND
JT Penafortes et al. 2014 (101)	Cystic Fibrosis	24.5[22-34]	6/8	14(47%)	Self-administered
EJ Dill et al. 2013 (102)	Cystic Fibrosis	32.5(10.6)	153/125	278(92%)	ND
L Kelemen et al. 2012 (105)	Cystic Fibrosis	29.4(8.5)	42/35	73(95%)	Self-administered
CA Sandsund et al. 2011 (103)	Cystic Fibrosis	27[25-32]	5/5	10(100%)	Self-administered
AC Young et al. 2008 (106)	Cystic Fibrosis	37(8)	2/6	8(89%)	ND
L Gee et al. 2000 (108)	Cystic Fibrosis	27[16-53]	15/17	32(100%)	Self-administered
SF-12 – Physical Functioning or Physical Component Summary					
WT Liu et al. 2011 (76)	Asthma	50.4(1.9)	22/22	43 (72%)	ND
B Kligler et al. 2011 (77)	Asthma	45.7(9.5)	64/13	77 (100%)	ND
AA Perez et al. 2020 (53)	LTx	31(7.9)	12/15	27(90%)	ND
Promis-29 – Physical Functioning					
CJ Fisher et al. 2017 (109)	ILD	51.9(11.8)	59/14	73(100%)	Assessor applied
SE Yount et al. 2016 (110)	ILD	61(5.6)	155/65	220 (100%)	ND
ME Hinchcliff et al. 2015 (71)	ILD	52[27-71]	90/10	100 (100%)	Self-administered
Living with Asthma Questionnaire (LWAQ) – Physical Health Construct					
Y Tohda et al. 2006 (134)	Asthma	57.9(15.3)	16/28	44(100%)	ND

First Author (ref)	Disease	Age	Sex (F/M)	Complete n (% of initial)	Protocol
T Van der Molen et al. 1998 (224)	Asthma	40.8 (13.2)	28/28	56 (100%)	Assessor applied
T Van der Molen et al. 1997 (70)	Asthma	44(14)	56/54	110 (100%)	Self-administered
Asthma Quality of Life from EPM – Physical Limitation					
HJ Pai et al. 2015 (115)	Asthma	32.5	ND	31 (100%)	Self-administered
FA Mendes et al. 2013 (114)	Asthma	34.9(8.2)	17/4	21 (100%)	ND
MA De Oliveira et al. 2005 (113)	Asthma	28.2(11.3)	19/6	35 (100%)	Self-administered
M-AQLQ – Activity Limitation					
G Georga et al. 2019 (98)	Asthma	49.4 (13)	16/7	21(91%)	ND
J Ma et al. 2017 (97)	Asthma	52.2(11.9)	34/12	44(95%)	Self-administered
Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) - ACTIVITY					
K Bunclark et al. 2021 (112)	PAH	54.4(16.4)	64/65	129(70%)	ND
LA Matura et al. 2012 (73)	PAH	52.2 (16.0)	76/17	93	ND
London – ADL – Physical Activity Score					
N Duruturk et al. 2018 (120)	Asthma	46.5 (13.3)	14/6	16(80%)	ND
Functional performance inventory					
FX McCormack et al. 2011(122)	ILD	45(10.9)	ND	46(100%)	ND
Multi-Dimensional Health Assessment Questionnaire – Physical function					
JJ Swigris et al. 2010 (80)	ILD	52.8(19.7)	35/13	48(100%)	Self-administered
Minessota living with heart failure – Physical Sub score					

First Author (ref)	Disease	Age	Sex (F/M)	Complete n (% of initial)	Protocol
GK Aslan et al. 2020 (117)	PAH	47.2(13.2)	13/12	20(100%)	ND
E Cenedese et al. 2006 (116)	PAH	50 [46-54]	31/17	48(100%)	Self-administered
QoL – Bronchiectasis – Physical Functioning					
A José et al. 2021[c] (119)	Bronchiectasis	44.4(16.1)	16/17	27(82%)	ND
CO De Camargo et al. 2020(118)	Bronchiectasis	48(14.1)	61/57	108(125%)	Assessor applied
Seattle Obstructive Lung Disease Questionnaire SOLQ – Physical function score					
E Bulcun et al. 2015 (124)	Bronchiectasis	48.1(13.5)	46/32	78 (100%)	ND

Captions: ILD – Interstitial lung disease. PAH – Pulmonary arterial hypertension. LT – patients with chronic respiratory disease waiting/submitted to lung transplantation. NS-CRD – non-specified chronic respiratory diseases. ND – no description. 1min-STS – 1minute sit-to-stand, 4MGS – four-metre gait speed, 30sec-STS – 30 seconds sit-to-stand, 5rep-STS – 5 repetitions sit-to-stand, SPPB – short physical performance battery, TUG – timed-up-and-go, 8-FUGT – 8-foot-up-and-go, BBS – berg balance scale, Glitre ADL – Glittre Activities of daily living, FRT– function reach test, CS-PFP – continuous scale physical function performance test, 3min-STS – 3-minute sit-to-stand, 15-steps climbing, Chair-SR – chair sit and reach, SF-36 – Medical Outcomes Study 36-item Short Form of Health Survey, SGRQ – Saint´s George Respiratory Questionnaire, WHOfc – World Health Organization functional class, NYHA – New York heart association, AQLQ – Asthma Quality of Life Questionnaire, CFQoL – Cystic fibrosis quality of life, SF-12 – Medical Outcomes Study 12-item Short Form of Health Survey, Promis-29 – Patient-Reported Outcomes Measurement Information System, LWAQ – Living with Asthma Questionnaire, M-AQLQ – Mini Asthma Quality of Life Questionnaire, CAMPHOR – Cambridge pulmonary hypertension outcome review, London ADL – London Activities of Daily Living, QoL-EPM – Asthma Quality of Life from Escola Paulista de Medicina, FPI – Functional performance inventory, MDHAQ – Multi dimensional health assessment questionnaire, MLHFQ – Minessota living with heart failure questionnaire, QoL-B – Quality of Life in Bronchiectasis, SOLQ – Seattle Obstructive Lung Questionnaire.

[a]It was performed mean of man´s and woman´s age.

[b]The results is mean of age and sum of asbestosis and silicosis.

[c]Number of men and women of n initial, without loss.

Table S2. Methodological quality of included studies assessed by Cosmin Checklist.

Author, year (ref)	PROM Development	Internal Consistency	Cross-cultural validity	Reliability	Measurement Error	Criterion Validity	Construct Validity	Responsiveness
T Van der Molen,1997 (70)	N/A	Very Good	N/A	N/A	N/A	Very Good	N/A	N/A
T Radtke, 2016 (28)	N/A	N/A	N/A	Adequate	N/A	Very Good	N/A	N/A
T Radtke, 2017 (27)	N/A	N/A	N/A	N/A	N/A	Very Good	N/A	N/A
CM Nolan,2018 (46)	N/A	N/A	N/A	Adequate	Adequate	Very Good	N/A	Very Good
ME Hinchcliff, 2015 (71)	N/A	N/A	N/A	N/A	N/A	Very Good	N/A	N/A
AL Olson, 2015 (64)	N/A	Very Good	N/A	Adequate	N/A	Very Good	N/A	N/A
SE Yount, 2016 (110)	N/A	N/A	N/A	Doubtful	N/A	N/A	N/A	N/A
C Zimmermann, 2007 (67)	N/A	N/A	N/A	N/A	N/A	Doubtful	N/A	N/A
S Witt, 2019 (68)	N/A	Very Good	N/A	Doubtful	N/A	Very Good	N/A	Very Good
AEM Bloem,2018 (40)	N/A	N/A	N/A	Doubtful	N/A	Very Good	N/A	N/A
JM Oliveira, 2020 (25)	N/A	N/A	N/A	Very Good	Very Good	Very Good	N/A	N/A
R Hirabayashi, 2020 (47)	N/A	N/A	N/A	N/A	N/A	Very Good	N/A	N/A
B Wallaert, 2020 (29)	N/A	N/A	N/A	N/A	N/A	Very Good	N/A	N/A
T Labrecque, 2020 (22)	N/A	N/A	N/A	Doubtful	Doubtful	Very Good	N/A	N/A
B Kahraman, 2020 (36)	N/A	N/A	N/A	Doubtful	Doubtful	Very Good	N/A	N/A
CL Zamboti, 2021 (30)	N/A	N/A	N/A	Very Good	Very Good	Very Good	N/A	N/A
A Fedi, 2021 (17)	N/A	N/A	N/A	Very Good	N/A	Very Good	N/A	N/A
E Juniper 1993 (95)	N/A	Very Good	N/A	Very good	Very Good	Very Good	N/A	Very Good
AL Lee 2009 (72)	N/A	N/A	N/A	N/A	N/A	Very Good	N/A	N/A
E Shepard, 2019 (33)	N/A	N/A	N/A	N/A	N/A	Very Good	N/A	N/A
L Gee, 2020 (108)	Doubtful	Very Good	N/A	Very Good	Inadequate	Very Good	Very Good	Very Good
B Vainshelboim, 2019 (52)	N/A	N/A	N/A	N/A	N/A	Very Good	N/A	N/A
Fisher,2017 (109)	N/A	Very Good	N/A	Doubtful	N/A	Very Good	Very Good	Very Good
HF Alexandre, 2021 (60)	N/A	N/A	N/A	Very Good	Very Good	Very Good	N/A	N/A
JJ Swigris, 2010 (80)	N/A	N/A	N/A	N/A	N/A	Very Good	N/A	N/A
V Rusanov, 2008 (65)	N/A	N/A	N/A	N/A	N/A	Very Good	N/A	N/A

WF Aguiar,2021 (81)	N/A	Very Good	Doubtful	Very Good	Very Good	Very Good	Very Good	Very Good
R Hena et al. 2018 (61)	N/A	N/A	N/A	N/A	N/A	Very Good	N/A	N/A
T Van der Molen et al. 1998 (224)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Very Good
E Bulcun et al.2015 (124)	N/A	N/A	Doubtful	Very Good	N/A	Very Good	N/A	N/A
MA Oliveira et al. 2005 (113)	N/A	N/A	N/A	Very Good	N/A	Very Good	N/A	Very Good
CO De Camargo et al. 2020 (118)	N/A	Very Good	N/A	Very Good	N/A	Very Good	Very Good	N/A
E Cenedese et al. 2006 (116)	N/A	N/A	N/A	Doubtful	N/A	N/A	N/A	Very Good

Captions: ref – reference, N/A - Not applicable.

Table S3. Values of measurement properties of functional performance tests.

		Asthma	Bronchiectasis	Cystic Fibrosis	ILD	PAH	LT	NS-CRD
1min-STS	Validity	6MWD (r=0.48; p<0.0001) QS MIVC (r=0.41; p=0.003) (25)		Watts$_{máx}$ CPET (r=0.93; p<0.05) VO_2 peak (0.62<r<0.91; p<0.05) (28)	6MWD (0.33<r<0.82; p<0.05) HGS (r=0.35; p<0.05) QS MIVC (0.34>r>0.60; p<0.05) FVC%pred (r=0.48; p<0.05) TCLO%pred (r=0.47; p<0.001) (17, 22, 29, 30)			
	Reliability	Intra-rater [ICC:0.87(0.73-0.93)] Inter-rater [ICC: 0.80(0.62-0.89)] (25)		Intra-rater [ICC:0.98(0.96-0.99)] (28)	Intra-rater [ICC:0.88(0.82-0.94)] Inter-rater [ICC: 0.91(0.85-0.95)] (30)			
	Interpretability			MID: 5.4 repetitions (28)				
30sec-STS	Validity	6MWD (r=0.45; p<0.0001) QS MIVC (r=0.43; p=0.002) (25)		QS peak torque (r=0.55; p=0,034) (33)	6MWD (r=0.28; p>0.05) HGS (r=0.41; p<0.05) QS MIVC (r=-0.41; p<0.05) (30)	QS MIVC (r=0.54; p<0.001) (36)		
	Reliability	Intra-rater [ICC:0.91(0.81-0.95)] Inter-rater [ICC: 0.86(0.73-0.93)] (25)			Intra-rater (0.90>ICC>0.92) Inter-rater [ICC: 0.85(0.73-0.91)] (30)	Intra-rater [ICC:0.95 (0.90-0.97)] (36)		
	Interpretability							
5rep-STS	Validity	6MWD (r=-0.56; p<0.0001)			6MWD (-0.26>r>-0.41; p>0.05) HGS (r=-0.38; p<0.05)			

		HGS (r=0.49; p<0.0001) QS MIVC (r=-0.34; p=0.018) (25)		QS MIVC (r=-0.50; p<0.05) mMRC (r=0.18;p>0.05) (30)	
	Reliability	Intra-rater [ICC:0.84(0.72-0.90)] Inter-rater [ICC: 0.86(0.75-0.92)] (25)		Intra-rater (0.85<ICC<0.87) Inter-rater [ICC: 0.90(0.82-0.94)] (30, 40)	
	Interpretability				
3min-STS	Validity			FVC%pred (r=0.43; p<0.05) TCLO%pred (r=0.55; p<0.001) (17)	
	Reliability			Test-retest [ICC:0.96(0.92-0.98)] (17)	
	Interpretability				
4MGS	Validity	6MWD (r=-0.64; p<0.0001) HGS (r=-0.52; p<0.0001) QS (r=-0.30; p=0.040) (25)		6MWD (0.55<r<0.77; p>0.05) KBILD total (r=0.44; p<0.001) mMRC (-0.56<r>0.40; p>0.05) GAP index (r=-0.41; p=0.002) HGS (0.32<r>0.57; p>0.05) (22, 30, 40, 43, 46, 47)	
	Reliability	Intra-rater [ICC: 0.86(0.73-0.92)]		Intra-rater (0.92>ICC>0.95) Inter-rater (0.56>ICC>0.98) (22, 30, 40, 46)	

		Inter-rater [ICC: 0.58(0.26-0.76)] (25)				
	Interpretability					
SPPB	Validity	6MWD (r=0.61; p<0.0001) HGS (r=0.50; p<0.0001) (25)		6MWD (r=0.35; p<0.05) (30)		
	Reliability	Intra-rater [ICC:0.75(0.56-0.86)] Inter-rater [ICC: 0.75(0.56-0.86)] (25)		Intra-rater [ICC:0.83(0.71-0.91)] Inter-rater [ICC: 0.75(0.59-0.86)] (30)		
	Interpretability					MID:1 point (53)
TUG	Validity	6MWD (r=-0.62; p<0.0001) HGS (r=-0.49; p<0.0001) (25) QS MIVC (r=-0.43; p=0.002)		6MWD (r=-0.69; p<0.05) QS MIVC (r=-0.48; p<0.05) HGS(r=0.56; p<0.05) (30)	QS MIVC (r=-0.38; p=0.017) (36)	
	Reliability	Intra-rater [ICC: 0.90(0.82-0.94)] Inter-rater [ICC: 0.76(0.56-0.87)] (25)		Intra-rater [ICC:0.88(0.79-0.93)] Inter-rater [ICC: 0.89(0.81-0.94)] (30)	Intra-rater [ICC:0.96 (0.93-0.98)] (36)	
	Interpretability					
8-FUGT	Validity			6MWD (r=-0.61; p<0.05) CPET (r=-0.72; p<0.05) 30sec-STS (r=-0.65; p>0.001) (52)		
	Reliability					

	Interpretability					
BBS	Validity Reliability Interpretability					
Glittre ADL	Validity		6MWD (r=-0.41; p<0.05) (61)		6MWD (r=-0.70; p=0.002); Total EE (r=-0.52; p=0.02) (17)	
	Reliability				Test-retest [ICC:0.90(0.75-0.96)] (17)	
	Interpretability					
FRT	Validity Reliability Interpretability					
CS-PFP	Validity				SGRQ – activities (r=-0.80; p=0.0002) 6MWT (r=0.66; p=0.008) SF-36 – Physical function (r=0.64; p=0.007) D_{LCO} %predicted (r=0.67; p=0;006) FVC %predicted (r=0.63; p=0.009) (64)	
	Reliability				Intra-rater (ICC:0.83) (64)	
	Interpretability					
15-steps climbing	Validity				6MWD (r=-0.49; p=-.0003) D_{LCO}% (r=-0.11; p>0.05). (65)	
	Reliability Interpretability					

Captions: Interpretability refers to Minimal important difference (MID); ILD – Interstitial lung disease. PAH – Pulmonary arterial hypertension. LT – patients with chronic respiratory diseases waiting/ submitted to lung transplantation. NS-CRD – non-specified chronic respiratory diseases. ND – no description. 1min-STS – 1minute sit-to-stand,

4MGS – four-metre gait speed, 30sec-STS – 30 seconds sit-to-stand, 5rep-STS – 5 repetitions sit-to-stand, SPPB – short physical performance battery, TUG – timed-up-and-go, 8-FUGT – 8-foot-up-and-go, BBS – berg balance scale, Glittre ADL – Glittre Activities of daily living, FRT– function reach test, CS-PFP – continuous scale physical function performance test, 3min-STS – 3-minute sit-to-stand, 15-steps climbing; Vo_2 - maximum volume of oxygen utilization; 6MWT – six-minute walt test; 6MWD – distance in six-minute walk test, QS – Quadriceps strength; HGS – Handgrip strength; QS – Quadriceps strength; Total EE – Total energy expenditure in daily physical activities, in kilocalories; MIVC – Maximal isometric voluntary contraction; FEV1 – Forced expiratory volume in 1 s; FVC – Forced vital capacity; mMRC – Modified medical respiratory council dyspnoea score; TLC – Total lung capacity.

Table S4. Metric properties of patient-reported outcome measures to assess functional performance.

		Asthma	Bronchiectasis	Cystic Fibrosis	ILD	PAH	LT	NS-CRD
SF-36 (PFd or PCS)	Validity	Symptoms score (r=0.50; p<0.001) (70)	6MWD (r=-0.709; p>0.001) (72)		BDI (r=-0.73; p<0.05) 6MWD (r=0.69; p<0.05) mMRC (-0.61<r<-0.48; p<0.0001) D_{LCO} %predicted (r=0.47; p<0.05) TLC %predicted (r=0.61; p<0.05) FEV_1 %predicted (r=0.50; p<0.05) VC %predicted (r=0.54; p<0.05) FVC %predicted (0.35; p<0.05) NYHA (-0.41<r<-0.33; p<0.0001) HAQ-DI (r=-0.50; p>0.001) (67, 68)			
	Reliability				No difference in test-retest (p<0.05) (68)			
	Interpretability				MID: 4 points in PCS (68)	MID: 13 points in PFd and 5 points in PCS (69)		
SGRQ (activities)	Validity		6MWD (r=-0.76; p=0.000) (72)		SGRQ-I 6MWD (r=-0.66; p<0.0001) BDI %predicted (r=0.75; p<0.05) FEV_1 %predicted (r=0.57; p<005)			

	Reliability				TLC %predicted (r=0.65; p<0.05) VC %predicted (r=0.54; p<0.05) SF36 – PF (r=-0.71; p<0.05) SF36 – PCS (r=-0.32; p>0.05) (47, 67, 81) Intra-rater [ICC:0.93(0.85-0.97)] Inter-rater [ICC: 0.88(0.77-0.94)] (81)	
	Interpretability					
WHOfc	Validity					
	Reliability					
	Interpretability					
NYHAfc	Validity					
	Reliability					
	Interpretability					
AQLQ (activities)	Validity	Asthma Control (r=0.57; p<0.05) Health Survey (Physical; r=0.51; p<0.05) (95)				
	Reliability	Test-retest (ICC:0.93) (95)				
	Interpretability	MID: 0.51 points (96)				

CFQoL	Validity Reliability Interpretability			SF36-PF (r=0.73; p<0.001) (108) Intra-rater (r=0.93; p<0.05) (108)		
Promis-29 (PFd)	Validity Reliability Interpretability				SF-36 – PCS (r=0.52; p<0.001) SF-36 – PF (r=0.89; p<0.05) HAQ-DI (r=0.52; p<0.001) (71, 109) Intra-rater [0.65<ICC<0.71) (71, 109)	
SF-12 (PFd or PCS)	Validity Reliability Interpretability					
LWAQ (PHC)	Validity Reliability Interpretability	PCS SF-36 (r=0.41; ł) Symptoms score (r=0.50; p<0.001) (70)				

M-AQLQ (AL)	Validity Reliability Interpretability					
CAMPHOR (AL)	Validity Reliability Interpretability				MID: -4 points (112)	
QoL-EPM (PL)	Validity Reliability Interpretability	SF-36 domains (-0.34<r<0.46; p>0.05) (113) Test-retest (ICC:0.87) (113)				
MLHFQ (PSS)	Validity Reliability Interpretability				6MWT and NYHA (0.4<r<0.59;ł) (116) Test-retest (r=0.93; p<0.001) (116)	
QoL-B (PFd)	Validity		SGRQ (activities) (r=-0.70; p<0.01)			

	Reliability Interpretability		mMRC (r=-0.57; p>0.05) ISWT (r=0.59; p>0;05) (118) Intra-rater [ICC:0.91 (0.86-0.93) (118)			
London ADL (PAS)	Validity Reliability Interpretability					
FPI	Validity Reliability Interpretability					
MDHAQ (PF)	Validity Reliability Interpretability				FVC% (r^2=0.15; p=0.3) (80)	
SOLQ (PFS)	Validity Reliability		PCS of SF-36 (r=0.53; p<0.001) (124) Test-retest (ICC:0.83; α=0.72) (124)			

	Interpretability

Captions: Interpretability refers to minimal important difference (MID); ILD – Interstitial lung disease, PAH – Pulmonary arterial hypertension, LT – patients with chronic respiratory disease waiting/submitted to lung transplantation, NS-CRD – Non-specified chronic respiratory diseases, MID – Minimal important difference, SF-36 – Medical Outcomes Study 36-item Short Form of Health Survey, SGRQ – Saint´s George Respiratory Questionnaire, WHOfc – World Health Organization functional class, NYHA – New York heart association, AQLQ – Asthma Quality of Life Questionnaire, CFQoL – Cystic fibrosis quality of life, SF-12 – Medical Outcomes Study 12-item Short Form of Health Survey, Promis-29 – Patient-Reported Outcomes Measurement Information System, LWAQ – Living with Asthma Questionnaire, M-AQLQ – Mini Asthma Quality of Life Questionnaire, CAMPHOR – Cambridge pulmonary hypertension outcome review, QoL-EPM – Asthma Quality of Life from Escola Paulista de Medicina, MLHFQ – Minessota living with heart failure questionnaire, QoL-B – Quality of Life in Bronchiectasis, London ADL – London Activities of Daily Living, , FPI – Functional performance inventory, MDHAQ – Multi dimensional health assessment questionnaire, SOLQ – Seattle Obstructive Lung Questionnaire, 6MWD – 6 minute walk distance, mMRC – modified Medical Respiratory Council dyspnoea score, D_{LCO} – Diffusion capacity of carbon monoxide, FEV1 – Forced expiratory volume in 1 s, FVC – Forced vital capacity, BDI – Baseline dyspnoea index, TLC – Total lung capacity, VC – Vital capacity, PF – Physical functioning, HAQ-DI – Scleroderma Health Assessment Questionnaire Disability Index, PFd – Physical functioning domain, PCS – Physical component score, AL – Activity limitation, PHC – Physical health construct, PL – Physical limitation, PFS – Physical functional score; PSS – Physical sub score, PAS – physical activity score; ISWT – Incremental shuttle walk test; ł: p value not described.

Table S5. Description of functional performance tests based on protocols used in included studies.

Measure	Outcome	Better result of FP	Equipment	Description
1min-STS	Number of repetitions.	Higher number of repetitions	Standard chair (i.e. with no armrest, 40-48cm height, ideally with 90º hip and knee flexion) against a wall.	Patients seated with crossed arms is instructed to get up from the chair and sit down many times as possible in one-minute.
30sec-STS				Patients seated with crossed arms is instructed to get up from the chair and sit down many times as possible in 30 seconds.
3min-STS				Patients seated with crossed arms is instructed to get up from the chair and sit down many times as possible in 3 minutes.
5rep-STS	Time (seconds)	Shorter time spent		Patients seated with crossed arms is instructed to get up from the chair and sit down five times as quickly as possible and the duration taken to complete the 5 repetitions is timed.
4MGS	Velocity (m/s) of time (seconds).	Higher velocity or shorter time spent	Corridor (i.e. 4m or 8m)	The patient is instructed to walk, and the time spent to walk the four-metre is timed. The test can be performed in usual pace or as fast as possible.

SPPB	Score	Higher score	Chair and 4m corridor	Three aspects are evaluated and summarized in the total score: balance, gait-speed and strength. To assess balance the patient is instructed to stay at least 10s in three positions (romberg, semi-tandem and tandem). Gait-speed is assessed by the time to walk four-metre and strength is assessed by the time to sit to stand five times as fast as possible.
TUG	Time (seconds)	Shorter time spent	Chair and 3m corridor	The patient is instructed to rise from a chair, walks 3 meters, turns, walks back, and sits down again. The protocol can be performed, in usual pace and as fast as possible without run.
8-FUGT	Time (seconds)	Shorter time spent	Chair and 2.40m corridor	The patient got up from the chair, walked around a cone that was placed 8 feet (2.40 m) from the chair, and returned to a seated position on the chair as fast as possible.
BBS	Score	Higher score	2 Chairs, measurement tape and step	Consists of 14 tasks including sitting to standing, standing unsupported, and picking up object from the floor from a standing position

Glittre ADL	Time (minutes)	Shorter time reflects better functional performance	Three objects of 1 kg and backpack with weight (2.5Kg for women and 5Kg for men)	Consists of a 10-meter circuit in which the individual starts from a sitting position, walks, goes up and down two interposed steps and walks again until reaching a shelf, individually adjusted according to the height of the shoulder and waist. The patients were instructed to complete five laps in the shortest time, using a backpack.
FRT	Distance (cm)	Higher distance	Measurement tape	Patient is asked to achieve the maximum distance able to reach forward from an initial upright posture to maximal leaning posture is recorded, without moving feet.
CS-PFP	Score	Higher score	Furniture developed to simulate ADL (e.g. Laundry, washer, sandbag...)	The CS-PFP test is a series of 10 tasks covering everyday life activities required to maintain independence. Subjects are asked to complete the tasks at maximal effort.
15-steps climbing	Time (seconds)	Shorter time spent	Step (25 cm length; 50 cm width; 20 cm)	Patients were asked to climb up and down the step 15 times as fast as they could, without any fixed pacing.

Captions: FP: Functional performance; 1min-STS – 1minute sit-to-stand, 4MGS – four-metre gait speed, 30sec-STS – 30 seconds sit-to-stand, 5rep-STS – 5 repetitions sit-to-stand, SPPB – short physical performance battery, TUG – timed-up-and-go, 8-FUGT – 8-foot-up-and-go, BBS – berg balance scale, Glittre ADL – Glittre Activities of daily living, FRT– function reach test, CS-PFP – continuous scale physical function performance test, 3min-STS – 3-minute sit-to-stand, 15-steps climbing.

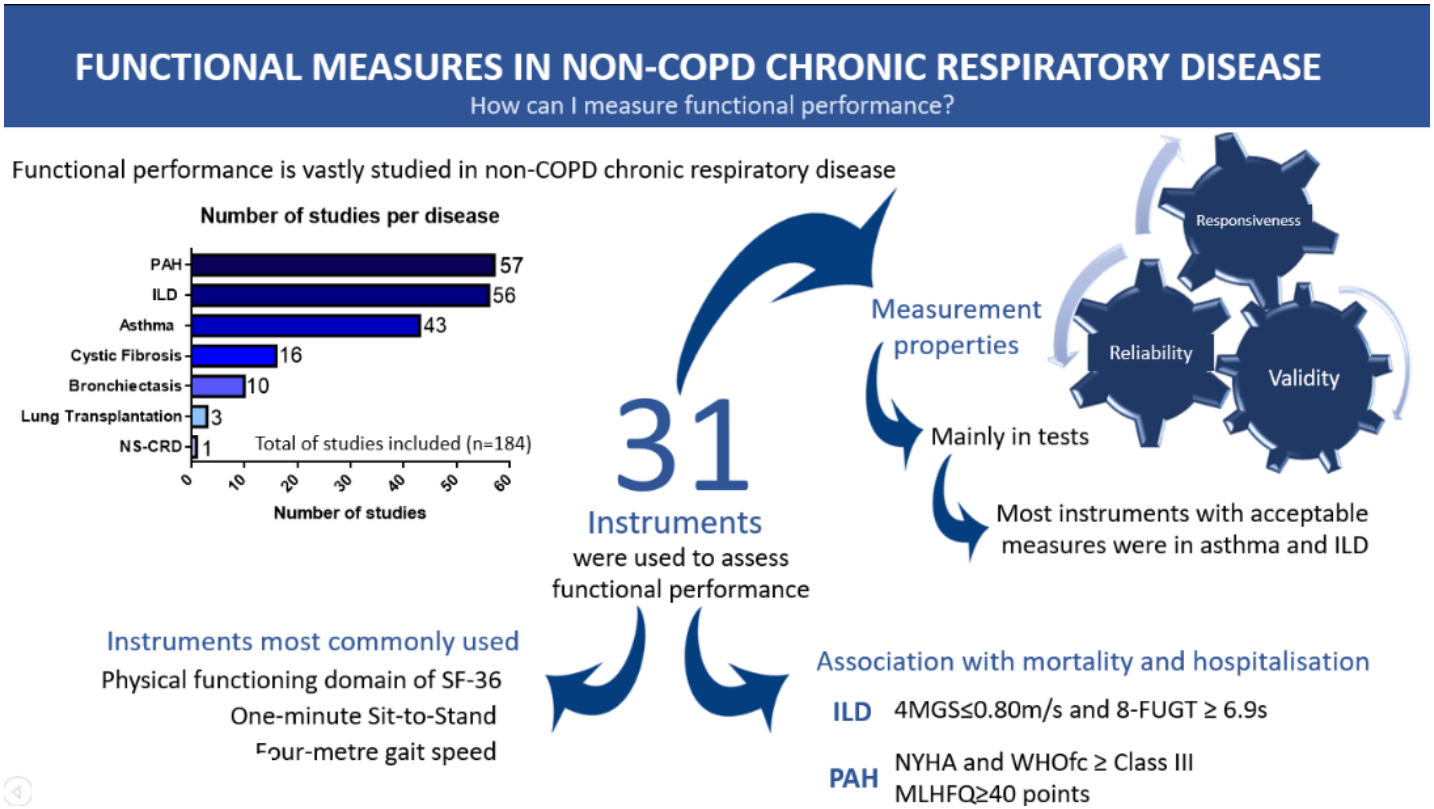

Figure S1. Infographic: Functional measures in non-COPD chronic respiratory disease.

Functional performance tests in interstitial lung disease: Impairment and measurement properties.

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Functional performance tests in interstitial lung disease: Impairment and measurement properties.

Running title: functional performance in ILD.

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Abbreviations list

1min-STS: Sit-to-stand test in one-minute

4MGS: Four-metre gait speed

5rep-STS: Five repetition sit-to-stand test

6MWT: Six-minute walk test

30sec-STS: Sit-to-stand test in thirty seconds

BMI: Body-mass index

CI: Confidence interval

COPD: Chronic obstructive pulmonary disease

D_{LCO}: Diffusion capacity of the lung for carbon monoxide

FEV_1: Forced expiratory volume in the first second

FVC: Forced vital capacity

HG: Handgrip force

ICC: Intraclass correlation coefficient

ILD: Interstitial lung disease

IPF: Idiopathic pulmonary fibrosis

MDC: Minimal detectable change

MVICq: Maximal voluntary isometric contraction of quadriceps

Rep: Repetition

Sec: Seconds

SEM: Standard error of measurement

SPPB: Short Physical Performance Battery

QS: Quadriceps strength

TUGu: Timed up and go in usual pace

TUGf: Timed up and go in fast pace

Abstract

Background: There is limited information regarding impairment in functional performance tests and their measurement properties in ILD. The present study aimed to verify the impairment and measurement properties of functional performance tests in ILD. **Methods:** ILD and healthy individuals underwent assessments of pulmonary function, peripheral muscle strength (handgrip force and maximum isometric contraction of quadriceps femoris – MIVCq) and exercise capacity (6-minute walk test – 6MWT). Functional performance was assessed by timed up and go with usual (TUGu) and fast (TUGf) gait speeds, four-metre gait speed (4MGS), sit-to-stand in 30 seconds (30sec-STS), one minute (1min-STS) and with 5 repetition (5rep-STS) and Short Physical Performance Battery (SPPB). Functional performance was compared between groups, validity (correlation with 6MWT and MIVCq) and reliability of tests were checked in subjects with ILD (intra- and inter-rater agreement analysis). **Results:** Seventy-six participants (40 ILD [25 women, 61±11 years, FVC 75±17 %pred] and 36 healthy [22 women, 61±9 years, FVC 97±11 %pred]) were included. Functional performance in ILD was worse than in healthy individuals in all tests, except for the 30sec-STS ($p=0.13$). Pre-specified validity criteria were reached for TUGu, TUGf, 4MGS and 5rep-STS ($-0.69<r<0.55$; $p<0.05$ for all). Except for 4MGS and SPPB, all tests showed good to excellent inter-rater ($0.85<ICC<0.93$; $p<0.05$ for all) and all tests showed good to excellent intra-rater ($0.83<ICC< 0.94$; $p<0.05$ for all) reliability. **Conclusions:** Subjects with ILD present worse functional performance than healthy individuals. According to reliability and validity results, TUGu, TUGf and 5rep-STS seem to be the most appropriate tests to evaluate functional performance in ILD.

Key words: Physical functional performance; Lung diseases; Reproducibility of results.

Introduction

Interstitial lung diseases (ILD) represent a heterogeneous group of pathologies [1], which share a typical pattern of clinical and functional abnormalities of pulmonary manifestations [2]. Also, subjects with ILD frequently present extrapulmonary manifestations, such as muscle dysfunction, lower exercise capacity and reduced quality of life [3]. As extrapulmonary manifestations may influence negatively the activities of daily living, there is growing interest in tools that assess specifically functional performance and not only exercise capacity [4,5].

Functional performance tests are used in the clinical setting and usually include movements related to subjects' autonomy (i.e. walking and moving, changing body position and balance) [6]. Functional performance tests, are widely used in other respiratory diseases such as Chronic Obstructive Pulmonary Disease (COPD) [4] as they are more practical in terms of required space, time and ease of application in the clinical practice [7]. The functional limitations observed in COPD span from impaired muscle function [8] to reduced activities of daily living, and exercise tolerance [9] and independence [10]. Despite the paucity of studies investigating functionality in ILD, there is some evidence of the reductions in gait speed [11] and lower limbs strength [12] in this group of patients compared to healthy subjects.

Different functional performance tests have been investigated in studies including subjects with ILD. The timed up and go (TUG) [12], the sit-to-stand test (in 30 seconds [13], one minute [14] and five repetitions [15]), the four-metre gait speed (4MGS) [11] and the short physical performance battery (SPPB) [12] are among them. Each functional performance test measures different aspects of functionality [6]. The TUG requires a series of movements performed daily,

reflects mobility and dynamic balance [16,17]. The 4MGS also evaluates mobility and has relation with mortality in patients with idiopathic pulmonary fibrosis (IPF) [5]. The sit-to-stand test indirectly aims to assess lower limb strength [14,18], and SPPB reflects mobility, indirect lower limb strength and static balance, in addition to its association with falls [17].

Albeit functional tests are widely investigated in respiratory diseases [4,19,20], there are particularities of ILD that may result in different outcomes in functional tests. For instance, patients with idiopathic pulmonary fibrosis have a faster disease progression an present an uneven distribution of the loss of muscle function [3]. Additionally, patients with connective tissue disease-related ILD experience joint problems impairing activities of daily living [21]. Since functional performance tests reflect specific characteristics of the investigated disease, It is necessary to investigate whether these tests present adequate measurement properties also in ILD [22]. As functionality is multidimensional [23], patients with ILD may need to be assessed by more than one functional test. The aims of this study were: 1) to investigate impairment in widely used functional performance tests in subjects with ILD in comparison to a healthy control group; and 2) to investigate the reliability and validity of these tests in ILD patients.

Methods

Study design and ethical aspects

This is a cross-sectional study investigating measurement properties (i.e. reliability, validity and minimum detectable change) of different functional performance tests in patients with ILD and their impairment in comparison to healthy control group. This study is part of a larger ongoing trial (BELIEVE-ILD)

which was approved by the institutional ethics committee (#2.484.871), and all participants provided informed consent form for participation in the study.

During an initial visit, all participants received information about the study procedures and answered a general questionnaire for sample characterisation. Participants performed thrice, in a random sequence, a battery of tests comprising seven functional tests: timed up and go at usual pace (TUGu) and at fast pace (TUGf), four-metre gait speed test (4MGS), sit-to-stand test using three protocols: 30 seconds (30SEC-STS), one minute (STS1) and five-repetition (5rep-STS) and Short Physical Performance Balance (SPPB). Importantly, the sequence of the performance of the tests randomised in the first visit was kept for all three batteries. Tests were performed on two separate visits with an interval of seven days apart. Two batteries of tests were applied with the same assessor (intra-rater) and one with a different assessor (inter-rater). To avoid fatigue, in both visits all tests were performed before any other clinical assessment, and individuals rested between the executions.

Sample characteristics

Subjects with ILD were recruited to partake in the present study from the outpatient clinic of the University Hospital of the Londrina State University, Brazil whilst healthy individuals were invited to participate using local and social media. Participants were included if they were between 40 and 75 years old and had no clinical conditions (other than ILD) that could interfere with the study assessments. Additionally, ILD patients needed to present diagnosis of ILD according to internationally accepted guidelines [24–26], a stable clinical condition (i.e. absence of exacerbations) for at least 1 month prior to their inclusion. Participants would be excluded if presented an acute exacerbation during the study, or presented incapacitating comorbidities (not unveiled upon

inclusion), or presented other respiratory conditions (i.e. COPD) only observed in pulmonary function test after inclusion, or withdrew consent to the study participation.

Functional tests

Timed up and go: The timed up and go test is a test of general mobility. Subjects are requested to stand up from a chair, walk a distance of 3 m, turn and walk back to the chair to sit down again [16]. This is a quick and straightforward test used in different clinical settings which incorporates a series of tasks necessary for independent living [27]. The TUG was performed using two protocols: participants performed it at usual walking pace (TUGu), and as fast possible without running (TUGf) [12,28]. Faster walking speeds are indicative of better mobility [17]. Thus, the fastest executed speed of two attempts was used for the analysis in both protocols.

Four-metre gait speed: The 4MGS measures usual gait speed and is used to stratify the risk of disability and falls, in addition to cardiovascular and all-cause mortality [29]. To perform the four-metre gait speed, participants were required to walk in a usual gait speed measured over 4 m (4MGS). The protocol took place using an 8-m course (i.e. a 2-m acceleration zone, a 4-m timing area, a 2-m deceleration zone) [30]. Faster gait speeds reflect better mobility; thus, the fastest speed of two attempts was used in the analysis.

Sit-to-stand: The STS is used to evaluate exercise tolerance and independence in elderly people [31]. Participants performed three different protocols of the STS: STS during 30 seconds (30sec-STS), during one minute (1min-STS) and the five repetition STS (5rep-STS). In both 30sec-STS and 1min-

STS participants were requested to perform the highest number of sit-to-stand movements during 30 seconds and 1 minute, respectively. In the 5rep-STS the time necessary to perform 5 movements was recorded [32–34]. In both visits, each participant performed the three protocols twice and the best result of each protocol was used for the analysis [15]. Heart rate, peripheral oxygen saturation and subjective sensation of dyspnoea and exertion (using the Borg scale) were monitored during the three protocols [35]. Participants would be allowed to continue the set of tests only if resting values of heart rate, dyspnoea and oxygen saturation were re-established. Resting time between sets were not restricted and participants were allowed to rest longer if desidered.

Short Physical Performance Balance: The Short Physical Performance Battery (SPPB) is commonly used as a standard measure of physical performance both for research and in clinical practice. The test is a composite of 3 balance tests (romberg, tandem and semi-tandem), a gait speed test and 5rep-STS. To perform balance tests, subjects were asked to remain 10 seconds in each position. Each component yields scores varying from 0 to 4 and add up to scores ranging from 0 to 12 where higher scores indicate better performance [6,17].

Other assessments

In another visit, all participants performed testing to assess their clinical condition. Lung function (whole-body plethysmography and diffusion capacity for carbon monoxide (D_{LCO}), (Vmax, CareFusion©) was evaluated following internationally accepted guidelines and were compared to normative data for the Brazilian population [36–40]. Exercise capacity was assessed by the 6-minute walk test (6MWT) following international guidelines for field tests [41,42]. The test

was performed twice, and the highest achieved walking distance was used for analysis. Quadriceps force was assessed by the maximal voluntary isometric contraction (MVICq) of the dominant limb using a strain gauge (EMG System®, Brazil) attached to a stationary multigym device. Participants were instructed to perform the MVICq for six seconds, with 90º flexion of hip and knee [43]. At least four and at most 15 attempst were performed and the higher result was used for the analysis [43]. Finally, handgrip force of the dominant member was evaluated with a handheld dynamometer (SH1001, Saehan Corporation. Korea), three trials with the elbow flexed at 90°, with the arm unsupported [44]. The higher result was used for the analysis.

Statistical Analysis

Data is described as mean and standard deviation or median and interquartile range according to its distribution. Normality was checked using the Shapiro-Wilk test. Performance on the tests was compared between ILD group and the control group using unpaired t test or Mann-Whitney test. Categorical data were compared using chi-squared test. Intra- and inter-rater agreement was performed to verify reliability of tests using the intra-class correlation (ICC) coefficient. Reliability was classified as poor (ICC<0.5), moderate (0.5≤ICC<0.75), good (0.75≤ICC<0.9) or excellent (ICC≥0.9) [45]. Statistical analyses were performed using software SAS Studio 9.4 and Graph Pad Prism 8.0.

Absolute reliability of the data was determined using the standard error of measurement (SEM). The lower the SEM value, the more reliable the measurement [45]. The minimum detectable change (MDC) was calculated using the equation $MDC = z - score \times SD \times \sqrt{2}(1 - r)$ [46]. The learning effect of

each functional test was calculated using the equation: $LE = test1 - test2$; where test1 is the best result of the first visit and test2 is the best result of the second visit. LE was also expressed as percentage and was calculated using the following equation: $LE\% = [(test1 - test2)]/test1) \times 100$ [47]. To investigate validity, the performance on TUGu, TUGf and 4MGS were correlated with 6MWT [15,48,49], performance in three protocols of sit-to-stand test and SPPB were correlated with quadriceps strength [12,14,15]. A test was deemed valid if presenting a correlation of r>0.50 with 6MWT or quadriceps strength (as specifically described above) using the Pearson correlation coefficient. Significance was set as $p<0.05$.

Results

Eighty-two participants were screened for inclusion. A total of seventy-six (ILD group=40 and control group=36) were included in the final analysis of the study (**Figure 1**). ILD group was composed of patients with idiopathic interstitial pneumonia, ILD associated with connective tissue disease, sarcoidosis and asbestosis.

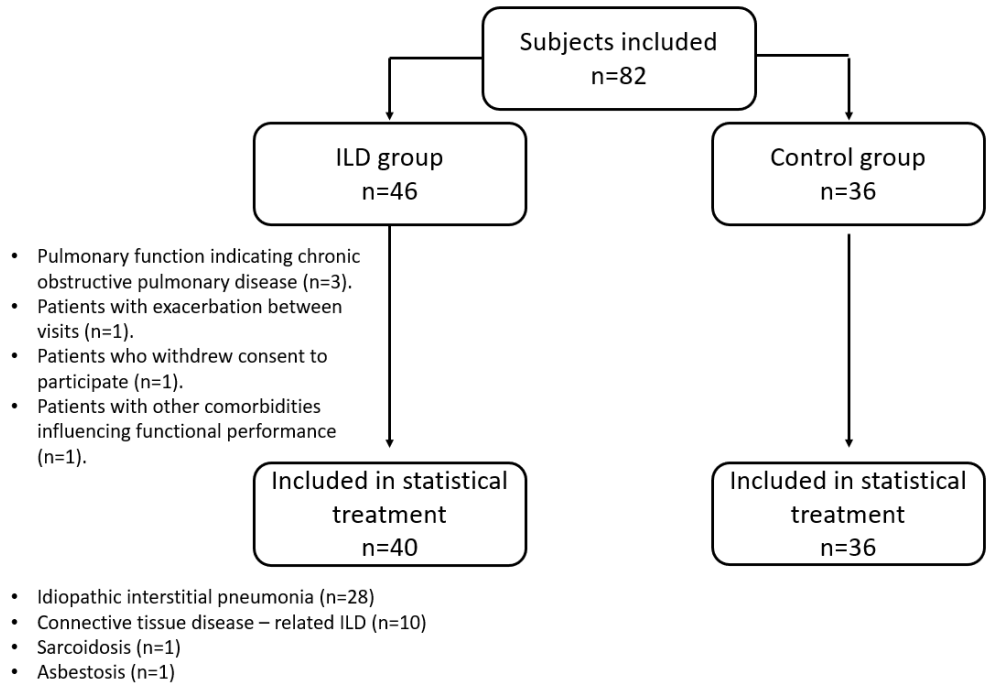


Figure 1 – Flow chart of recruitment and inclusion of the subjects in the study.

Characteristics of all participants are described in **Table 1**. Healthy individuals and subjects with ILD were similar for age, sex and body mass index (BMI). Subjects with ILD presented worse lung function, exercise capacity, quadriceps muscle strength and handgrip force. Except for the 30sec-STS, patients with ILD presented worse performance in all other functional tests. Oxygen desaturation was only mild and did not differ between groups ($p>0,05$ for all). Differences in oxygen saturation between before and after each test were of Δ1±3% in the 30sec-STS, Δ3±4% in the 1min-STS, and Δ0±1% in the 5rep-STS.

Table 1. Participant's characteristics and comparation of functional performance in ILD patients and control group.

	ILD group (n=40)	**Control group (n=36)**	p
Sex (% of women)	25 (62%)	22 (61%)	0.71
Age (years)	60.8±11.0	61.2±8.9	0.48
BMI (kg/m^2)	27.9 [25.5 – 30.3]	26.7 [24.5 – 29.9]	0.18
FVC (% of predicted)	74.7 ± 17.2	97.5±11.4	<0.0001
FEV_1 (% of predicted)	75.7 ± 18.3	99.6±13.2	<0.001
FVC/FEV_1 ratio	83.4 [77.1 – 87.3]	82.0 [76.2 – 84.5]	0.71
D_{LCO} (% of predicted)	50.7±18.1	79.2±12.8	<0.0001
6MWT (metres)	468.3±93.1	567.9±71.0	<0.0001
6MWT (% of predicted)	88.0±15.1	106.3±11.5	<0.0001
Quadriceps Strength (N)	296.9 [243.5 – 416.7]	423.6 [363.6 – 516.0]	0.0009
Handgrip Force (Kgf)	23.0 [19.0 – 33.0]	27.0 [25.0 – 36.0]	0.012
TUGu (seconds)	9.8±1.5	8.7±1.2	0.0009
TUGf (seconds)	7.7 ±1.2	6.7 ±0.91	0.0001
4MGS (m/s)	1.08 ± 0.15	1.32 ± 0.14	<0.001
30sec-STS (repetitions)	14.0 [11.0 – 17.0]	13.0 [12.0 – 19.0]	0.13
1min-STS (repetitions)	24.0 [21.0 – 31.0]	28.5 [25.0 – 36.0]	0.0018
5rep-STS (seconds)	11.4 ± 2.6	9.3 ± 2.25	0.0072
SPPB (total score)	11 [11.0 – 12.0]	12 [11.0 – 12.0]	0.006

Captions: FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second; D_{LCO}: diffusion capacity of the lungs for carbon monoxide; TUGu: timed up and go in usual pace; TUGf: timed up and go in fast pace; 4MGS: four-metre gait speed; 30sec-STS: sit-to-stand in 30 seconds; STS1: sit-to-stand in one-minute; 5rep-STS: five repetitions of sit-to-stand; SPPB: short physical performance battery.

Table 2. Intraclass correlation coefficient of functional tests in ILD group.

Tests	Intra-rater		Inter-rater	
	ICC	CI95%	ICC	CI95%
TUGu	0.88	[0.79 – 0.93]	0.89	[0.81 – 0.94]
TUGf	0.94	[0.89 – 0.96]	0.93	[0.87 – 0.96]
4MGS	0.92	[0.73 – 0.91]	0.56	[0.32 – 0.74]
30sec-STS	0.90	[0.89 –0.95]	0.85	[0.73 – 0.91]
1min-STS	0.88	[0.82 – 0.94]	0.91	[0.85 – 0.95]
5rep-STS	0.85	[0.80 – 0.93]	0.90	[0.82 – 0.94]
SPPB	0.83	[0.71 – 0.91]	0.75	[0.59 – 0.86]

Captions: ICC: intraclass correlation coefficient; CI95%: confidence interval 95%; SEM: Standard error of measure; MDC: Minimal detectable change; TUGu: timed up and go in usual pace; TUGf: timed up and go in fast pace; 30sec-STS: sit-to-stand in 30 seconds; STS1: sit-to-stand in one-minute; 5rep-STS: five repetitions of sit-to-stand; 4MGS: four-metre gait speed; SPPB: short physical performance battery.

Table 2 shows the intra- and inter-reliability of functional performance tests for subjects with ILD. All functional tests demonstrated good to excellent intra-rater and inter-rater reliability except for 4MGS and SPPB in inter-rater analysis.

Values of SEM, MDC, and learning effect are provided in **Table 3.** All tests showed low values of SEM and learning effect.

Table 3. Standard error of measurement (SEM), minimal detectable change (MDC), and learning effect of functional tests in patients with ILD.

Tests	Intra-rater			Inter-rater			Learning effect	
	SEM	SEM%	MDC	SEM	SEM%	MDC	unit	%
TUGu	0.51	5.3	1.44	0.49	5.07	1.37	1.80±0.24	2.14±4.75
TUGf	0.29	3.78	0.80	0.31	4.08	0.87	0.78±0.05	0.66±4.62
4MGS	0.04	3.92	0.11	0.05	5.37	0.16	-0.02±0.11	2.84±12.55
30sec-STS	1.82	9.31	3.71	1.72	8.83	3.52	-0.79±2.25	6.58±16.99
1min-STS	3.31	9.75	7.02	3.02	8.90	6.41	-0.85±4.28	4.39±14.41
5rep-STS	0.87	8.84	2.79	1.49	15.14	4.78	0.36±1.62	2.45±14.55
SPPB	0.42	3.79	1.16	0.51	4.60	1.41	-0.07±0.70	0.94±7.29

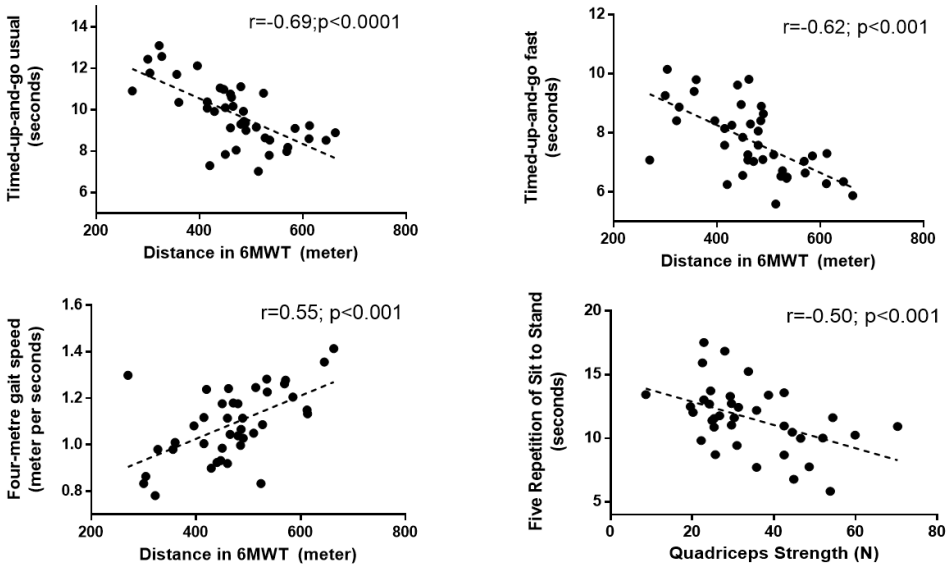
Captions: SEM: Standard error of measure; MDC: Minimal detectable change; TUGu: timed up and go in usual pace; TUGf: timed up and go in fast pace; 30sec-STS: sit-to-stand in 30 seconds; STS1: sit-to-stand in one-minute; 5rep-STS: five repetitions of sit-to-stand; 4MGS: four-metre gait speed; SPPB: short physical performance battery.

Validity criteria was reached for TUGu, TUGf, 4MGS and 5rep-STS tests. The full description of correlations is provided in **Table 4**. **Figure 2** demonstrates moderate correlation of TUGu, TUGf and 4MGS with 6MWT and 5rep-STS with quadriceps strength ($-0.69 < r < 0.55$; $p < 0.05$ for all).

Table 4. Functional tests correlation with exercise capacity and muscle strength.

Tests	**6MWT**(m)	**Handgrip force** (Kgf)	**Quadriceps strength** (N)
TUGu (seconds)	-0.69 *	-0.56*	-0.48*
TUGf (seconds)	-0.62*	-0.60*	-0.49*
4MGS (m/s)	0.55*	0.37*	0.28
30sec-STS (repetitions)	0.28	0.41*	0.41*
1min-STS (repetitions)	0.33*	0.35*	0.34*
5rep-STS (seconds)	-0.26	-0.38*	-0.50*
SPPB (total score)	0.35*	0.22	0.19

Captions: TUGu: timed up and go in usual pace; TUGf: Timed up and go in fast pace; 4MGS: four-metre gait speed; 30sec-STS: sit-to-stand in 30 seconds; STS1: sit-to-stand in one-minute; 5rep-STS: five repetitions of sit-to-stand; SPPB: short physical performance battery; * p<0.05.



Captions: N: Newton; 6MWT: 6-minute walk test.

Figure 2 - Validity of functional performance tests with 6MWT and quadriceps strength.

Discussion

Subjects with ILD presented worse functional performance compared to healthy individuals in TUGu, TUGf, 4MGS and 1min-STS. Validity in ILD subjects was stablished for TUGu, TUGf, 4MGS and 5rep-STS. All tests showed good-to-excellent reliability in both intra- and inter-rater analysis, except for SPPB and 4MGS inter-rater analysis which presented moderate reliability. Albeit these functional performance tests are found in different studies with ILD patients, few of them assessed their measurement properties. This was the first study to assess different aspects of measurement properties (i.e. validity, reliability and minimum detectable change) and the comparison with a control group of TUGu, TUGf, 30sec-STS, 1min-STS, 5rep-STS and SPPB in subjects with ILD.

Functional performance

Subjects with ILD have worse performance compared to control group in six out of seven functional tests. Five studies [5,11,15,48,50] investigated performance in the 4MGS, three of them only in idiopathic pulmonary fibrosis. Bloem *et al*. [15] used the protocol of fast pacing which is different than the protocol used in the present study. The range of performance in usual pace across the different studies was from 0.91 to 1.33m/s [5,11,48,50]. The performance of the 4MGS in the ILD group (1.08m/s) was within this range but close to the lower limit observed in patients with IPF. To the best of authors

knowledge, this is the first study comparing performance of the 4MGS between subjects with ILD and a control group. In the past, Guler *et al*. [50] investigated the performance of the test comparing genders but found no differences (p=0.16). The average difference of gait speed to roughly 1km/h (i.e. Δ -0.24m/s) slower in ILD in the present study is in line with the reduction found in the average speed during the 6MWT (i.e. Δ -0.27m/s).

Subjects with ILD had slower gait speeds than matched subjects in our cohort. Only one study observed functional performance using the TUGu in ILD [12]. In line with our results, Mendes and colleagues found reduction [12] on the average speed of the test in comparison to a healthy control group (p=0.023). Interestingly, the later only included advanced ILD and yet the average duration for the test was 9.6s compared to 9.4s in the present cohort (which included a somewhat large range of lung impairment). Our results suggest that even in earlier stages of the disease, subjects with ILD seem to have reductions on TUGu performance.

Six studies [13–15,33,34,51] used different protocols of the sit-to-stand test in ILD, but only one[33] compared the performance with a control group. The present study did not demonstrate differences in the the 30sec-STS between the two groups. This, however, is not an isolated finding as Vainshelboim *et al.* [33] also could not identify differences in the performance of the test between IPF and control subjects. On the contrary, we oberved a marked difference in the performance of the 1min-STS between the two groups. Subjects in our control group roughly doubled the number of repetitions when comparing the 30sec-STS to the 1min-STS (i.e.115% increase in the number of repetitions), which did not occur in subjects with ILD (i.e. 71% increase in the number of repetitions). One could hypothesize that physiological limitations causing reduction in physical

function in these patients will need more than 30 seconds of relatively high intensity to be elucidated. It is, therefore, unlikely that the 30sec-STS provides good discriminative capacity to identify reduction in functional performance of subjects with ILD. We could find only one study [15] investigating the 5rep-STS in ILD (specifically IPF), with an average of 12±4s, in line with our findings (i.e.11±2s).

Validity

The two protocols of the TUG, the 4MGS, and the 5rep-STS were deemed valid for subjects with ILD. There were moderate correlations between TUG (TUG and TUGf) with 6MWT (r=-0.69 and r=-0.62, respectively; $p<0.05$ for both). One study [12] previously showed weak correlations between TUG and 6MWT in ILD. Of note, this was an exploratory finding of a trial investigating muscle atrophy in ILD and did not aim to validate the TUG [12]. Previous investigations from the Netherlands, the United Kingdom and Japan already validated the 4MGS in ILD [11,15,48]. Our findings corroborate to those showing the 4MGS to be valid in ILD, reinforcing that the test relates to clinically relevant outcomes regardless of the population studied so far.

In the present study there were moderate correlations between the 30sec-STS, 5rep-STS and quadriceps strength. Only the 5rep-STS, however, reached the minimum criteria to be considered valid in subjects with ILD. Importantly, a previous investigation already tried to check validity of the 5rep-STS in IPF and could not find a strong association between the test and the 6MWT [15]. Wallaert *et al*. reported a moderate correlation between the 1min-STS and quadriceps muscle strength in ILD [14].

Reliability

All tests showed good to excellent reliability in both intra- and inter-rater analysis (except for the inter-rater analysis of the 4MGS and the SPPB which presented moderate reliability). Previously, two studies showed excellent intra- and inter-rater reliability for the 4MGS [11,15]. Excellent intra-rater reliability in performance was found in 1min-STS [51] and 5rep-STS [15], similarly to our findings. These results, however, were the only available evidence investigating reliability of functional tests in ILD. Our findings suggest that the TUG (both TUGu and TUGf), all three STS protocols (30sec-STS, 1min-STS and 5rep-STS) and the SPPB are highly reliable to be applied in subjects with ILD.

Additionally, we observed low values of SEM and somewhat small learning effects across all investigated tests. This is in line with the intra- and inter-rater reliabity reinforcing that the tests are consistent in ILD. Although all tests presented low values of learning effect, the values of TUGu and TUGf are higher than the value of SEM, therefore it is recommended to perform TUGu and TUGf twice. Furthermore, MDC of the tests are within the range of values of the same tests observed in different respiratory populations [7,49,52,53]. In spite of that, it is unclear whether the values of MDC reported in the present manuscript match patients' minimal important difference (MID) of the tests. Future studies, therefore, are necessary to verify whether the MDC estimates resemble clinically relevant changes in patient's functional performance.

The results of the present study need to be interpreted under the light of some potential limitations. One could argue that the presence of different diagnosis is a limitation. Albeit it is known that subjects with different ILD do present differences in terms of functional capacity [54], this did not impact on the analysis of reliability and validity. Another limitation of this study was the order of the assessor. Assessor's randomisation was not possible due to the data

collection routine. However, other factors which could potentially influence the assessments of functional performance were thouroughly controlled (i.e. none of the tests were performed after any exercise or muscle testing).

Conclusions

Subjects with ILD present worse functional performance in six out of seven investigated functional performance tests compared to healthy individuals. Amongst the investigated tests, TUGu, TUGf and 5rep-STS seem to be the most appropriate tests to evaluate functional performance in ILD.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Timed up and go stratifies daily physical activity in patients with interstitial lung disease

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Title Page

Timed up and go stratifies daily physical activity in patients with interstitial lung disease

Running title: TUG to stratify daily PA in ILD

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Abstract

Objectives: To investigate the relationship between timed up-and-go (TUG) and daily physical activity (DPA) levels in patients with interstitial lung disease (ILD) and identify a cut-off point that adequately stratify inactive patients. **Methods:** Patients with ILD were recruited and performed the timed up and go (TUG) in both usual pace (TUGu) and fast pace (TUGf). Exercise capacity (6-minute walk test), pulmonary function (whole-body plethysmography) and DPA levels (activity monitor, Actigraph®, wGT3x-BT) were also assessed. DPA outcomes included time spent in activities of different intensities, body postures and daily steps. A Receiver Operating Characteristic (ROC) curve was done to stratify inactive patients according to their DPA levels using daily steps (i.e. 5000steps/day) and moderate to vigorous DPA, MVPA (i.e. 30min/day). **Results:** Fifty-four patients with ILD were included (26 women, 60±11 years). TUGu and TUGf correlated moderately with daily steps and intensity of activities (light and moderate) ($-0.60<r<-0.41$; $p<0.05$ for all). Opposed to results of TUGf, ROC curves identified the cut-offs of 9.25s and 7.9s in the TUGu as acceptable to stratify inactive patients using respectively the 5000 steps/day (AUC: 0.74; sensitivity 82%, specificity 63%) and the 30min/day MVPA (AUC: 0.84, sensitivity 90%, specificity 75%). Patients with worst performance in TUGu (i.e. ≥9.25s) present lower pheriperal muscle strength, exercise capacity and DPA ($p<0.05$). **Conclusion:** TUGu and TUGf correlate moderately with DPA in ILD. The performance on TUGu≥9.25s seems capable of stratifying inactive ILD patients.

Keywords: Physical functional performance; Interstitial lung diseases; Activities of daily living.

Introduction

Patients with Interstitial Lung Diseases (ILD) may course over time with a progressive reduction in lung function and physical performance, worsening of symptoms, and experience a deterioration in health-related quality of life (1). Furthermore, it is increasingly recognised that extrapulmonary manifestations are related to a worse prognosis in ILD (2, 3).

Amongst the extrapulmonary manifestations, reduced levels of daily physical activities (DPA) are a known feature in respiratory patients (4). Inactivity is also one of the critical factors of the vicious cycle of chronic respiratory diseases and is related with worse prognosis in patients with idiopathic pulmonary fibrosis (5). Also, functional performance is being increasingly assessed in chronic respiratory diseases as it reflects physical function (6, 7).

Functional performance tests are generally simpler and more practical to be performed (6). The timed up and go (TUG) test is a reliable test (8) used in different clinical settings incorporating a series of tasks necessary for independent living such as walking and sitting/standing movements, and changing directions (6, 9). Therefore, it is used to assess functional mobility, walking ability, dynamic balance and risk of falling in subjects with chronic respiratory diseases (10, 11), and even diseases severity, morbidity and mortality in different populations (12, 13).

Methods capable of accurately estimating DPA levels and quantifying the level of disability are becoming increasingly important in clinical practice (14, 15). Albeit physical function and DPA are associated in differing respiratory diseases and functional performance tests been described to predict DPA (16), the relationship between functional performance and DPA in ILD remains unknown.

Since patients with ILD share common clinical and functional characteristics of other respiratory diseases, we hypothesised that a functional performance test (i.e, the TUG) associates with clinical and functional outcomes in ILD. Furthermore, we hypothesised that the performance in the TUG can be used to stratify patients with ILD according to their DPA levels. Thus, the aim of the present study is to investigate the relationship between timed up-and-go (TUG) and DPA levels in patients with ILD and identify a cut-off point that adequately stratify inactive patients.

Methods

This is a cross-sectional study conducted in the outpatient clinics of the University Hospital of the State University of Londrina. The research was approved by the institutional review board (#2.484.871) and all participants provided a written informed consent form for participating in the study

Patients with a diagnosis of interstitial lung disease according to international guidelines (17) were included if they had a stable clinical condition (absence of respiratory exacerbations) for at least one month before the recruitment. Patients of both sexes with the age between 40 - 75 years that did not present any clinical condition that could interfere on the assessments were included. Participants would be excluded if showed incapacitating comorbidities (not unveiled upon inclusion), presented other respiratory diseases (i.e. COPD) observed in the pulmonary function test or withdrew consent to the study participation.

During the testing, all participants were informed about the research procedures and answered a general questionnaire for sample characterisation. Then, participants performed the TUG at a usual pace (TUGu) and at a fast pace

(TUGf) (18-20). In both tests, patients were requested to stand up from a chair, walk a distance of 3 m at a safe pace, turn and walk back to the chair to sit down again (8). The use of walking aids and oxygen was allowed (21). To guarantee no influence in the assessment, the performance on TUG for participants on oxygen therapy, a trained physical therapy was recruited to carry the device for delivering oxygen (21, 22). The time in seconds to complete the test was recorded and used as the primary outcome of the analysis. The timing started when the participant got up from the chair and ended when the participant touched the chair when sitting after the walk (20). Faster walking speeds are indicative of better mobility. Thus, the fastest executed speed of two attempts was used for the analysis in both protocols (23). Participants were allowed to rest between the trials, if necessary (21).

The assessment of DPA was done using an activity monitor (Actigraph®, wGT3x-BT) on their waist for six consecutive days, for 24 hours, including sleeping time. This activity monitor is validated in other patients with respiratory diseases as a reliable method to assess DPA (24). The device measures wearing time and records daily steps, time spent in different postures (i.e. lying, sitting and standing) and time spent in activities of different intensities (i.e. sedentary, light and moderate to vigorous physical activity, MVPA) (25). DPA measurement data were analysed by the software ActiLife® (Actigraph).

Exercise capacity was evaluated by the 6-minute walk test, performed twice with 30 minutes of rest between tests following the international guidelines. The largest walking distance was used for analysis and compared to normative values (26). One week later, participants returned to the laboratory to give back activity monitor and to perform lung function. Lung function was assessed using post-bronchodilator spirometry, whole-body plethysmography and diffusion

capacity of carbon monoxide (D_LCO) (Vmax, CareFusion®) according to international guidelines (27-30). Obtained values were compared to normative data for the Brazilian population (31).

Quadriceps force was assessed by the maximal voluntary isometric contraction (MVICq) of the dominant limb using a strain gauge (EMG System®, Brazil) attached to a stationary multigym device. Participants were instructed to perform the MVICq for 6s, with 90◦ flexion of hip and knee. At least four and at most 15 attempts were performed and the higher result was used for the analysis (32). Finally, handgrip force of the dominant member was evaluated with a handheld dynamometer (SH1001, Saehan Corporation. Korea), three trials with the elbow flexed at 90◦, with the arm unsupported (33). The higher result was used for the analysis. Health-Related Quality of Life (HRQoL) was assessed by the IPF-specific version of the St. George's Respiratory Questionnaire (SGRQ-I), which is validated for different diagnoses of ILD and higher scores indicating a more impaired health-related quality of life (34).

Statistical Analysis

Statistical analyses were performed using software SAS Studio 9.4 and Graph Pad Prism 6.0. According to data distribution, data are described as mean (standard deviation) or median [interquartile range]. Data normality was assessed by the Shapiro-Wilk test. Reference equations for Brazilian population was used to analyse performance of TUGu and TUGf in % of predicted (35). Correlations between TUG (both TUGu and TUGf) and daily steps, time spent in different postures (sitting, standing and lying) and time spent in activities of different intensities (light, sedentary and MVPA) were done using the Spearman correlation coefficient. To identify cut-offs capable of discriminating inactive

patients, a receiver operating characteristic (ROC) curve analysis was carried out. Criteria of inactivity was set as MVPA <30min/day) (36) and daily steps <5000/day according to previous evidence (37, 38). The area under the curve and sensitivity and specificity of the proposed cut-offs were estimated. Relevant characteristics for interstitial lung disease patients were compared based on the proposed cut-off points, using unpaired t-test and Mann-Whitney, according to data distribution and p value established was 0.5.

Results

A total of fifty-four patients with ILD were included in this study. Characteristics of all participants are described in **Table 1**. Significant correlations were found between TUGu and TUGf with steps, light intensity activity and MVPA (-0.60<r<-041; p<0.05 for all). Moderate correlation was found only in TUGf % of predicted with steps and MVPA (-0.48<r<-0.57; p<0.05 for all). The full description of correlations is provided in **Table 2**.

Table 1. Characteristics of included subjects.

Outcomes	**ILD patients (n=54)**
Sex, women (%)	26 (48)
Age, years	60 ± 11
BMI (Kg/m^2)	27 [25 – 30]
Pulmonary function	
FVC, % of predicted	68 ±17
$FEV_{1,}$ % of predicted	69 ± 18

FVC/FEV_1	84 [78 – 87]
D_LCO, % of predicted	45 ± 18
Physical Daily Activity	
Steps, n/day	4925±1878
Light activity, min/day	301±95
MVPA, min/day	8.7 [2.8 – 14.0]
Sedentary activity, min/day	737±180
Standing, min/day	293±86
Lying, min/day	294[226 – 337]
Sitting, min/day	440±99
Functional Performance	
TUGu, s	9.5±1.4
% of predicted	101 [95 – 113]
TUGf, s	7.8±1.3
% of predicted	104 [94 – 119]

Captions: ILD: interstitial lung disease; FVC: forced vital capacity; FEV1: forced expiratory volume in the first second; D_LCO: diffusion lung capacity of carbon monoxide; 6MWT: 6-minute walk test; TUGu: timed up and go at usual pace; TUGf: timed up and go at fast pace; m: metre, N: Newton; S: seconds; MVPA: moderate-to-vigorous physical activity.

Table 2. Correlation between both protocols of the TUG and the domains of daily physical activity and sedentarism.

Tests	**TUGu** (seconds)	**TUGf** (seconds)
Steps, n/day	-0.52*	-0.47*
Light activity, min/day	-0.43*	-0.41*
MVPA, min/day	-0.60*	-0.49*
Sedentary activity, min/day	-0.06	0.22
Standing, min/day	-0.38*	-0.34*
Lying, min/day	0.14	0.10
Sitting, min/day	-0.03	-0.14

Captions: TUGu: timed up and go at usual pace; TUGf: timed up and go at fast pace; Min: minutes; MVPA: moderate-to-vigorous physical activity; * $p<0.05$.

Twenty-nine patients (54%) perform less than 5000 steps/day and forty-nine patients (90%) perform less than 30 minutes of MVPA. The ROC curves analysis identified the cut-offs of 9.25s and 7.9s in the TUGu as acceptable to stratify inactive patients using respectively the 5000 steps/day (AUC: 0.74; sensitivity 76%, specificity 71%) and the 30min/day MVPA (AUC: 0.84, sensitivity 90%, specificity 75%) (**Figure 1**). The ROC curve analysis for the TUGf in seconds and for TUGu and TUGf % of predicted demonstrated weaker capacity to discriminate active from inactive patients.

Thirty patients with ILD (55% of the sample) presented performance in the TUGu higher than 9.25s whilst forty-six (85%) of patients presented a performance in the TUGu higher than 7.9s. **Tables 3** show the demographics, exercise capacity, muscle force, quality of life, pulmonary function and DPA in

patients with ILD according to 9.25s cut-off. Patients with worse performance in TUGu showed: lower number of steps per day ($p<0.001$), spent less time in light activity ($p<0.001$), MVPA ($p=0.0004$), less time in standing position ($p=0.002$) and more time in lying position ($p=0.01$). No differences were observed in demographics and pulmonary function ($p>0.05$). Also, patients with TUGu≥7.9s present lower steps per day, MVPA and more time in lying position and no difference in pulmonary function and demographics ($p<0.05$).

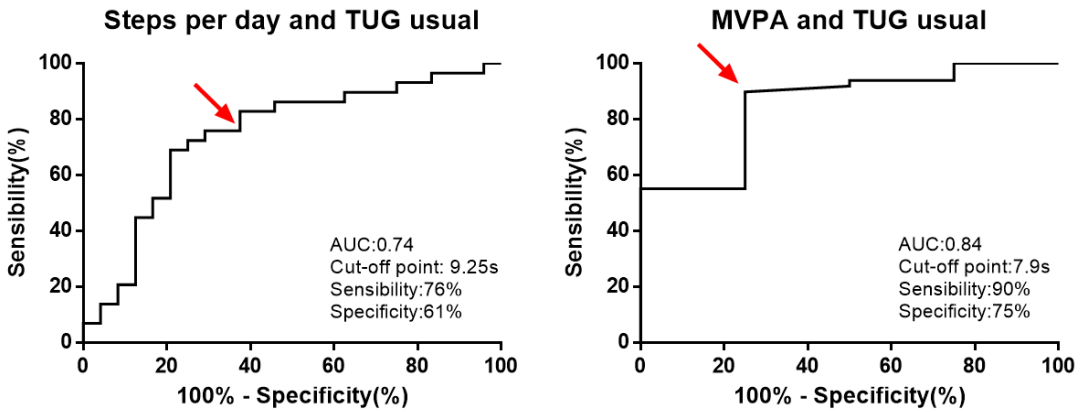

Figure 1 – Area under the curve of the timed-up-and-go test at usual pace with steps and MVPA.

Table 3. Characteristics of patients stratified by the cut-off of 9.25s in TUGu from ROC curves.

Outcomes	**Slow performance** (n=30)	**Normal performance** (n=24)	***p***
Sex, women (%)	12 (40)	16 (66)	0.08
Age, years	64 [57 – 70]	58 [47 – 67]	0.24
BMI, Kg/m^2	27 [25 – 30]	26 [23 – 29]	0.25
Pulmonary function			
FVC, % of predicted	66 ± 21	69 ± 12	0.55
FEV_1, % of predicted	69 ± 21	69 ± 14	0.80
FVC/FEV_1	84 ± 6	79 ± 10	0.08
D_LCO, % of predicted	42 ± 19	48 ± 18	0.31
Daily physical activity and sedentarism			
Steps, n/day	4041 ± 1787	6068 ±1422	<0.001
Light activity, min/day	254 ± 88	360 ± 78	<0.001
MVPA, min/day	4.1 [1.1 – 9.2]	10.4 [8.8 – 21.7]	0.0004
Sedentary activity, min/day	756 ± 195	710 ± 163	0.37
Standing, min/day	255 ± 69	340 ± 82	0.002
Lying, min/day	334 ± 137	259 ± 67	0.01
Sitting, min/day	428 ± 109	455 ± 86	0.35
Exercise Capacity			

6MWT, m	389 ± 68	537 ± 81	<0.001
6MWT, % of predicted	75 ± 14	96 ± 12	<0.001
Pheriperal muscle strength			
Quadriceps Strength, N	271 [227 – 309]	404 [258 – 477]	0.002
Handgrip Force, Kgf	21 [18 – 25]	30 [22 – 35]	0.003

Captions: FVC: forced vital capacity; FEV1: forced expiratory volume in the first second; D_LCO: diffusion lung capacity of carbon monoxide; MVPA: moderate-to-vigorous physical activity.

Discussion

In the present study, the timed up and go test was correlated with variables of DPA (i.e. steps per day, light intensity activity and MVPA). Additionally, it was showed that proposed the cut-off of 9.25s can discriminate patients with ILD that accomplish less than 5000 steps/day.

To date, only two studies (18, 23) investigated the performance in the TUGu in ILD patients. In both studies, the average durations of the test were 9.6 and 9.8 seconds, which is in line with the results in our study. Also, the correlations between the performance in the TUG protocols and clinical outcomes has been previously done by other study (23). Mendes and colleagues found a weak correlation between the TUGu and quadriceps (r=-0.28; p=0.164) and 6MWT (r=0.37; p=0.062)(18). In line with the results of this study, other study of our group also showed previously similar findings of the correlations between the TUGu and quadriceps (r=-0.48) and 6MWT (r=-0.69) (23). Our results expand the current knowledge regarding clinical associations of the TUG test demonstrating

its association with DPA. In fact, this seems to be the first study in ILD showing that low performance in the test is associated with worse patterns in daily physical activity. As DPA plays an important role in the morbidity and mortality of ILD (39), identifying a limitation in the test could help clinicians to seek for a more specific assessment of DPA in the population.

The predictive power of the TUG to stratify patients according to different clinical outcomes is demonstrated in patients with COPD. Mesquita et. Al. showed that performance in TUG has acceptable specificity and sensitivity to predict lower exercise capacity (21). To the best of our knowledge, this is the first study proposing cut-offs to stratify ILD patients as inactive according to a functional performance test. Yoshida and colleagues conducted a similar trial and showed that velocities below 1.07m/s in the 4-metre gait speed were capable of identifying inactive patients in various respiratory diseases (16). Authors reported that a limitation of their study, however, was the inclusion of only patients who did not need oxygen for the execution of the tests. This is perhaps more important for ILD patients as oxygen desaturation during exertion is a common feature. The present study, therefore, reinforces the impact of low performance in functional tests in ILD patients on DPA.

In the present study, worse performance in the TUGu did not seem to provide discrimination of ILD severity (i.e. pulmonary function), although present worst exercise capacity and lower pheriperal muscle force. As demonstrated in our results section, there was virtually no differences between patients with better/worse performance in the test regarding lung function. This is not in line with previous investigations that reported worse performance in functional tests to be associated with worse clinical condition in chronic respiratory diseases (10, 16). Although the proposed cut-off seems to adequately stratify inactive patients,

one cannot extrapolate these findings to a better/worse overall health condition. Further studies are necessary to confirm whether a worse performance in functional performance measured by the TUGu is indeed only associated with DPA levels in ILD.

The results of the present study need to be interpreted considering some potential limitations. The sample size is somewhat small. Although this limits our findings' external validity, the sample size is similar to previous studies on DPA and functional performance tests in ILD (16, 40). The sample size has also an impact on the ROC curves, as larger samples are needed to confirm the actual discriminative capacity of the TUGu to identifying inactive patients. Finally, patients included in the present study do not cover the entire spectrum of severities of ILD. Our results show a significant disbalance between the sample of patients below and above the proposed 7.9s cut-off regarding MVPA. Only 15% of the sample performed at least 30 minutes of MVPA per day and the disbalance might potentially influence the findings. Future prospective studies should verify if these cut-offs (i.e. 9.25 and 7.9s) are valid to discriminate negative clinical outcomes as hospitalisations or mortality.

In conclusion, the timed up and go in both protocols (TUGu and TUGf) is associated with daily physical activity in patients with ILD. Additionally, the cut-off of 9.25s in the TUGu seems acceptable to stratify inactive patients using the 5000 steps/day.

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CAPÍTULO 6

Functional performance, static balance and history of falls in interstitial lung disease: a preliminary one-year prospective cohort study

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Functional performance, balance and falls in interstitial lung disease: a preliminary one-year prospective cohort study

Running head: Balance and Fall in interstitial lung disease

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Abstract

Background: Functional performance (FP) associates with balance deficits and increased fall risk, especially in frail patients. In subjects with interstitial lung diseases (ILD), reductions in FP are described but it remains unclear whether balance is also impaired and to which extent both FP and balance differ between patients with history of falls over one year period. **Aims:** To assess fall, balance, FP prospectively and to verify whether they differ between ILD subjects who did or did not report falls during one year. **Methods:** ILD subjects underwent assessments of pulmonary function, peripheral muscle strength and exercise capacity. Functional performance was assessed by six tests: timed-up-and-go with usual and fast gait speeds, four-metre gait speed, sit-to-stand in 30 seconds, one-minute and with 5-repetition. Balance was assessed using a force platform in two-leg stance with eyes open and eyes closed, and in one-leg stance with eyes open. Falls was collected prospectively via monthly telephone calls, functional performance, and balance of ILD patients were prospectively collected in three moments, six months apart each other. Outcomes were compared between patients who did or did not report falls during one year. **Results:** 52 patients (33 women, 59±10 years, CVF 69±18%pred) with ILD were included. Twelve patients (22% of total) had at least one fall during the follow up. Comparisons between fallers and non-fallers, resulted in no differences in all investigated outcomes in three moments. **Conclusion:** This preliminary analysis, suggest that, despite a relatively large proportion of patients presenting falls, functional performance or balance does not differ between fallers and non-fallers ILD over one year.

Key words: Physical functional performance, lung diseases, balance, falls.

Abbreviations list

1min-STS: Sit-to-stand test in one-minute

4MGS: Four-metre gait speed

5rep-STS: Five repetition sit-to-stand test

6MWT: Six-minute walk test

30sec-STS: Sit-to-stand test in thirty seconds

BMI: Body-mass index

CI: Confidence interval

COP: Center of pressure

COPD: Chronic obstructive pulmonary disease

CTD: Connective pulmonary disease

D_{LCO}: Diffusion capacity of the lung for carbon monoxide

FEV_1: Forced expiratory volume in the first second

FVC: Forced vital capacity

HG: Handgrip force

ILD: Interstitial lung disease

IPF: Idiopathic pulmonary fibrosis

MVICq: Maximal voluntary isometric contraction of quadriceps

MVPA: Moderate to vigorous physical activity

OLS – EO: One-legged stance with eyes open

Rep: Repetition

Sec: Seconds

SPPB: Short Physical Performance Battery

QS: Quadriceps strength

TLS – EO: Two-legged stance with eyes open

TLS – EC: Two-legged stance with eyes closed

TUGu: Timed-up-and-go in usual pace

TUGf: Timed-up-and-go in fast pace

Vel-AP: Velocity sway of COP in antero-posterior direction

Vel-ML: Velocity sway of COP in medio-lateral direction

Introduction

Interstitial lung diseases (ILD) are a heterogeneous group of pathologies with similar clinical, radiological and functional characteristics, characterized by respiratory problems caused by chronic alveolar inflammation, diffuse parenchyma pulmonary fibrosis and, as a consequence, a deficit in gas exchange[1-4]. Extrapulmonary symptoms also are frequently in ILD, such as reduced muscle strength and exercise capacity[5,6]. Besides the impaired muscle strength, patients with ILD also present worse functional performance[7], which may contribute to experience difficulties while performing daily activities.

Balance deficits are known in patients with other chronic respiratory diseases, such as chronic obstructive pulmonary disease (COPD)[8]. The main consequence of poor balance is the increased risk of falls. Risk of falls are relevant in the literature because of its association with negative repercussions on the clinical status, such as loss of functional independence, reduced quality of life, hospital complications and mortality[9,10]. The increased fall risk is related to the respiratory and systemic manifestations of the disease in COPD patients[11]. Considering the similar extrapulmonary characteristics between COPD and ILD patients, such as reduced exercise capacity and reduced peripheral muscle strength[5,12], the high proportion of falls and impairment in functional performance and balance also occur ILD patients.

There is scarce evidence demonstrating falls in ILD, it is also unclear whether there are outcomes associated with falls over a long follow-up. The aim of this study was to observe falls prospectively in patients with ILD, and to assess balance and functional performance over one year in ILD. Additionally, it was

verified whether there were differences between ILD subjects between fallers and non-fallers during the follow-up.

Methods

Study design and ethical aspects

This is a one-year prospective cohort study investigating functional performance, static balance and falls in patients with ILD. This study is part of a larger ongoing trial (BELIEVE-ILD) which was approved by the institutional review board (#2.484.871) and all participants provided informed consent form for their participation in the study.

Sample characteristics and procedures

Subjects with ILD were recruited to partake in the present study from the outpatient clinic of the University Hospital of the Londrina State University, Brazil. Participants were included between March 2018 and March 2020, if they were between 40 and 75 years old and had no clinical conditions (other than ILD) that could interfere with the study assessments. The diagnosis of ILD was done using internationally accepted guidelines[3,13,14], and all participants must had a stable clinical condition (i.e. absence of exacerbations) for at least 1 month prior to their inclusion. Participants would be excluded if presented an acute exacerbation during the study, or presented incapacitating comorbidities (not unveiled upon inclusion), or presented other respiratory conditions (i.e. COPD) only observed in

pulmonary function test after inclusion, or withdrew consent to the study participation.

Participants attended the clinics in two-days for the assessments, and returned at 6 and 12 months to perform the same testing again. Prospectively, patients were contacted monthly via telephone calls and falls during the period was recorded. During the first day of assessment, all participants received information about the study procedures and answered a general questionnaire for sample characterisation. At the same day, they were assessed for exercise capacity and muscle strength. On the second day, patients were assessed regarding static balance, functional performance, and pulmonary function.

Assessments

Primary outcomes

Static balance was assessed by three positions on a force platform (BIOMEC 400, EMG System): two-legged stance with eyes open (TLS-EO) and closed (TLS-EC) and one-legged stance with eyes open (OLS-EO). The participants performed at least two 30s trials, with one-minute of rest between attempts in three positions[15]. A mark on the force platform was used to standardize the position of the feet. The assessments were conducted with patients barefoot and their arms relaxed. Participants were instructed stand as still as possible in the position[16]. At least nine seconds in one-legged stance position was necessary to consider the trial valid[17]. Functional performance was assessed by six functional tests: timed up and go at usual pace (TUGu) and at fast pace (TUGf)[5,18], four-metre gait speed test (4MGS)[19,20], sit-to-stand test using three protocols: 30 seconds (30sec-STS), one-minute (1min-STS) and five-repetition (5rep-STS)[21-23]. All tests followed previously published protocols in

patients with ILD[7]. Reference equations for Brazilian population was used to analyse functional performance in % of predicted[24]. Functional performance tests were performed twice each visit with the same assessor and resting time was allowed between attempts, until symptoms of fatigue and dyspnoea (i.e. Borg scale), heart rate and peripheral oxygen saturation returned to baseline, or for as long as the patient deemed necessary. Finally, falls were defined as ‘‘an unexpected event in which the participants come to rest on the ground, floor, or lower level”[25].

Secondary assessments

Lung function (whole-body plethysmography and diffusion capacity for carbon monoxide (D_{LCO}), (Vmax, CareFusion©) was evaluated following internationally accepted guidelines and were compared to normative data for the Brazilian population[26-29]. Exercise capacity was assessed by the 6-minute walk test (6MWT) following international guidelines for field tests. The test was performed twice and the highest achieved walking distance was used for analysis[30,31]. Quadriceps force was assessed by the maximal voluntary isometric contraction (MVICq) of the dominant limb using a strain gauge (EMG System®, Brazil) attached to a stationary multigym device. Participants were instructed to perform the MVICq for six seconds, with 90º flexion of hip and knee. At least four and at most 15 attempts were performed and the higher result was used for the analysis[32]. Finally, handgrip force of the dominant member was evaluated with a handheld dynamometer (SH1001, Saehan Corporation. Korea), three trials with the elbow flexed at 90°, with the arm unsupported. The higher result was used for the analysis[33].

Statistical Analysis

Data is described as mean and standard deviation or median and interquartile range according to its distribution. Normality was checked using the Shapiro-Wilk test. Based on the reporting of falls, patients were divided into two groups: fallers and non-fallers. Performance on the functional tests was compared between groups using unpaired t test or Mann-Whitney test. Categorical data were compared using chi-squared test. A linear mixed model using compound symmetry as covariant structure and a post hoc Bonferroni adjustment was performed to compare fallers and non-fallers regarding functional performance and static balance in three moments over a year. Statistical analyses were performed using software SAS Studio 9.4.

Results

From the fifty-seven patients recruited, fifty-two were included (**Figure 1**). Characteristics of participants included are described in **Table 1**.

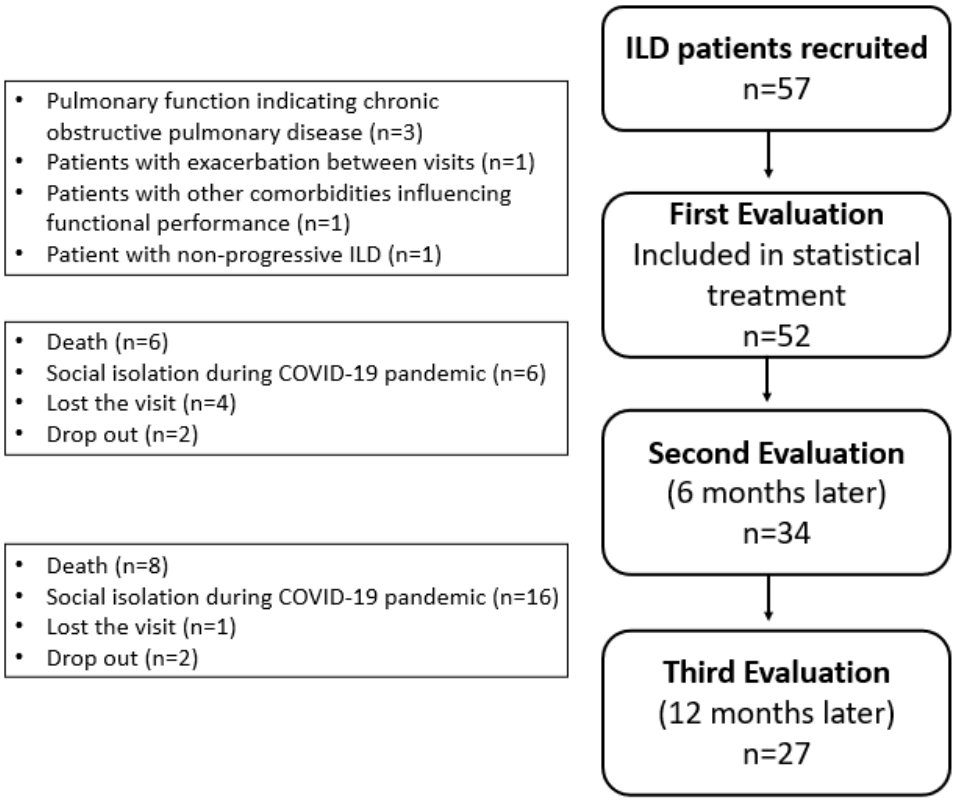

Figure 1. Flow chart of recruitment, inclusion and assessments of the subjects in the study.

Table 1. Characteristics of patients with ILD at baseline.

	ILD group (n=52)
Sex (% of women)	33 (63%)
Age (years)	59.6±10.8
BMI (kg/m^2)	27.8±5.1
Diagnosis n (%)	
- ILD with CTD	27(52%)

- IIP	23(44%)
- Sarcoidosis	1(2%)
- Asbestosis	1(2%)
Pulmonary function	
FVC (% of predicted)	69.7±18.9
FEV_1 (% of predicted)	72.1±19.2
FVC/FEV_1 ratio	83.3±6.0
D_{LCO} (% of predicted)	45.5±18.9
Exercise capacity	
6MWT (m)	446.5±99.1
6MWT (% of predicted)	83.1±16.7
Functional performance	
TUGu (seconds)	9.53 [8.3-10.6]
% of predicted	147 [133 – 161]
TUGf (seconds)	7.52 [6.8-8.4]
% of predicted	159 [143 – 174]
4MGS (m/s)	1.13 [1.0-1.3]
% of predicted	89 [81 – 100]
30sec-STS (repetitions)	12.5 [11-15]
% of predicted	55 [47 – 63]
1min-STS (repetitions)	24.0 [21-28]
% of predicted	51 [44 – 60]
5rep-STS (seconds)	10.64±2.19
% of predicted	163±37
Balance	
COP-area (cm^2) - TLS-EO	1.10[0.6-1.8]
COP-area (cm^2) - TLS-EC	1.21[0.7-2.5]
COP-area (cm^2) - OLS-EO	12.4[10.3-18.5]
Vel-AP (cm/s) - TLS-EO	1.54[1.4-1.8]
Vel-AP (cm/s) - TLS-EC	1.64[1.5-2.1]
Vel-AP (cm/s) - OLS-EO	3.94[3.4-4.9]
Vel-ML (cm/s) - TLS-EO	1.41[1.2-1.6]
Vel-ML (cm/s) - TLS-EC	1.44[1.3-1.6]
Vel-ML (cm/s) - OLS-EO	4.51[4.0-5.2]

Captions: ILD: interstitial lung disease; IIP: Idiopathic interstitial pneumonia; CTD: Connective tissue disease; MVPA: Moderate to vigorous activity; TUGu: timed-up-and-go in usual pace; TUGf: timed-up-and-go in fast pace; 30sec-STS: sit-to-stand in 30 seconds; STS1: sit-to-stand in one-minute; 5rep-STS: five-repetitions of sit-to-stand; 4MGS: four-metre gait speed; COP: center of pressure; Vel-AP: velocity sway of COP in antero-posterior direction; Vel-ML: velocity sway of COP in medio-lateral direction; TLS: two-legged stance; OLS: one-legged stance; EO: eyes open; EC: eyes closed.

Twelve patients with ILD presented at least one fall (22% of total) in twelve months and four of them presented more than one episode. **Table 2** describes comparison between results of fallers in the closer visit to the fall episode and results of initial assessment in non-fallers (Visit 1). Both groups were similar in age, sex, functional performance and static balance. The comparison of the outcomes between groups in three moments are described in **Table 3**. There were no differences between fallers and non-fallers groups across the visits in none investigated outcomes.

Table 2. Comparison of functional performance and static balance between fallers and non-fallers.

	Fallers (n=12)	**Non-Fallers (n=40)**	***p***
Age (years)	60.6±11.9	59.6±10.7	0.83
Sex, Fem, n (%)	8(66%)	25(62%)	0.83
Diagnosis n (%)			
- ILD with CTD	5 (42%)	21 (58%)	
- IIP	6 (50%)	14 (39%)	
- Sarcoidosis	1 (8%)	0	
- Asbestosis	0	1 (3%)	
Functional performance			
TUGu (seconds)	10.66[8.7-11.9]	9.44[8.3-10.3]	0.15
% of predicted	157 [133 – 178]	147[133 – 160]	0.30
TUGf (seconds)	8.17[6.5-9.2]	7.64[7.1-8.4]	0.65
% of predicted	163 [155 – 173]	155[143 – 177]	0.51
4MGS (m/s)	1.11[0.84-1.27]	1.13[1.0-1.2]	0.51
% of predicted	86 [78 – 100]	91[81 – 104]	0.26
30sec-STS (repetitions)	11.5[10-14]	13.0[11-16]	0.31
% of predicted	53 [45 – 59]	55 [47 – 72]	0.29
1min-STS (repetitions)	24.0[19-29]	25.0[21-32]	0.61
% of predicted	51 [44 – 57]	51 [44 – 66]	0.51

5rep-STS (seconds)	11.85±2.08	10.68±2.41	0.67
% of predicted	160±28	164±38	0.75
Static Balance			
COP-area (cm^2) - TLS-EO	0.89[0.6-1.8]	1.10[0.7-1.8]	0.73
COP-area (cm^2) - TLS-EC	1.36[1.0-2.0]	1.19{0.8-2.1]	0.66
COP-area (cm^2) - OLS-EO	11.70[9.2-14.8]	12.01[10.3-16.9]	0.47
Vel-AP (cm/s) - TLS-EO	1.58[1.4-1.9]	1.55[1.3-1.7]	0.37
Vel-AP (cm/s) - TLS-EC	1.78[1.6-2.2]	1.65[1.5-2.1]	0.22
Vel-AP (cm/s) - OLS-EO	3.56 [3.0-4.6]	3.92[3.4-4.8]	0.37
Vel-ML (cm/s) - TLS-EO	1.43[1.2-1.6]	1.40[1.2-1.6]	0.97
Vel-ML (cm/s) - TLS-EC	1.47[1.3-1.7]	1.43[1.3-1.7]	0.99
Vel-ML (cm/s) - OLS-EO	4.62[4.3-5.1]	4.59[4.1-5.5]	0.91

Captions: ILD: interstitial lung disease; IIP: Idiopathic interstitial pneumonia; CTD: Connective tissue disease; TUGu: timed-up-and-go in usual pace; TUGf: timed-up-and-go in fast pace; 30sec-STS: sit-to-stand in 30 seconds; STS1: sit-to-stand in one-minute; 5rep-STS: five-repetitions of sit-to-stand; 4MGS: four-metre gait speed; COP: center of pressure; Vel-AP: velocity sway of COP in antero-posterior direction; Vel-ML: velocity sway of COP in medio-lateral direction; TLS: two-legged stance; OLS: one-legged stance; EO: eyes open; EC: eyes closed.

Table 3. Comparison of functional performance and center of pressure in static balance between fallers and non-fallers in three visits over a year.

	Group	First evaluation Initial (n=52)	Second evaluation (6 months) (n=34)	Third evaluation (one-year) (n=27)	*p interaction*
TUGu	F	10.31±0.49	9.85±0.54	9.82±0.68	0.10
(seconds)	NF	9.38±0.26	9.94±0.30	10.15±0.32	
	p	0.10	0.88	0.66	
TUGf	F	8.41±0.44	8.05±0.49	7.71±0.59	0.43
(seconds)	NF	7.76±0.24	7.83±0.27	7.78±0.28	
	p	0.95	0.20	0.09	
4MGS	F	1.13±0.05	1.04±0.05	1.14±0.07	0.63
(m/s)	NF	1.13±0.02	1.10±0.03	1.15±0.02	
	p	0.95	0.37	0.92	
30sec-STS	F	12.3±1.15	11.9±1.26	14.1±1.56	0.27
(repetitions)	NF	13.6±0.63	13.9±0.71	13.6±0.78	
	p	0.29	0.17	0.77	
1min-STS	F	23.4±2.23	24.3±2.31	28.5±2.78	0.16
(repetitions)	NF	26.4±1.17	25.8±1.28	26.2±1.37	

	p	0.24	0.57	0.46	
5rep-STS	F	11.45±0.87	11.21±0.94	9.85±1.12	0.32
(seconds)	NF	10.66±0.47	11.01±0.52	10.65±0.56	
	p	0.43	0.85	0.52	
COP (cm^2)	F	1.58±0.36	1.19±0.39	1.36±0.44	0.25
TLS-EO	NF	1.34±0.20	1.46±0.22	1.18±0.23	
	p	0.55	0.56	0.71	
COP(cm^2)	F	2.03±0.45	1.61±0.54	1.66±0.67	0.83
TLS-EC	NF	1.84±0.24	1.74±0.31	1.30±0.34	
	p	0.71	0.83	0.63	
COP (cm^2)	F	12.9±3.06	12.7±3.39	12.0±4.17	0.35
OLS-EO	NF	12.7±1.59	17.5±2.06	18.2±2.22	
	p	0.94	0.23	0.19	

Captions: Mean estimate ± Standard error; F: fallers; NF: non-fallers; TUGu: timed-up-and-go in usual pace; TUGf: timed-up-and-go in fast pace; 30sec-STS: sit-to-stand in 30 seconds; STS1: sit-to-stand in one-minute; 5rep-STS: five-repetitions of sit-to-stand; 4MGS: four-metre gait speed; COP: center of pressure; Vel-AP: velocity sway of COP in antero-posterior direction; Vel-ML: velocity sway of COP in medio-lateral direction; TLS: two-legged stance; OLS: one-legged stance; EO: eyes open; EC: eyes closed.

Discussion

The results of this study shows that about one at every 5 patients with ILD patients experienced at least one fall in twelve months, whilst the proportion of healthy older adults (i.e. 55 to 64 years) was one to seven[34]. No differences in age, sex, functional performance and static balance were observed comparing patients with ILD fallers and non-fallers.

Twelve patients with ILD reported at least one fall during the follow up period in the present study. Unexpectedly, there were no differences in functional performance and static balance between fallers and non-fallers. No previous studies have investigated falls or fall risk in ILDs. Similar to our findings, no difference were observed in functional performance (i.e. berg balance scale) between fallers, non-fallers and frequent fallers (i.e. >2 falls in one year) in COPD

patients[9]. Static balance was not different between fallers and non-fallers in healthy elderly, even in one-leg stance which is more challenging[16].

The proportion of fallers during one year in our cohort, is in line with observed in older adults (i.e. 2 – 14%)[34] and healthy elderly (i.e.16 – 33%)[35-37] and despite being high, is smaller comparing with other studies in COPD one year (i.e. 32-39%)[9,38,39]. Falls incidence is even higher in patients with severe COPD (i.e. 36% in six months)[40], although the small sample size limited the assessment to the incidence of falls according to the ILD severity. Also, older age is crucial variable related to poor static balance[41]. In fact, patients in the present cohort are younger than those in COPD studies. Studies including other chronic respiratory diseases have higher prevalence of falls compared to ILD. The generally poor prognosis of ILD and the age of our sample may have played a role in the lack of differences between fallers and non-fallers in the present study.

No other previous study compared the performance in functional tests between different moments in patients with ILD over time, but slow gait speed in 4MGS and higher timed performance (i.e. worst score) in 8-foot-up-and-go are associated with mortality and hospitalisation in idiopathic pulmonary fibrosis (IPF) for one-year and for forty months, respectively[42,43]. Both studies investigated the association of functional performance with negative outcomes and not the comparison of longitudinal changes in functional performance or static balance, as the aim of this study.

Study Limitations

This one-year prospective cohort needs to be interpreted considering some potential limitations. The sample was small and composed by different diseases with different progression rates, which prevented it from being stratifies

according to the disease severity. Thus, it is difficult to anticipate a known pattern of disease progression, and therefore, a worsening of overall condition of patients taking place similarly. Also, the COVID-19 pandemic impacted largely on the data collection in the present study. A larger sample size was initially planned but could not be recruited due to government impositions of social isolation and the small sample size may have influenced results. Due to the methodology of a larger cohort to whitch this study is part, it was not possible to compare difference between moments with a control group. Future studies may include a group of healthy individuals paired by age to make this comparison possible. May tests and positions used to assess static balance is not the most appropriated to ILD patients, as other chronic respiratory diseases, future studies should explore instruments of dynamic balance (i.e. mini-BESTest) or global assessment of balance. This study contributes to the literature on the follow-up of functional performance in individuals with ILD, and mainly, on the assessment of the static balance, aspects that, of our knowledge, have not been described in the literature yet.

Conclusion

This preliminary analysis, suggest that, despite a relatively large proportion of patients present falls, functional performance or balance was not different between fallers and non-fallers over one year. It is likely that the limited sample size and the one-year follow-up played a role in the lack of observed difference in functional performance and balance between fallers and non-fallers. Future studies with adequate power and with longer follow-ups are needed to confirm the findings of the present study.

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42. Nolan CM, Maddocks M, Maher TM, et al. Gait speed and prognosis in patients with idiopathic pulmonary fibrosis: a prospective cohort study. *The European respiratory journal.* 2019;53(2).
43. Vainshelboim B, Kramer MR, Myers J, Unterman A, Izhakian S, Oliveira J. 8-Foot-Up-and-Go Test is Associated with Hospitalizations and Mortality in Idiopathic Pulmonary Fibrosis: A Prospective Pilot Study. *Lung.* 2019;197(1):81-88.

Highlights

- 22% patients with ILD reported at least one fall in one-year.
- No differences in static balance were observed in fallers compared to non-fallers.
- Functional tests and static balance did not change over one year in ILD.

CONCLUSÃO GERAL DA TESE

Conclusão Geral da Tese

No primeiro estudo desta tese (**Capítulo 3**), trinta e um instrumentos foram encontrados para avaliação do status funcional em pacientes com DRC não-DPOC. A maioria dos estudos avaliaram o desempenho funcional por meio de questionários, o instrumento mais comum foi o SF-36 e os testes de performance funcional mais utilizados foram 1min-STS e 4MGS. A maioria dos instrumentos com propriedades de medida adequadas descritas foram em pacientes com asma e DPI. Poucos estudos avaliaram a relação do desempenho funcional com desfechos clínicos negativos.

No segundo estudo realizado (**Capítulo 4**), foi observado pior desempenho funcional nos seguintes testes: TUGu, TUGf, 4MGS, SPPB, 5rep-STS e 1min-STS em pacientes com DPI comparados a indivíduos saudáveis. Os testes 5rep-STS e TUG foram os testes mais apropriados para avaliação do desempenho funcional em pacientes com DPI. Ou seja, apresentaram validade com a contração isométrica voluntária máxima de quadriceps e TC6min, com moderada correlação ($r>0.5$), e também apresentaram valores de reprodutibilidade intra e inter-avaliadores classificadas como boa a excelente.

No terceiro estudo incluído nesta tese (**Capítulo 5**) foi obervado moderada correlação dos testes TUGu e TUGf com as variáveis da AFVD: número de passos por dia, atividade leve e moderada a vigorosa. O desempenho no TUGu superior a 9,25 segundos parece ser um bom ponto de corte discriminativo para pacientes com DPI inativos. Pacientes com pior desempenho no TUGu apresentaram também piores resultados de AFVD, maior tempo em postura deitada e menor tempo gasto em pé, menor força muscular periférica e menor capacidade de exercício.

No quarto estudo (**Capítulo 6**), foi observado que 22% dos pacientes apresentaram ao menos uma queda em um ano, porém não houve diferença no desempenho funcional e equilíbrio estático em pacientes com DPI caidores e não caidores. Ademais, a idade e características dos pacientes com DPI incluidos podem

ter influenciado os achados do presente estudo e parece que um ano de acompanhamento em pacientes com DPI não foi suficiente para observar alteração do desempenho funcional e do equilíbrio estático em pacientes com DPI.

Considerando os resultados obtidos nos estudos realizados, pacientes com DPI apresentam pior desempenho funcional no TUG comparado a individuos saudáveis, o TUG em velocidade usual e rápida é válido e reprodutível em análise intra e interavaliadores, possui relação com a AFVD e poder discriminativo para pacientes com DPI inativos. Assim, o TUG parece ser o melhor teste descrito na literatura até o presente momento para avaliar o desempenho funcional de pacientes com diferentes diagnósticos de DPI.

Ademais, futuros estudos que investiguem a associação do desempenho funcional em pacientes com DPI com desfechos clínicos negativos como exacerbação aguda, hospitalização e mortalidade são necessários. Bem como, a investigação da performance funcional e equilíbrio corporal com maior tamanho amostral de pacientes com DPI em períodos superiores a um ano são necessários para a compreensão do impacto da evolução da doença e tempo de diagnóstico nestes desfechos clínicos.

Sumarização da tese

Além das menifestações pulmonares, pacientes com diferentes doenças crônicas respiratórias também apresentam manifestações extrapulmonares, como por exemplo, diminuição da força muscular periférica, diminuição da capacidade de exercício e funcionalidade. O foco desta tese é apresentar uma narrativa sobre a avaliação do status funcional nos pacientes com doenças respiratórias crônicas não-DPOC, especialmente nos pacientes com DPI. Para tanto o **Capítulo 1** consiste na introdução dos principais tópicos abordades nesta tese, e também uma breve contextualização para justificar e apresentar as hipóteses de cada estudo incluído nesta tese.

Na contextualização desta tese (**Capítulo 2)** é possível compreender as características, etiologia, manifestações pulmonares e extrapulmonares, intolerância ao exercício, limitações funcionais da DPI e a relevância das alterações funcionais em pacientes com DPI. Conceitos e classificações da funcionalidade, tipos de instrumentos disponíveis para avaliação do desempenho funcional, conceitos relacionados as propriedades de medida e equilibrio corporal também foram descritos. Além disso, foi descrito com maior detalhamento alguns testes funcionais amplamente utilizados na literatura e utilizados em três estudos incluídos nesta tese, são eles: *timed up and go, four-metre gait speed*, *sit-to-stand test* e *short physical performance battery* (**Capítulo 2**).

Por meio de uma revisão sistemática foi apresentado as evidencias disponíveis na literatura com instrumentos para investigação do desempenho funcional em pacientes com doenças respiratórias crônicas não-DPOC (**Capítulo 3**). Testes funcionais e questionários com domínios específicos para avaliação do desempenho funcional foram observados, suas propriedades de medida e sua relação com desfechos negativos foram avaliados. Deste modo, por meio da leitura deste artigo

científico é capaz de se observar os instrumentos mais utilizados e com propriedades de medida adequadas para cada doença crônica respiratória não-DPOC.

Após o levantamento dos testes funcionais específicos para os pacientes com DPI no capítulo anterior, o **Capítulo 4**, apresenta um estudo transversal para comparar o desempenho funcional de pacientes com DPI e pessoas saudáveis por meio dos testes funcionais. Além disso, o estudo busca avaliar a validade e reprodutibilidade da execução destes testes nos pacientes com DPI. Após a leitura deste artigo científico é possível estabelecer os testes funcionais mais adequados para a avaliação do desempenho funcional nos pacientes com DPI.

O desempenho funcional está relacionado às atividades de vida diária, e portanto, no **Capítulo 5** foi descrito um estudo científico que observou a relação das variáveis de AFVD com o desempelho do teste funcional *timed up and go*. Devido ao TUG ser um teste de baixo custo, rápido e prático de ser realizado na prática clínica, principalmente quando comparado aos métodos objetivos de avaliação da AFVD, a avaliação do TUG pode ser útil para discriminar pacientes inativos. Após a leitura deste artigo é possível compreender a relação do teste timed up and go na velocidade usual com a inatividade e inatividade extrema em pacientes com DPI e o seu poder discriminativo para distinguir pacientes ativos, inativos e inativos extremos.

O **Capítulo 6** aborda um estudo científico que avaliou o equilíbrio estático pela plataforma de força em pacientes com DPI. Ademais, este estudo avaliou a história de queda em indivíduos com DPI e comparou desfechos clínicos relacionados ao equilíbrio entre os pacientes com DPI caidores e não caidores em um ano. Análises de comparação do desempenho funcional e equilíbrio estático em três momentos diferentes durante um ano foram apresentados neste estudo. Após a leitura deste estudo é possível caracterizar o equilíbrio estático de pacientes com DPI e ainda analisar o comportamento do desempenho em testes funcionais e no equilíbrio estático durante um ano.

Por fim, o **Capítulo 7** sintetiza as principais conclusões observadas em cada capítulo desta tese, de modo abranger os principais tópicos abordados neste estudo, facilitando a assimilação do conteúdo dos diferentes estudos incluídos e a sua relação com a prática clínica.

LISTA DE PUBLICAÇÕES

Lista de Publicações

1. Autoria e coautoria de publicações em períodicos internacionais

Zamboti CL, Goncalves AFL, Garcia T, et al. Functional performance tests in interstitial lung disease: Impairment and measurement properties. *Respiratory medicine.* 2021;184:106413

Aguiar WF, Mantoani LC, Silva H, **Zamboti CL**, Garcia T, Cavalheri V, Ribeiro M, Yorke J, Pitta F, Camillo CA. Translation, cross-cultural adaptation, and measurement properties of the Brazilian-Portuguese version of the idiopathic pulmonary fibrosis-specific version of the Saint George's Respiratory Questionnaire (SGRQ-I) for patients with interstitial lung disease. Braz J Phys Ther. 2021 Jul 21:S1413-3555(21)00075-7.

Silva H, Mantoani LC, **Zamboti CL**, Aguiar WF, Ries AL, Garcia T, Garcia T, Ribeiro M, Pitta F, Camillo CA. Validation of a translated version of ucsd shortness of breath questionnaire in patients with interstitial lung diseases. Accept in J. Bras Pneumol. 2021

2. Capítulos de livro publicados

Krinski GG, **Zamboti CL**, Pitta F, Camillo CA. Tratamento do paciente respiratório em cuidados de fim de vida. Programa de atualização PROFISIO: Fisioterapia cardiovascular e respiratória, Ciclo 7, Vol. 1, Pg 55-102, 2020.

Currículo Vitae Resumido

Camile Ludovico Zamboti, nascida no municipio de Londrina no dia 28 de outubro de 1992. Realizou sua formação educacional de ensino fundamental e médio nos colégios Londrinense e Marista. No ano de 2013 se formou no curso superior de fisioterapia pela Universidade Estadual de Londrina (UEL), em 2016 completou pós-graduação lato-senso, do tipo residência em fisioterapia traumato-ortopédica funcional pela mesma instituição. Iniciou a pós-graduação stricto-senso pelo programa de ciências da reabilitação (UEL/UNOPAR) sob orientação da professora Dra. Christiane de Souza Guerino Macedo, com conslusão do seu mestrado no ano de 2017. Subsequentemente, no ano de 2018 iniciou o doutorado no programa de ciências da reabilitação (UEL/UNOPAR), sob orientação do professor Doutor Carlos Augusto Camillo.

APÊNDICES

APÊNDICE A – Termo de Consentimento Livre e Esclarecido

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Conforme a Resolução 466 de 12 de Dezembro de 2012, do Conselho Nacional de Saúde/Ministério da Saúde.

Prezado(a) Senhor(a):

O(A) Sr(a) está sendo convidado para participar de um projeto de pesquisa chamado "**Associação entre progressão da doença e desfechos clínicos em pacientes com doenças intersticiais pulmonares**", realizado no Laboratório de Pesquisa em Fisioterapia Pulmonar da Universidade Estadual de Londrina (Londrina, Brasil). O objetivo do estudo é avaliar por um período de até 2 anos o impacto de possíveis mudanças na função pulmonar em diferentes aspectos clínicos (incluindo os níveis de atividade física na vida diária) em indivíduos com doenças intersticiais pulmonares e em indivíduos sem a doença. A sua participação é muito importante e ela se daria da seguinte forma: Os participantes realizarão algumas avaliações em cinco momentos: no início do protocolo, após 6 meses, 1 ano, 18 meses e 2 anos. Em cada momento serão realizadas as seguintes avaliações:

- Avaliação da função pulmonar por meio de pletismografia/espirometria e capacidade de difusão de monóxido de carbono (DLCO);
- Atividade física na vida diária que será realizada durante 6 dias consecutivos pelo aparelho Actigraph® (aparelho pequeno e leve, utilizado na cintura, de manuseio extremamente simples que monitora todas as atividades físicas realizadas pelo participante, permitindo saber o quanto ativo ele é). Nos 6 dias de avaliação, o participante permanecerá durante 24 horas com o aparelho, havendo a necessidade de retirá-lo apenas durante o banho e atividades realizadas em piscina (por exemplo: natação, hidroginástica).

- Força muscular por meio de dinamometria de membros superiores e inferiores e teste de 1 repetição máxima; força muscular respiratória por meio de manovacuometria; fadiga muscular periférica por meio eletromiografia de superfície;
- Capacidade funcional de exercício por meio do teste da caminhada de 6 minutos e; capacidade máxima de exercício por meio do teste cardiopulmonar de esforço;
- Capacidade funcionais por meio dos testes: Teste de caminhada de 4 metros, teste de Sentar e levantar por 30 segundos e Teste do degrau de 6 minutos
- Composição corporal por meio do teste de bioimpedância elétrica;
- Ansiedade e depressão por meio da *Hospital Anxiety and Depression Scale (HADS);* Qualidade de vida relacionado à saúde por meio dos questionários: *Short Form Health Survey (SF-36)* e *Saint George Respiratory Questionnaire* específico para pacientes com doença intersticial pulmonar (SGRQ-I); Função congnitiva por meio do Mini Exame do Estado Mental (MEEM); sono e sonolência por meio do Índice de Qualidade de Sono de Pittsburgh (PSQI) e escala de sonolência de Epworth (ESE); Falta de ar no dia-a-dia por meio da escala do *Medical Research Council (MRC) e pelo Short of breath questionnaire do centro médico UCSD (UCSD-SOBQ).* HADS, SF-36, MRC, MEEM, PSQI, ESE e UCSD-SOBQ serão administrados a todos os pacrticipantes. SGRQ-I será administrado apenas para pacientes com doenças intersticiais pulmonares;
- Exames de sangue (marcadores inflamatórios e estresse oxidativo).

Benefícios esperados do estudo: Os resultados deste estudo ajudarão a compreender o efeito que uma possível progressão da doença (ou seja, mudanças na função pulmonar) tem sobre diferentes aspectos clínicos da doença. Isso poderá contribuir para que, no futuro, novos tratamentos surjam e ajudem pacientes com doença pulmonar intersticial. **Benefícios diretos ao participante:** Após cada avaliação, se for de seu interesse, você receberá um relatório com os resultados de todos os testes. Esses resultados podem ser entregues ao seu médico para uma avaliação mais completa do seu estado de saúde. Além disso, os participantes sem acompanhamento médico no momento da inclusão do estudo serão cadastrados no

Ambulatório de Especialidades do Hospital Universitário da UEL. **Riscos:** Nenhum dos procedimentos utilizados constitui risco direto para a integridade física ou moral dos participantes. Em alguns casos, após a coleta de sangue é possível que se forme um pequeno hematoma na região onde a coleta ocorreu. Além disso, caso algum teste gere mal estar (físico ou emocional) ele será interrompido sem que haja risco real para a saúde do participante. **Custos:** Informamos que o(a) senhor(a) não pagará nem será remunerado por sua participação. Garantimos, no entanto, que todas as despesas de transporte, por meio público, serão ressarcidas, se necessário, quando devidas e decorrentes especificamente de sua participação na pesquisa. No entanto, em caso de eventuais danos ocorridos exclusivamente por causa deste estudo, o(a) Sr(a) terá direito a tratamento médico completo oferecido pela instituição do estudo. **Participação no estudo:** Uma vez que o(a) Sr(a) aceitar participar do estudo, os pesquisadores iniciarão o agendamento das visitas e realizarão as avaliações após garantir que o(a) Sr(a) tenha compreendido o que será avaliado em cada momento. É importante que o(a) Sr(a) saiba que tem a opção de não fornecer o seu consentimento e não participar desta pesquisa. Sua decisão não interferirá no seu atendimento no Hospital Universitário Regional do Norte do Paraná da Universidade Estadual de Londrina. Além disso, os participantes poderão abandonar o estudo a qualquer momento que se achar conveniente, sem qualquer prejuízo em nenhum sentido. **Sigilo:** Embora os resultados da pesquisa possam ser divulgados em publicações e eventos científicos, a identidade dos participantes será sempre preservada de maneira sigilosa, ou seja, em segredo, conforme previsto pela lei. Quando os resultados forem analisados, não aparecerá o nome de nenhum participante e sim um código. Desse modo, a identidade não será revelada. **Acompanhamento da pesquisa:** Você poderá solicitar informações ou esclarecimentos sobre o andamento da pesquisa em qualquer momento da pesquisa. Para tanto, você poderá telefonar para (43) 3371-2490 / 3371-2477 e falar com o Professor Carlos Augusto Marçal Camilo. Se você tiver reclamações sobre a condução ética deste estudo, assim como preocupações, dúvidas ou reclamações

sobre seus direitos como participante da pesquisa, você poderá entrar em contato com o Comitê de Ética em Pesquisa (CEP) do Hospital Universitário Regional do Norte do Paraná da Universidade Estadual de Londrina no endereço: LABESC - Laboratório Escola de Pós-Graduação - sala 14 - Campus Universitário - Rodovia Celso Garcia Cid, Km 380 ou pelo telefone (43) 3371-5455, de segunda a sexta, das 08:00 às 11:30hrs. O CEP trata-se de um grupo de indivíduos com conhecimentos científicos e não científicos que realizam a revisão ética inicial e continuada de propostas de pesquisas para mantê-lo seguro e proteger seus direitos. Você também tem a opção de entrar em contato diretamente com a Comissão Nacional de Ética em Pesquisa (CONEP) através do Fone de denúncia: (61) 3315-3927 ou (61) 3315-2472.

Caso o(a) Sr(a) aceite esse convite e concorde voluntariamente em participar do estudo assinando este termo de consentimento, consideramos que o(a) Sr(a) acredita que foi suficientemente informado(a) por um dos pesquisadores responsáveis sobre a pesquisa, os procedimentos envolvidos nela, assim como os possíveis riscos e benefícios decorrentes dessa participação. Ressaltamos novamente que o(a) Sr(a) pode retirar seu consentimento a qualquer momento, sem que isto leve a qualquer prejuízo em nenhum sentido.

Colocamo-nos à disposição para qualquer esclarecimento que se fizer necessário nos telefones (43) 3371-2490 / 3371-2477 ou pessoalmente no Ambulatório de Fisioterapia Respiratória do Hospital Universitário Regional Norte do Paraná: Av. Robert Koch, 60 – Vila Operária – Londrina – PR (perguntar pelo Professor Carlos Augusto Marçal Camilo).

Atenciosamente,
Prof. Dr. Carlos Augusto Marçal Camilo
Prof. Dr. Fábio de Oliveira Pitta
Prof. Dr. Marcos Ribeiro

Eu, abaixo assinado

.....
(Nome do participante em maiúsculas)

Declaro ter sido informado verbalmente além de ser provido com as informações do estudo por escrito. Eu também tive a oportunidade de fazer perguntas e discutir o estudo com os Professores Carlos Augusto Marçal Camillo e/ou Fábio de Oliveira Pitta e/ou Marcos Ribeiro ou ainda por algum pesquisador do estudo.

Declaro que recebi respostas para todas as minhas perguntas (caso tenham ocorrido). Estou ciente de que a minha participação é completamente voluntária e que a qualquer momento posso retirar meu consentimento, sem que isto leve a qualquer prejuízo em nenhum sentido. Eu também sei que a participação no estudo não me trará vantagem ou prejuízo em nenhuma atenção médica atual ou futura oferecida pelo Sistema Único de Saúde – SUS.

Paciente ou Responsável:

___ / ___ / ___ (DD/MM/AA) _____
Assinatura (ou impressão papiloscópica)

Pesquisador:

___/___/___(DD/MM/AA) _____
Assinatura

ANEXO A - Aprovação do projeto pelo comitê de ética em pesquisa

UNIVERSIDADE ESTADUAL DE LONDRINA - UEL

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Associação entre progressão da doença e desfechos clínicos em pacientes com doenças intersticiais pulmonares

Pesquisador: CARLOS AUGUSTO MARCAL CAMILLO

Área Temática:

Versão: 2

CAAE: 69598317.5.0000.5231

Instituição Proponente: CCS - Progr. de Pós-Grad. em Ciências da Reabilitação

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.143.496

Apresentação do Projeto:

O Pesquisador afirma que "doenças intersticiais pulmonares (DIP) são um grupo heterogêneo de patologias com características clínicas, radiológicas e funcionais muito semelhantes. Além disso, pacientes sofrem ainda com alterações extrapulmonares como a disfunção muscular periférica, piora da qualidade de vida relacionada a saúde e ainda capacidade de exercício reduzida. Uma característica marcante das DIP é a diminuição progressiva da função pulmonar em um prazo relativamente curto. Em indivíduos com outras doenças respiratórias (como a doença pulmonar obstrutiva crônica), a redução da função pulmonar ocorre paralelamente a uma redução na AF. É possível hipotetizar que esta relação entre declínios na AF e na função pulmonar também esteja presente nas DIP, porém até o momento não há estudos que tenham demonstrado isto."

Objetivo da Pesquisa:

Objetivo Primário:

Avaliar o impacto do declínio da função pulmonar nas mudanças nos níveis de atividade física de pacientes com doenças intersticiais pulmonares

Objetivo Secundário:

Avaliar o impacto do declínio da função pulmonar em outros desfechos clínicos: função muscular (força, resistência e fadigabilidade); capacidade de exercício (máxima e funcional), qualidade de

vida relacionada à saúde e sintomas. Além disso, investigar associações entre o nível de atividade física (e suas mudanças ao longo do tempo) e hospitalizações e mortalidade em pacientes com DIP durante o período do estudo. Por último, também serão verificadas possíveis associações entre função pulmonar (e suas mudanças ao longo do tempo) com os demais desfechos investigados.

Avaliação dos Riscos e Benefícios:

Riscos:

Segundo o pesquisador, "nenhum dos procedimentos utilizados constitui risco direto para a integridade física ou moral dos participantes. Em alguns casos, após a coleta de sangue é possível que se forme um pequeno hematoma na região onde a coleta ocorreu. Além disso, caso algum teste gere mal estar (físico ou emocional) ele será interrompido sem que haja risco real para a saúde do participante.

Benefícios:

Benefícios esperados do estudo: Os resultados deste estudo ajudarão a compreender o efeito que uma possível progressão da doença (ou seja, mudanças na função pulmonar) tem sobre diferentes aspectos clínicos da doença. Isso poderá contribuir para que, no futuro, novos tratamentos surjam e ajudem pacientes com doença pulmonar intersticial.

Benefícios diretos ao participante: Ao realizarem as reavaliações, todos os participantes receberão relatório com os resultados de todos os testes. Além de servirem como avaliação a ser entregue ao médico responsável, os participantes sem acompanhemento médico que desenvolvam algum problema de saúde grave (identificados através de alguma avaliação realizada no estudo), receberão suporte médico gratuito pelo médico responsável do estudo.

Comentários e Considerações sobre a Pesquisa:

Trata-se de estudo de coorte relevante para a área e qualidade de vida de indivíduos com DIP.

Critério de Inclusão:

Pacientes com doença intersticial pulmonar: Pacientes de ambos os gêneros com idade entre 40 e 75 anos com diagnóstico de doença pulmonar intesticial de acordo com critérios internacionalmente aceitos (fibrose pulmonar idiopática, sarcoidose, doença vascular do colágeno, doença pulmonar ocupacional, sarcoidose, pneumonite hipersensitiva e outras formas de pneumonia pulmonar idiopática); Além disso, também deverão: possuir estabilidade clínica nas últimas 4 semanas e; ausência de comorbidades que interfiram na realização dos testes propostos. Adultos do grupo controle deverão: ser indivíduos adultos aparentemente saudáveis de ambos os gêneros com idade entre 40 e 75 anos e; não possuir comorbidades que interfiram na realização dos testes propostos.

Critério de Exclusão:

Participantes serão excluídos caso: apresentem doença cardíaca grave ou instável identificada durante o teste cardiopulmonar de esforço realizado no início da participação do indivíduo no estudo; não demonstrem condições cognitivas para realização dos testes ou; desenvolvam câncer pulmonar ou sejam alocados na lista de espera para transplante pulmonar durante o estudo.

Considerações sobre os Termos de apresentação obrigatória:

Apresenta folha de rosto devidamente preenchida e assinada pela coordenadora do programa de pós graduação em ciências da reabilitação.

Apresenta cronograma e orçamento detalhados e factíveis.

Apresenta autorização da instituição co-participante - Hospital Universitário/UEL.

Apresenta TCLE bem escrito e claro.

Recomendações:

Recomendo aprovação.

Conclusões ou Pendências e Lista de Inadequações:

Não há.

Considerações Finais a critério do CEP:

Prezado (a) Pesquisador (a),

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

Coordenação CEP/UEL.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_894925.pdf	27/06/2017 10:21:53		Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_Camillo_Versao02.pdf	27/06/2017 10:20:57	CARLOS AUGUSTO MARCAL CAMILLO	Aceito
Cronograma	Cronogramas_Camillo_Versao01.pdf	09/06/2017 15:38:20	CARLOS AUGUSTO MARCAL CAMILLO	Aceito
Orçamento	Orcamento_Camillo_Versao01.pdf	09/06/2017 15:35:25	CARLOS AUGUSTO MARCAL CAMILLO	Aceito

Declaração de Instituição e Infraestrutura	Declaracao_Infraestrutura_Camillo_Versao01.pdf	09/06/2017 15:32:25	CARLOS AUGUSTO MARCAL CAMILLO	Aceito
Projeto Detalhado / Brochura Investigador	Protocolo_Camillo_Versao01.pdf	09/06/2017 15:30:39	CARLOS AUGUSTO MARCAL CAMILLO	Aceito
Folha de Rosto	Folha_de_rosto_Camillo.pdf	09/06/2017 14:36:27	CARLOS AUGUSTO MARCAL CAMILLO	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

LONDRINA, 28 de Junho de 2017

Assinado por:
Alexandrina Aparecida Maciel Cardelli
(Coordenador)

ANEXO B – Normas para submissão do periódico *European Respiratory Review*

Manuscript preparation

Presentation of manuscripts should be consistent with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, as recommended by the International Committee of Medical Journal Editors (ICMJE).

All manuscripts must be submitted electronically using the online submission at ScholarOne Manuscripts. Detailed instructions of how to submit are available on the website itself and the process is self-explanatory. However, if you do experience problems, please contact the submission helpline direct on +44 114 2672864.

Before entering the ERR ScholarOne online submission area, please read and carefully follow the instructions below.

Brief requirements for articles are summarised in the following table.

General

The manuscript file you submit must be saved as .rtf (rich text format) or .doc (MS Word document).

Abbreviations and unusual terms should be described at the first time of use.

Symbols as defined by the ad hoc working group of the Commission of the European Communities (see Eur Respir J 1993; 6: Suppl. 16) are recommended.

The manuscript should be written in UK English.

Système International (SI) units are recommended.

Equations should be created as normal text.

Title page

Please provide a concise and informative title, limited to 90 characters, including spaces between words.

Include a list of all contributing authors (full names) and all of their affiliations, with a clear indication of who is associated with each institution.

Supply the full correspondence details for the corresponding author, including e-mail address. Please note that only one corresponding author per manuscript should be provided.

Provide a 256-character (including spaces) summary of the "take home" message of your paper, which can be used to publicise your study via social media.

Tables

Tables should be created and inserted into the text document using the 'Table', 'Insert Table'; function in your word processing package. Do not supply tables in a separate file.

Tables should be numbered consecutively with Arabic numerals.

Limit data to a sensible number of significant figures.

Large tables should be avoided if possible. Due to space restrictions, they may need to be split over two pages.

Please provide a clear footnote for each table, making sure all abbreviations and symbols used are defined.

For reference numbering schemes, citations made in tables should continue in numerical order from the point in the main body text where the table is cited.

Figures

Supply line-art figures in JPG, JPEG, TIF, TIFF, Adobe Illustrator (.ai) or EPS format. Please ensure image files are not layered and that the image size does not exceed 180 x 250mm. Graphs or bar charts may be supplied in Excel or similar spreadsheet format. PDF's can be uploaded but the figure legend must be included on the PDF.

Supply halftone and photographic images in PSD, JPG, JPEG, TIF or TIFF format. Minimum resolution should be 300 dpi at the final printable size (90 mm to 180mm wide maximum).

Don’t embed images in the main manuscript file. Supply them separately.

If your figures were originally created in another format that contains extra information (e.g. embedded data in an Excel graph), consider supplying them as supplementary material (Original Articles only).

SIZE AND QUANTITY

Figures constitute a key element of manuscripts submitted to the ERS research journals. However, figures should be limited (both in size and number) to those required to show the essential features described in the manuscript.

Avoid large figures comprising many individual parts: as a maximum, each individual figure must fit to a single PDF page of the journal, with sufficient space for its accompanying caption.

If you have a large number of figures, consider publishing some of them as an online supplement.

Images should be submitted in as close a size as possible to the final publication size. There are three options: 90, 140 or 180 mm.

Figure presentation

All submitted figures must be clearly named and numbered.

Whether for images, drawings or graphs, no more than four components should be used for a given figure. These should be labelled as a), b), c) and d).

Due to space restrictions, it is essential that each submitted figure show only the areas of interest with enough surrounding area for orientation purposes.

Radiographic images should be of high quality and combined into one array, such as posteroanterior and lateral views. They should also be sized the same to facilitate reproduction.

When several images of a given type are being shown, please reproduce all at the same magnification.

Photomicrographs must have internal linear scale markers (scale bars), since the size and magnification may be altered by the publisher or by the reader’s monitor/display.

Images should correspond in appearance to the tonal relations of the original radiograph (i.e. showing the bones white on a dark background), with the patient's right to the observer's left. CT scans and magnetic resonance images should employ the internationally-accepted 'view from below'.

Please label your images such that all important details are clearly visible. Avoid obscuring large areas of the images with excessive labelling.

Use a sans serif font for all labelling (preferably Arial), and ensure that the font size is reasonable and uniform throughout all the figures in your manuscript.

Please ensure that bar charts and graphs have a white background, with no shading or gridlines.

Use greyscale shading on bar charts and graphs (different weights can be used, e.g. from 0% (white) to 100% (black) for purposes of differentiation), in preference to hatching and patterning.

Three-dimensional effects should not be used in the presentation of bar charts.

For reference numbering schemes, citations made in figures should continue in numerical order from the point in the main body text where the figure is cited.

Guidelines for handling image data

If an image has been enhanced electronically, please explain the alterations that have been made and submit the original image along with the enhanced one. Moreover, keep an electronic set of original images, since our reviewers might ask you to modify their content and the display modus.

The Council of Science Editors (CSE) has established four basic guidelines for handling image data, which authors submitting to the ERR are urged to comply with. 1) No specific feature within an image may be enhanced, obscured, removed or introduced. 2) Adjustments of brightness, contrast or colour balance are acceptable if they are applied to the whole image and as long as they do not obscure, eliminate or misrepresent any information present in the original. 3) The grouping of images from different parts of the same gel, or from different gels, fields or exposures must be made explicit by the arrangement of the figure (e.g. dividing lines) and in the text of the figure legend. 4) If the original data cannot be produced by an author when asked to provide it, the acceptance of the manuscript may be revoked.

Captions

- Please provide a clear caption for each figure.
- Captions should be brief and not repetitive of information given in the text.
- Where appropriate, they should include the imaging technique used, the body part imaged and any noteworthy details.

- All abbreviations should be expanded.
- Use of internal scales should be mentioned.

Acknowledgements

All acknowledgements should be grouped into one paragraph placed after the Discussion section. Only acknowledge persons who have made substantial contributions, and provide the affiliation of those you name. Provide the names and affiliation details of members of collaborating bodies. Financial support should be acknowledged in a separate support statement; financial support provided to individuals must be disclosed on the conflict of interest declaration.

References

Number references consecutively in the order in which they first appear in the text, using full size Arabic numerals in square brackets to cite references.

The first three authors should be listed, followed by et al.

References should conform to the style used in Index Medicus (Vancouver style) as shown in the following examples:

1. Bannerjee D, Khair OA, Honeybourne D. Impact of sputum bacteria on airway inflammation and health status in clinical stable COPD. Eur Respir J 2004; 23: 685-692.

2. Bourbon J, Henrion-Caude A, Gaultier C. Molecular basis of lung development. In: Gibson GJ, Geddes DM, Costable U, Sterk PJ, Corrin B, eds. Respiratory Medicine. 3rd Edn. Edinburgh/Philadelphia, Elsevier Science, 2002; pp. 64-81.

Sources published as websites should be listed in the reference list, not in the text, and only used when an original citation is unavailable; citations should be listed as follows (include the author of the webpage, its title, the URL on which the cited

material can be found, and the dates on which the webpage was last accessed by you, and on which it was last updated):

3. WHO. Severe Acute Respiratory Syndrome (SARS). www.who.int/csr/sars/en/index.html. Date last updated: June 1 2004. Date last accessed: June 1 2004.

Citations made in figures or tables should continue in numerical order from the point in the main body text where the figure/table is cited.

Works that have not yet been accepted for publication and personal communications should not appear in the reference list.

A copy of any paper cited as "in press" should be uploaded to the ScholarOne submission platform as supplementary material, if at the time of submission they are not yet (or will not be) published online ahead of print.

For further general guidance on how to write papers, please refer to: Sterk PJ, Rabe KF. The joy of writing a paper. Breathe 2008; 4: 224-232, and guidelines for authors on how to write scientific articles to be published in English at http://www.ease.org.uk/publications/author-guidelines

Review and series articles (including systematic reviews and meta-analyses)

Review articles provide an overview and discussion of recent and current studies/practices in a particular area of respiratory research.

They should include an abstract of no more than 200 words in length, which provides an overview of the full article and which is easily understood without reference to the text.

Review articles should not exceed 5000 words in length (you do not need to include abstract, references, tables and figure captions in this word count); if

manuscripts exceed this limit, please state the final word count and explicit reasons for exceeding the limit in your covering letter.

Review articles can include a maximum of five figures and/or tables (i.e. any combination of tables and figures up to a total of five overall, not five figures and five tables).

Given the nature of review articles, it is appropriate to include a higher number of references than in original articles, but this should not exceed 150 references in total.

Systematic reviews and meta-analyses should be registered on the PROSPERO database. Reporting should follow PRISMA guidelines. Meta-analysis of observational data should follow MOOSE guidelines. A completed PRISMA or MOOSE checklist should be included with the submission.

Correspondence

Correspondence can be submitted for discussion of recently published European Respiratory Review articles.

Correspondence should not exceed 1200 words (you do not need to include references, tables and figure captions in this word count), should have no more than 12 references and should not include more than one figure or one table.

The European Respiratory Review will not publish online supplementary material for correspondence.

Online supplementary material

Authors have the option of providing supplementary data or figures, and accompanying videos, as an online supplement. This is an optional function and can be used at the discretion of the author and/or editor. The European Respiratory Review will not accept supplementary material for editorials, letters or correspondence.

Documents should be uploaded as "Supplementary material" during the submission process.

Videos to be presented as part of the online depository should be supplied in one of the following formats: Quicktime; MPEG; Microsoft AVI; Windows media video; Shockwave Flash.

Authors should note that their supplementary material will not be edited by the publications office, and will be published online as it is supplied.

Permission to re-publish materials

The European Respiratory Review discourages the use of previously published figures and tables, or any other material previously published elsewhere, unless absolutely essential. If it is essential that such material be included in your manuscript, you must obtain permission from the copyright owner before you submit your manuscript to the ERR. The copyright owner is usually the publisher, and not the original author. Please note that in order to secure the re-use of the material in question, you may be required to pay a fee to the original publisher. Furthermore, some publishers will not provide permission for publication, which precludes the material from being published in the ERR.

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reproduction and modification of questionnaires, the ERR reserves the right to take appropriate action.

Once your manuscript has been accepted for publication, the ERR publications team will contact you requesting that all the written permission agreements you have obtained are forwarded to the office for our records.

Authorship

There is no maximum for the number of authors of a manuscript, although all work must have been approved by all co-authors.

Authorship credit should be based on fulfillment of all of the following four criteria:

1) substantial contributions to either: the conception and design of the work; or the acquisition, analysis or interpretation of data for the work; and 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published; and 4) agreement to be accountable for all aspects of the work, in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All persons designated as authors should qualify for authorship, and all those who qualify should be listed.

Acquisition of funding, collection of data, or general supervision of the research group does not justify authorship.

Writing assistance from medical writers or agencies must be included in the acknowledgements section, or should be given appropriate credit as authorship.

As manuscripts must have been approved by all authors prior to submission, any changes to the list of authors that are proposed after manuscript submission will

require written approval from all named authors; this is in accord with the procedures outlined by the Committee on Publications Ethics (COPE).

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- use of article content by for-profit organisations for promotional purposes;
- use for the purposes of monetary reward by means of sale, resale, licence, loan, transfer or other form of commercial exploitation such as marketing products.

ANEXO C – Normas para submissão do periódico *Brazilian Journal of Pneumology*

O Jornal Brasileiro de Pneumologia (JBP) ISSN-1806-3756, publicado de modo contínuo, em seis números ao ano, é um órgão oficial da Sociedade Brasileira de Pneumologia e Tisiologia, destinado à publicação de trabalhos científicos referentes à Pneumologia e áreas correlatas. O JBP está registrado no PubMed Central (**www.ncbi.nlm.nih.gov/pmc/journals/2395**) e no SciELO (**http://www.scielo.br/jbpneu**).

Os manuscritos serão analisados e, de acordo com definição do Conselho Editorial, serão encaminhados para revisores qualificados, sendo o anonimato (dos autores e revisores) garantido no processo de julgamento, exceto quando previamente incluídos em um servidor de preprint: nesses casos, o processo de revisão por pares é simples-cego (os autores são cegados quanto à identidade dos revisores). Os artigos que não apresentarem mérito suficiente, que contenham erros significativos de metodologia ou não se enquadrem na política editorial do JBP serão rejeitados diretamente pelo Conselho Editorial, não cabendo recurso.

Todos os artigos submetidos devem estar escritos somente em inglês (americano ou britânico, mas evitar a mistura dos dois). É fundamental que o texto seja escrito em inglês de boa qualidade. Se os autores não forem fluentes na língua inglesa, recomenda-se que o artigo seja editado por um serviço de edição profissional antes do envio ou avaliado por um cientista nativo na língua inglesa. A avaliação por um serviço de edição profissional não é um pré-requisito para publicação no jornal e também não implica ou garante que o artigo seja encaminhado para revisão ou aceito para publicação. Qualquer submissão escrita em um idioma diferente do inglês será devolvida aos autores. No site do jornal (www.jornaldepneumologia.com.br), os artigos serão disponibilizados em versões em inglês e em português. Cada artigo receberá um número de referência na submissão para consulta futura.

*Não há taxas para submissão, avaliação e eventual publicação do artigo.

O JBP apoia as políticas para registro de ensaios clínicos da Organização Mundial da Saúde (OMS) e do International Committee of Medical Journal Editors (ICMJE), reconhecendo a importância dessas iniciativas para o registro e a divulgação internacional de informações sobre estudos clínicos em acesso aberto. Sendo assim, somente serão aceitos para publicação os artigos de ensaios clínicos que tenham recebido um número de identificação em um dos Registros de Ensaios Clínicos validados pelos critérios estabelecidos pela OMS e ICMJE, cujos endereços estão disponíveis no site do ICMJE. O número de identificação deverá ser registrado ao final do resumo.

Dentro desse contexto, o JBP adota a definição de ensaio clínico preconizada pela OMS, que pode ser assim resumida: "qualquer pesquisa que prospectivamente designe seres humanos para uma ou mais intervenções visando avaliar seus efeitos em desfechos relacionados à saúde. Tais intervenções incluem drogas, células e outros produtos biológicos, procedimentos cirúrgicos, radiológicos, dispositivos, terapias comportamentais, mudanças de processos de cuidados, cuidados preventivos, etc.".

Estudos com humanos devem incluir, na seção de Métodos, a informação sobre a aprovação da Comissão de Ética Local ou Nacional, preferencialmente com o número de aprovação, e estar de acordo com os princípios da Declaração de Helsinki. Estudos experimentais em animais devem estar alinhados com preceitos éticos.

Os autores garantem que os artigos submetidos ao JBP não foram publicados anteriormente e não estão sendo avaliados simultaneamente para a publicação em outro(s) periódico(s). O JBP utiliza o programa Crossref Similarity Check (iThenticate) para a avaliação do grau de similaridade com artigos previamente publicados.

Preprints

O Jornal Brasileiro de Pneumologia aceita a submissão de artigos depositados em

servidores de preprints. Para esses artigos, o sistema de revisão será simples-cego. O autor correspondente deverá preencher um termo de autorização informando que o artigo submetido está depositado em um servidor de preprint.

CRITÉRIOS DE AUTORIA

A inclusão de um autor em um manuscrito encaminhado para publicação só é justificada se ele contribuiu significativamente, do ponto de vista intelectual, para a sua realização. Fica implícito que o autor participou de pelo menos uma das seguintes fases: 1) concepção e planejamento do trabalho, bem como da interpretação das evidências; 2) redação e/ou revisão das versões preliminares e definitiva; e 3) aprovou a versão final.

A simples coleta e catalogação de dados não constituem critérios para autoria. Igualmente, não devem ser considerados como autores auxiliares técnicos que fazem a rotina, médicos que encaminham pacientes ou interpretam exames de rotina e chefes de serviços ou departamentos não diretamente envolvidos na pesquisa. A essas pessoas poderá ser feito um agradecimento especial. A contribuição de cada autor para o trabalho e eventuais agradecimentos devem constar da página de identificação (title page) obrigatoriamente (ver no item Página de Identificação). Os conceitos contidos nos manuscritos são de responsabilidade exclusiva dos autores.

Com exceção de trabalhos considerados de excepcional complexidade, a revista considera 10 o número máximo aceitável de autores para os artigos originais. No caso de haver um maior número de autores, enviar carta à Secretaria do JBP descrevendo a participação de cada um no trabalho.

APRESENTAÇÃO E SUBMISSÃO DOS MANUSCRITOS

Os manuscritos deverão ser obrigatoriamente encaminhados via eletrônica a partir do sistema de submissão ScholarOne

https://mc04.manuscriptcentral.com/jbpneu-scielo. As instruções e o processo de submissão estão descritos abaixo: O formulário de transferência de direitos autorais deve ser assinado eletronicamente por cada autor e deve ser anexado no ScholarOne. O modelo está disponível aqui: Clique aqui.

Pede-se aos autores que sigam rigorosamente as normas editoriais do JBP, particularmente no tocante ao número máximo de palavras, tabelas, quadros e figuras permitidas, bem como às regras para confecção das referências bibliográficas. A não observância das instruções redatoriais implicará na devolução do manuscrito pela Secretaria do JBP para que os autores façam as correções pertinentes antes de submetê-lo aos revisores. Instruções especiais se aplicam para a confecção de Diretrizes e Consensos e devem ser consultadas pelos autores antes da confecção desses documentos na homepage do JBP. Diretrizes e Consensos serão publicados como Artigos Especiais, também na modalidade de publicação contínua, em números regulares do JBP. O JBP reserva o direito de efetuar nos artigos aceitos adaptações de estilo, gramaticais e outras.

ESPECIFICAÇÕES POR TIPO DE ARTIGO

Os manuscritos principais deverão ser submetidos em arquivo Word (.doc ou .docx). Na tabela abaixo, segue um resumo das especificações dos tipos de artigos a serem submetidos.

Artigos originais

O texto deve ter entre 2.000 e 3.000 palavras, excluindo resumo, referências e ilustrações (isto é, tabelas, quadros e figuras). Deve conter no máximo 6 ilustrações. O número de referências bibliográficas não deve exceder 40. A sua estrutura deve conter as seguintes partes: Introdução, Métodos, Resultados, Discussão, (Agradecimentos e Contribuição dos Autores somente na title page) e Referências. A

seção Métodos deverá conter menção quanto à aprovação do estudo pelo Comitê de Ética em Pesquisa em Seres Humanos, ou pelo Comitê de Ética em Pesquisa em Animais, ligados a Instituição onde o projeto foi desenvolvido. Nessa seção também deve haver descrição da análise estatística empregada, com as respectivas referências bibliográficas. Ainda que a inclusão de subtítulos no manuscrito seja aceitável, o seu uso não deve ser excessivo e deve ficar limitado às sessões Métodos e Resultados.

PREPARO DO MANUSCRITO

Página de identificação **(Title page)**

Ela deve conter o título do trabalho, em inglês, o nome de todos os autores e das instituições as quais estão vinculados, endereço completo, inclusive telefone, celular e e-mail do autor correspondente e, se houver, nome do órgão financiador da pesquisa e identificação do protocolo de financiamento. O Open Researcher and Contributor ID (ORCID) de cada autor deverá ser fornecido. Para instruções sobre como obter o identificador ORCID, acesse **https://orcid.org/**. Devem-se incluir os locais onde o estudo foi realizado. Além disso, as informações sobre a contribuição de cada autor para o trabalho e eventuais agradecimentos devem constar aqui. Primeiro o item agradecimentos e depois, o item contribuição dos autores.

Essas informações serão publicadas ao final do manuscrito, antes das referências. A página de identificação deve ser enviada como um arquivo a parte em Word, separado do manuscrito principal.

Resumo (**Abstract**)

Deve conter informações facilmente compreendidas, sem necessidade de recorrer-se ao texto, não excedendo 250 palavras. Deve ser feito na forma estruturada para os Artigos Originais e Meta-análises com os seguintes subtítulos: Objetivo, Métodos, Resultados e Conclusões. Quando se tratar de Artigos de Revisão e Ensaios

Pictóricos, o resumo não deve ser estruturado. Para Comunicações Breves, não deve ser estruturado nem exceder 100 palavras. O resumo deve ser escrito exclusivamente em inglês.

Descritores (**Keywords**)

Devem ser fornecidos de três a seis termos em inglês, que definam o assunto do trabalho, de acordo com os termos dos Medical Subject Headings (MeSH), disponíveis na homepage **http://www.nlm.nih.gov/mesh/MBrowser.html.**

Corpo do texto

Com exceção das unidades de medidas, siglas e abreviaturas devem ser evitadas ao máximo, devendo ser utilizadas apenas para termos consagrados. Estes termos estão definidos na Lista de Abreviaturas e Acrônimos aceitos sem definição. Clique aqui (**Lista de Abreviaturas e Siglas**).

Quanto a outras abreviaturas, o termo deve aparecer ao menos três vezes para que possa ser abreviado e sempre definido na primeira vez em que for citado - por exemplo, proteína C reativa (PCR). Após a definição da abreviatura, o termo completo não deverá ser mais utilizado. Termos com palavras únicas não devem ser abreviados - por exemplo, tuberculose (TB).

Quando os autores mencionarem qualquer substância ou equipamento incomum, deverão incluir o modelo/número do catálogo, o nome da fabricante, a cidade e o país, por exemplo: "... esteira ergométrica (modelo ESD-01; FUNBEC, São Paulo, Brasil)" No caso de produtos provenientes dos EUA e Canadá, o nome do estado ou província também deverá ser citado; por exemplo: "... tTG de fígado de porco da Guiné (T5398; Sigma, St. Louis, MO, EUA)"

Tabelas, Quadros e Figuras (Ilustrações)

Tabelas, quadros e figuras devem ser apresentados em preto e branco. As ilustrações devem ser enviadas no seu arquivo digital original; tabelas e quadros em arquivos Microsoft Word e figuras em arquivos JPEG com resolução mínima de 300 dpi. Fotografias de exames, procedimentos cirúrgicos e biópsias nas quais foram utilizadas colorações e técnicas especiais serão consideradas para impressão colorida, sem custo adicional aos autores. As tabelas e figuras devem ser numeradas com algarismos arábicos, de acordo com a ordem de citação no texto.

Legendas

Legendas deverão acompanhar todas as ilustrações. No caso de figuras (gráficos, fotografias, etc.), as legendas devem ser citadas logo abaixo da imagem e submetidas em arquivo Word. No caso de tabelas e quadros, as legendas devem estar no topo. Cada legenda deve ser numerada em algarismos arábicos, correspondendo a suas citações no texto. Notas de rodapé devem ser incluídas da seguinte maneira: primeiramente, todas as abreviaturas e siglas definidas por extenso; detalhes e informações extras a respeito da ilustração com letras em sobrescrito - p.ex., [a]Valores expressos em n (%) -; e sinais tipográficos em sobrescrito (exceto *) para estatística - p.ex., *p < 0,05. Eis a sequência de uso desses sinais: *, †; ††; ¶; §; ‖; and #.

Referências

Devem ser indicadas apenas as referências utilizadas no texto, numeradas com algarismos arábicos e na ordem em que foram citadas. Deve-se evitar a utilização dos nomes dos autores ao longo do manuscrito para referenciar partes do texto - utilize, ao invés, "um estudo" ou "um autor/um grupo de autores", por exemplo.

A apresentação deve estar baseada no formato Vancouver Style, conforme os exemplos abaixo. Os títulos dos periódicos citados devem ser abreviados de acordo com o estilo apresentado pela List of Journals Indexed in Index Medicus, da National Library of Medicine disponibilizada no seguinte endereço: https://www.ncbi.nlm.nih.gov/nlmcatalog/journals/.

Para todas as referências, cite todos os autores até seis. Acima desse número, cite os seis primeiros autores seguidos da expressão et al.

ANEXO D – Normas para submissão do periódico Archives of Physical Medicine and Rehabilitation

NEW-Submission checklist

Archives requires the completion and upload of a checklist with each manuscript. Please follow the instructions on the checklist to ensure all required manuscript elements are included with your submission. Please note that this submission checklist is NOT the same as a reporting guideline checklist or form noted above. This is a separate item specific to the Archives

THE SUBMISSION CHECKLIST CAN BE DOWNLOADED HERE.

For any further information please visit our customer support site at https://service.elsevier.com. Authors should prepare manuscripts according to the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" [1] as developed by the International Committee of Medical Journal Editors. The Requirements are available at http://www.icmje.org.

Document Formatting

Manuscripts must be double-spaced throughout, including the title page, abstract, text, acknowledgments, references, individual tables, and legends. Use only standard 12-point type and spacing. Use unjustified, flush-left margins. Number the pages of the text consecutively. Put the page number in the upper or lower right-hand corner of each page. Number each line on each page of the text to facilitate peer review.

Authors should format manuscripts for specific attributes such as italics, superscripts/subscripts, and Greek letters. The coding scheme for each such element must be consistent throughout the file.

Text Style: Enter only 1 space between words and sentences. Leave 1 blank line between paragraphs. Leave 2 blank lines between headings and text.

Your Paper Your Way

As part of the Your Paper Your Way service, at initial submission you may choose to submit your new manuscript as a single file to be used in the refereeing process. This can be a PDF file or a Word document, in any format or lay-out that can be used by referees to evaluate your manuscript. It should contain high enough quality figures for refereeing. If you prefer to do so, you may still provide all or some of the source files at the initial submission. Please note that individual figure files larger than 10 MB must be uploaded separately. If your paper is accepted, you will you be requested, at the revision stage, to put your paper in

the correct format by supplying individual files for the manuscript, tables, figures, etc. and any other items required for the publication of your article. To find out more, please read the rest of the Preparation section.

NEW SUBMISSIONS

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

References

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

Formatting requirements

There are no strict formatting requirements for articles at initial submission (for requirements for revised submissions, please see REVISED SUBMISSIONS section below) but all manuscripts must contain the essential elements needed to convey your manuscript, for example Abstract, Keywords, Introduction, Methods, Results, Conclusions, Artwork and Tables with Captions.

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

Please ensure the text of your paper is double-spaced — this is an essential peer review requirement.

Figures and tables embedded in text - Your Paper Your Way

If you choose the Your Paper Your Way option when submitting your manuscript for the first time, please ensure the figures and the tables included in the single file are placed next to the relevant text in the manuscript, rather than at the bottom or the top of the file.

NEW- Peer Review

Archives uses a double-blind peer-review process. The blinded submission should be submitted in a word document and should begin with a title followed by the abstract, keywords, list of abbreviations, body of the text, references, figure legends, and any relevant suppliers' list.

The entire main body of text should be blinded as well including obvious references to institutions and names in the methods section, etc.

REVISED SUBMISSIONS

Please note if you submitted your original manuscript following the Your Paper Your Way format you will now need to put the paper in the correct format by supplying individual files for the manuscript, tables, figures, etc. and any other items required for the publication of your article.

Use of word processing software

Regardless of the file format of the original submission, at revision you must provide us with an editable file of the entire article. Keep the layout of the text as simple as possible.

Most formatting codes will be removed and replaced on processing the article. The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the Guide to Publishing with Elsevier).

See also the section on Electronic artwork.
To avoid unnecessary errors you are strongly advised to use the 'spell-check' and 'grammar-check' functions of your word processor.

Subdivision

Manuscript files should be structured as follows: (1) Title page, including Disclosure of interest and Acknowledgments, etc.; (2) Manuscript file including Abstract, Keywords, Abbreviations, Main text, References, Legends of figures and tables; (3) Table files; (4) Figure files; (5) Supplementary files; (6) ICMJE forms.

Manuscript Headings

Original Article level 1 headings are: Methods, Results, Discussion, and Conclusions. Articles should include the level 2 subsection heading Study Limitations at the end of the Discussion section. Longer articles may need other level 2 and/or level 3 subsection headings to clarify their content, especially the Results and Discussion sections.

Other types of articles such as Commentaries and Special Communications do not require this format.

Title Page

Include these elements in the title page in the following sequence, double-spaced: (1) Running head of no more than 40 character spaces (no abbreviations); (2) Title (no abbreviations); (3) Author(s) full name(s) and highest academic degree(s); (4) The name(s) of the institution(s), section(s), division(s), and department(s) where the study was performed and the institutional affiliation(s) of the author(s) at the time of the study. An asterisk after an author's name and a footnote may indicate a change in affiliation; (5) Acknowledgment of any presentation of this material, to whom, when, and where; (6) Acknowledgment of financial support, including grant numbers and any other needed acknowledgments. Explanations of any conflicts of interest; (7) Name,

address, business telephone number, and e-mail address of corresponding author; and (8) Clinical trial registration number, if applicable. Please note that clinical trial registration will now be required as of January 1, 2016. The grace period will end January 1, 2017 when registration will be mandatory.

Abstract

For articles reporting original data (Original Articles, Brief Reports) and Review Articles (including Meta-Analyses), a structured abstract is required (see the Instructions for Structured Abstracts). Authors should make sure the key elements from the Reporting Guideline (eg. CONSORT, PRISMA, etc.) they followed for their manuscript are included in the abstract as well as the body of the paper. Structured abstracts for Original Research and for Systematic Reviews/Meta-Analyses should be no more than 300 words in length.

For other manuscripts (e.g., Commentaries, Editorials and Special Communications), include a conventional, unstructured abstract of no more than 250 words.

Keywords

All abstracts must include provide 1 to 10 Keywords identified by the author. Keywords must be selected from the US National Library of Medicine's (NLM) Medical Subject Headings, which is available at http://www.nlm.nih.gov/mesh/MBrowser.html.

Abbreviations

Archives' editorial policy is to minimize the use of abbreviations. Fewer abbreviations make it easier for the multidisciplinary readership to follow the text. Authors should include a list of abbreviations in their manuscript file directly following the keywords (just above the introduction). Archives uses only standard abbreviations with Davis's and Dorland's as our guides. Abbreviations that are used only in tables, appendices, or figures are not included in the list and should be defined in the table, appendix, or figure legend. However, abbreviations that are in the list need not be re-defined in a table footnote or figure legend. All abbreviation lists must be alphabetized. All abbreviations must be defined upon first mention in the body of the manuscript. The

abbreviations SD (standard deviation) and SE (standard error) require no definition in Archives.

Main Manuscript

Introduction

State the purpose of the article. Summarize the rationale for the study or observation. Give only pertinent references, and do not review the subject extensively. Do not include data or conclusions from the work being reported. Do not include a heading for this section.

Methods

Describe the selection of the observational or experimental subjects (patients or experimental animals, including controls) clearly. Discuss eligibility of experimental subjects. Give details about randomization. Describe the methods for any blinding of observations. Identify the methods, equipment and materials, and procedures in sufficient detail to allow others to reproduce the results. Reference established methods, including statistical methods (see below); provide very brief descriptions for methods that have been published but are not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration.

While there may be occasional exceptions, Archives is committed to the need for clinical trial reports to be accompanied by adequate periods of follow-up. A lack of sufficient follow-up may be detrimental to a paper's acceptance.

When reporting work with human subjects, indicate whether the procedures followed protocol and accord with the ethical standards of the responsible institutional review board, ethics committee or with the Helsinki Declaration of 1975, as revised in 2013, as appropriate for the country where the research took place. [2]

Do not use patients' names, initials, or hospital numbers, especially in any illustrative material. When reporting experiments on animals, indicate whether the procedures followed accord with the institution's committee on animal experimentation

or with the National Research Council's guide on the care and use of laboratory animals. Archives may require authors to verify the above procedures.

Describe statistical methods in enough detail to enable knowledgeable readers with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (eg, confidence intervals [CIs]). Avoid sole reliance on statistical hypothesis testing, such as P values, which fails to convey important quantitative information.

Researchers should report and identify the specific statistical test used and the obtained statistical value. Researchers should supplement the results of any statistical value. Researchers should supplement the results of any statistical significance test with the use of effect size values or CIs. Measures of effect size or CIs should be routinely included in quantitative clinical trials reported in rehabilitation research. The statistical power values and the corresponding type II error probability should always be reported for statistically nonsignificant results.

The investigator should ensure that there is sufficient power to detect, as statistically significant, a clinically meaningful treatment effect of an a priori specified size [4]. References for study design and statistical methods should be to standard works (with pages stated) rather than to papers in which designs or methods were originally reported.

Specify any general use computer programs used. Avoid nontechnical uses of technical terms in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlation," or "sample." Define statistical terms, abbreviations, and symbols.

When submitting manuscripts on randomized controlled trials (RCTs), authors must include the CONSORT (Consolidated Standards for Reporting Trials) flow diagram. See the Reporting Guidelines.

Results

When data are summarized in the Results section, specify the statistical methods used

to analyze them. Describe the success of any blinding of observations. Report treatment complications. Give numbers of observations. Report losses to observation (ie, dropouts from a clinical trial). Present results in logical sequence in the text, tables, and illustrations. Archives aims to publish no more than 5 figures per manuscript so restrict tables and figures to those needed to explain arguments and to assess their support. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Do not repeat in the text all the data in the tables, illustrations, or both; emphasize or summarize only important observations.

While there may be occasional exceptions, Archives is committed to the need for clinical trial reports to be accompanied by adequate periods of follow-up. A lack of sufficient follow-up may be detrimental to a paper's acceptance.

Discussion

Emphasize the new and important aspects of the study and the conclusions that follow from them. Do not repeat in detail data or other material given in the introduction or the Results section. Include in the Discussion section the implications of the findings and their limitations, including implications for future research. Authors should address the issue of effect magnitude, in terms of both the statistics reported and the implications of the research. Relate the observations to other relevant studies.

Study Limitations

Include the subsection (Level 2 heading), "Study Limitations" to discuss the limitations of the study.

Conclusions

Link the conclusions with the study's goals but avoid unqualified statements not supported by the data. Avoid claiming priority and alluding to work that is incomplete. State new hypotheses when warranted, but clearly label them as such. Recommendations, when appropriate, may be included.

Highlights

Highlights are optional yet highly encouraged for this journal, as they increase the discoverability of your article via search engines. They consist of a short collection

of bullet points that capture the novel results of your research as well as new methods that were used during the study (if any). Please have a look at the examples here: example Highlights.

Highlights should be submitted in a separate editable file in the online submission system. Please use 'Highlights' in the file name and include 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point).

Graphical abstract

Although a graphical abstract is optional, its use is encouraged as it draws more attention to the online article. The graphical abstract should summarize the contents of the article in a concise, pictorial form designed to capture the attention of a wide readership. Graphical abstracts should be submitted as a separate file in the online submission system. Image size: Please provide an image with a minimum of 531 × 1328 pixels (h × w) or proportionally more. The image should be readable at a size of 5 × 13 cm using a regular screen resolution of 96 dpi. Preferred file types: TIFF, EPS, PDF or MS Office files.

You can view Example Graphical Abstracts on our information site. Authors can make use of Elsevier's Illustration Services to ensure the best presentation of their images and in accordance with all technical requirements.

Acknowledgments

One or more statements should specify: (1) contributions that do not justify authorship (ie, third-party statistical analysis, writing/editing); and (2) acknowledgments of technical help. Persons who have contributed intellectually to the manuscript but whose contributions do not justify authorship must be named and their function or contribution described, e.g., "scientific adviser," "critical review of study proposal," "data collection," or "participation in clinical

trial." Clerical, administrative, laboratory staff, and participants/subjects in the study should not be acknowledged unless they have contributed significantly to the research, writing, or intellectual quality of the article. Such persons must give permission to be named. Authors are responsible for obtaining written permission from

persons acknowledged by name because readers may infer their endorsement of the data and conclusions.

Formatting of funding sources

List funding sources in this standard way to facilitate compliance to funder's requirements: Funding: This work was supported by the National Institutes of Health [grant numbers xxxx, yyyy]; the Bill & Melinda Gates Foundation, Seattle, WA [grant number zzzz]; and the United States Institutes of Peace [grant number aaaa].

It is not necessary to include detailed descriptions on the program or type of grants and awards. When funding is from a block grant or other resources available to a university, college, or other research institution, submit the name of the institute or organization that provided the funding.

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

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Units

Metric units are required. Blood pressures in millimeters of mercury (mmHg) and all hematologic and clinical chemistry measurements using the International System of Units (SI).

Footnotes

Footnotes other than for references are not allowed in the manuscript body.

Artwork

Preferred file formats are TIFF, EPS, JPEG, and PDF. 300 dpi is minimum resolution to achieve high quality images. Typical desired resolutions are 300 dpi for black and white and color figures; 500 dpi for combination art (combined photo with line art); and 1000 dpi for line art. Figures should be numbered consecutively in the order they are first cited in the text. If a figure has been published, acknowledge the original source in the reference list and the figure legend, and submit written permission

from the copyright holder to reproduce the material. Permission is required, irrespective of authorship or publisher, except for documents in the public domain.

Letters, numbers, and symbols should be clear and even throughout, and of sufficient size that when reduced for publication each item will still be legible. Titles and detailed explanations belong in the legends for figures, not on the figures themselves. For multi-part figures, please label each component separately with A, B, C, etc. both in the figure itself and in the legend.

Consistency in size within the article is strongly preferred. Any special instructions regarding sizing should be clearly noted. Photomicrographs must have internal scale markers. Symbols, arrows, or letters used in the photomicrographs should contrast with the background. If photographs of persons are used, either the subjects must not be identifiable or the author must obtain and archive permission to publish the pictures and attest that permission has been granted in the cover letter that accompanies the manuscript submission.

The Editorial Board reserves the right to determine which figures are appropriate for publication. There is no charge for publication of black and white illustrations.

Electronic artwork

General points

• Make sure you use uniform lettering and sizing of your original artwork.
• Preferred fonts: Arial (or Helvetica), Times New Roman (or Times), Symbol, Courier.
• Number the illustrations according to their sequence in the text.
• Use a logical naming convention for your artwork files.
• Indicate per figure if it is a single, 1.5 or 2-column fitting image.
• For Word submissions only, you may still provide figures and their captions, and tables within a single file at the revision stage.
• Please note that individual figure files larger than 10 MB must be provided in separate source files.

A detailed guide on electronic artwork is available.

You are urged to visit this site; some excerpts from the detailed information are given here.

Formats

Regardless of the application used, when your electronic artwork is finalized, please 'save as' or convert the images to one of the following formats (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below):

EPS (or PDF): Vector drawings. Embed the font or save the text as 'graphics'. TIFF (or JPG): Color or grayscale photographs (halftones): always use a minimum of 300 dpi. TIFF (or JPG): Bitmapped line drawings: use a minimum of 1000 dpi. TIFF (or JPG):

Combinations bitmapped line/half-tone (color or grayscale): a minimum of 500 dpi is required.Please do not:

•Supply files that are optimized for screen use (e.g., GIF, BMP, PICT, WPG); the resolution is too low.

•Supply files that are too low in resolution.

•Submit graphics that are disproportionately large for the content.

Color artwork

Color figures (minimum 300dpi) will be published without charge when color reproduction is essential to understanding of the material presented.

Figure legends

A list of figure legends should be provided after the reference list, listing each figure in order by number. Legends/captions should not be embedded in the figure files themselves.

Figure captions

Ensure that each illustration has a caption. A caption should comprise a brief title (not on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used.

Tables

Submit each table as a separate file. Accepted file formats are PDF and Word (Please do not upload Excel files). If needed, Excel files will be requested from the authors upon a final editorial decision of accept. Number tables consecutively in the order of their first citation in the text. Include a brief title for each table, include a short or abbreviated heading for each column. Place explanatory matter in footnotes, not in the title or column headings. Explain in footnotes all nonstandard abbreviations that are used in each table. For footnotes, use the following symbols, in this sequence: *, †, ‡, §, ||, ¶, #, **, ††, ‡‡

Identify statistical measures of variations such as standard deviation and standard error of the mean. Do not use internal horizontal and vertical rules. Be sure that each table is cited in the text in order. Using too many tables in relation to the length of the text may produce typesetting difficulties.

Data from another published or unpublished source may only be used with permission and must be acknowledged fully. It is the author's responsibility to obtain such permission.

Supplementary data

Archives accepts electronic supplementary material to support and enhance your scientific research. Supplementary files offer the author additional possibilities to publish supporting applications, high-resolution images, background datasets, sound clips, and more. Supplementary files supplied will be published online alongside the electronic version of your article in Elsevier Web products, including ScienceDirect: http://www.sciencedirect.com.

Suppliers

Before the References section, provide a Suppliers list with contact information (names and complete mailing addresses) for manufacturers of devices and other non-drug products used directly in a study (ie, do not provide such information for products not directly used in your research but mentioned in studies you cite). Identify equipment

and/or materials in text, tables, and legends by superscript lower case letters. List suppliers consecutively in the order they are mentioned in the text.

Manufacturer names and locations should not be listed in the text where the product is introduced. Do not list Suppliers in the References list. Do not list drug manufacturers in the Suppliers list.

References

References in manuscripts accepted by Archives shall include only material that is retrievable through standard literature searches. Number references consecutively in the order in which they first appear in the text. Identify references in text, tables, and legends by superscript Arabic numerals. References cited only in tables or in legends to figures should be numbered in accordance with a sequence established by the first identification in the text of the particular table or figure.

Try to avoid using abstracts as references; "unpublished observations" and "personal communications" may not be used as references, although references to written, not oral, communications may be inserted (in parentheses) in the text. Avoid "personal communication" unless it provides essential information not available from a public source. In this case, cite the name of the person and date of communication in parentheses in the text. For scientific articles, authors should obtain written permission and confirmation of accuracy from the source of personal communication.

Include among the references those papers accepted but not yet published; designate the journal and add "In press." Authors must obtain written permission to cite such papers as well as verification that they have been accepted for publication. Editors will request from the author(s) a copy of the letter from the journal accepting

the "in press" article if the manuscript in which it is cited is accepted by Archives. Information from manuscripts submitted but not yet accepted should be cited in the text as "(unpublished observations)" with written permission from the source.

The references must be verified by the author(s) against the original documents. List all authors and/or editors for each reference, up to 6 authors. If there are 7 or more authors, truncate the list to the first 3 names and add "et al." **Citations in the running text** Number references consecutively in the order in which they first appear in the text. Identify references in text, tables, and

legends by superscript Arabic numerals. References cited only in tables or in legends to figures should be numbered in accordance with a sequence established by the first identification in the text of the particular table or figure.

Data references

This journal encourages you to cite underlying or relevant datasets in your manuscript by citing them in your text and including a data reference in your Reference List. Data references should include the following elements: author name(s), dataset title, data repository, version (where available), year, and global persistent identifier. Add [dataset] immediately before the reference so we can properly identify it as a data reference. The [dataset] identifier will not appear in your published article.

Reference management software

Most Elsevier journals have a standard template available in key reference management packages. This covers packages using the Citation Style Language, such as Mendeley (http://www.mendeley.com/features/reference-manager) and also others like EndNote (http://www.endnote.com/support/enstyles.asp) and Reference Manager (http://refman.com/downloads/styles). Using plug-ins to word processing packages which are available from the above sites, authors only need to select the appropriate journal template when preparing their article and the list of references and citations to these will be formatted according to the journal style as described in this Guide. The process of including templates in these packages is constantly ongoing. If the journal you are looking for does not have a template available yet, please see the list of sample references and citations provided in this Guide to help you format these according to the journal style.

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When preparing your manuscript, you will then be able to select this style using the Mendeley plug-ins for Microsoft Word or LibreOffice. For more information about the Citation Style Language, visit http://citationstyles.org.

Reference formatting

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

Reference style

Text: Indicate references by (consecutive) superscript Arabic numerals in the order in which they appear in the text. The numerals are to be used outside periods and commas, inside colons and semicolons. For further detail and examples you are referred to the AMA Manual of Style, A Guide for Authors and Editors, Tenth Edition, ISBN 0-978-0-19-517633-9 (see http://www.amanualofstyle.com).

List: Number the references in the list in the order in which they appear in the text. Click here for examples of correct reference formats.

Journal abbreviations in references

The titles of journals should be abbreviated according to the style used in MEDLINE. Consult List of Serials Indexed for Online Users, which is available from the NLM at http://www.nlm.nih.gov/tsd/serials/lsiou.html.